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SCIENCE MEDICINES HEALTH

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Overview of comments received on ICH Q3E Guideline and supporting documentation for extractables and leachables (EMA/CHMP/ICH/236669/2025 and EMA/CHMP/ICH/236668/2025)

Please note that comments will be sent to the ICH Q3E EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
A3P	0	0		Extractable studies with stressful conditions generates a large list of potential leachable. Later on, when leachable studies are performed, such compounds are not often detected with the product of interest. Performing directly a leachable study (at least 6 months at accelerated conditions, and over shelf life under long term condition) with generic methods (such as methods used for extractible studies) can also support efficiently a risk analysis: any difference between a product in contact with the packaging and the same in an inert packaging would be linked to a leachable compound (or an interaction of a leachable with a component of the product) and would then be included in the risk analysis.	Include the fact that other strategies / methodologies are acceptable if justified.
AESGP	0	0	Supporting documentation: class 3 monographs	Most of the PDE have been derived from 28days or 90days studies. Thus a factor F3 of 1 has been applied for acute PDE derivation while 5 or 10 has been applied to derive chronic PDE (see also comment in line 57). However, if a chronic PDE is derived based on a PoD from long term studies, a factor of 1 (according to ICHQ3C) would still be used. In this case, which factor F3 should be used to derive an acute PDE from a PoD of e.g. 2 years rat study? Using the same chronic PDE for acute exposure would not be appropriate. For example, for HD solutions (or LPVs solution) for which a volume up to 75 L can used applied for 4 weeks, the chronic PDE (derived from long term tox studies) would not be appropriate and it results in an overestimation when also F6 and F7 are taken into account.	clarification is needed. An additional factor should be considered for extrapolation from chronic to acute. Additionally, a proposal justification for such specific drug products should be added within the guideline.
AESGP	0	0	Supporting documentation: class 3 monographs (p.12) Parenteral acceptable exposure level and PDE Irganox1310 (text and table on parenteral calculations)	Absoprtion and oral bioavailability have been derived from in silico predictions. The applied tool/method should be specified as highlighted in lines 1110 to 1118. Moreover, wihtin the table, F6 factor reports "(physicochemical characteristics)" while the F6 factor of 1 was based on in silico predictions	add details on the in silico tool and correct the text in brackets with "(bioavailability predicted)"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	0	0	Supporting documentation: class 3 monographs (p.22)	text in bold not necessary "different reaction sequences accommodate different structures (CIR, 2019)."	correct formatting
AESGP	0	0	Supporting documentation: class 3 monographs (p.22-23) fatty acid acceptable exposure	it is not clear which values should be used for the assessment of fatty acid (single or multiple fatty acids). Is 50 mg/day only relevant for parenteral chronic exposure and applicable only to multiple fatty acids? Where the threshold of ≤10 mg/day is coming from? Is ≤10 mg/day applicable also to both chronic and acute exposures? as well as for single and multiple fatty acid from parenteral exposure?	Reference should be added regarding the threshold of ≤10 mg/day. Explanation weather 50 mg/day or 10 mg/day should be applied for single and multiple fatty acid exposure is needed. Perhaps a table could be helpful.
AESGP	0	0	Supporting documentation: class 3 monographs BHT PDE derivation - Parenteral PDE	It is not clear why predictions were performed when related information is publicly available (EFSA 2012, JECFA 1996).	Available experimental data should be considered
AESGP	0	0	Supporting documentation: class 3 monographs Erucamide PDE derivation - Parenteral PDE	According to literature, absorption of Erucamide range 52.8 to 72.9% in rats (see references: ECHA and Health Canada). Accondigly, a F7 of 2 seems more appropriate for parenteral extrapolation instead of 10. in silico predictions should also be applied to see the concordance with physicochemical properties and available data.	Available experimental data should be considered
AESGP	0	0	Supporting documentation: class 3 monographs Rubber oligomer	it is not clear on which basis the surrogate was selected (e.g. structural similarity)	add an explanation (the tool is not enough to understand the selection)
AESGP	0	0	Supporting documentation: class 3 monographs Rubber oligomer - Table for parenteral PDE (F6)	F6 factor reports "(physicochemical characteristics)" while the F6 factor was based on in silico predictions. Moreover, based on the in silico predictions (100% and 95.6%) the F6 should be 1 instead of 10. it seems that the predictions results of absorption and oral bioavailability of Irganox and Rubber oligomer are the same. could this be a typo error?	to clarify and correct

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ALK (MANUS)	0	0	Figure 5	Concerns with performing a simulated leachables study for products that are compounded with other company products. For products that go to compounding groups, it is difficult to assess scope of leachable materials as the manufacturer may not/will not know how the end user uses the product or what the product is compounded with.	Addition of justification for not performing a leachables study as the manufacturer on compounded products as it is not possible to ascertain all other vendor products used in compunding.
AstraZeneca	0	0	6	Could some guidance on consideration for safety assessment of paediatric products be added- a statement on whether the 50 kg for PDE calculations is appropriate for all patient populations including paeds, and if so, why?	
BioPhorum	0	0	0	Document should not stipulate that both E & L are required in all cases - for process components, only extractables may be needed, while container closure systems require both.	Please ensure document is clear on this position.
BioPhorum	0	0	0	Inconsistent use of terms Extractables & Leachables throughout the document	Ensure consistent use.
EfPIA	0	0	0	Inconsistent Terminology is used throughout the document: "extraction study" and "extractable study"; "manufacturing" and "fabrication"; "quantitation" and "quantification"	To Harmonize.
EfPIA	0	0	0	General comment: Quantitative extractable study as described in the draft text is applicable only when performed by the Drug manufacture and not when data generated by external labs/Suppliers are used. Indeed, such study is to be done in the same extracted solution&same batches as used for the semiquantitative study, which is not doable in the latter described case. Furthermore, in paragraph 5 (line 455) it is reported that "An extraction study should include the establishment and application of an AET": again, this is applicable only to in-house studies, not for studies done by Suppliers/CRO whose methods cannot be AET based.	NA
EfPIA	0	0	0	It would be helpful to clarify the minimum expectations for early phase projects (Phase I and II) for example in a Q&A document.	NA
EfPIA	0	0	2	Drug substances are out of scope?	Clarify what is in/out of scope
EfPIA	0	0	3.3 and figure 4	If a component is evaluated as low risk according to the principles outlined in Figure 2, it should be considered qualified for use without further assessment i.e. without extractables/leachables testing.	Add box in Figure 4 between the "Selection of manufactoring equipment…" and "Does the semi-quantitative…." boxes with the following text: "Does risk assessment according to the principles outlined in Figure 2 indicate a low risk for the component/system." If yes, proceed to "No further assessment required". If no, proceed to "Does the semi-quantitative...."
EfPIA	0	0	All	The words "extraction study" and "extractable study" are used interchangeably	Harmonize
EfPIA	0	0	All	The terms "manufacturing" and "fabrication" appear to be used inconsistently, which may lead to confusion.	Harmonize
EfPIA	0	0	All	Review the use of terms "quantiation" and "quantification" throughout the document	Harmonize
EfPIA	0	0	Fig 1 Fig 3 Fig 4	The guideline should include the current industry practice of applying an initial risk ranking to determine whether identification of extractables or leachables is required. Prior to assessment of known extractables / leachables per figure 3, or even figure 1, single-use systems and components should be risk-ranked according to factors such as those shown in Figure 2 (i.e., distance along the process / proximity to final dosage form, susceptibility of the polymer to extraction / crystallinity of the polymer, solvent strength of the process stream, surface area to volume ratio, temperature, and duration of contact). This initial risk ranking, as described in the BioPhorum protocols, will determine whether full leachables per figures 1 and 3 (high risk), extractables only per figures 1 and 3 (medium risk) or only compendial data (low risk) are required.	A risk-based approach to determine how to define when and where to evaluate for E&L would be an important decision tool. Please add the initial risk ranking step at the top of the workflow of Figure 1 and Figure 3.
EfPIA	0	0	General	Is there an alignment of the ICH guideline with the ISO 10993-17? (e.g. device-specific risk factors, drug-device interface, functionality of devices) How to assess risk when the patient is exposed both to leachables in the drug product and potentially to direct contact with the device material itself?	Harmonization of ICH and ISO terminology and concepts for drug-device combinations

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	0	0	General	The guidance given in the guideline regarding the in-use leachables assessment and/or testing of Administration Materials is not clear. The guideline refers to delivery devices and related compounds but would benefit from definitions of what is considered a delivery device, administration material etc. and from more guidance on the in-use assessment/testing	Clarify expectations regarding assessment and testing of delivery devices and. administration materials, especially regarding in-use.
EFPIA	0	0	General	terminology: medical device versus device versus device part versus device component versus device constituent versus device constituent parts. All of these terms appear to be used interchangeably throughout the different ICH guidelines and are not well defined anywhere, often making it unclear what is actually meant. This requires clarification	use fewer terms e.g. device and device constituent part, define these in the glossary and use consistently throughout ALL ICH guidelines
EFPIA	0	0	General	It is recommended to align the ICH guideline with the ISO 10993-17 which has the toxicological risk assessment of device constituent parts in scope	Harmonization of ICH and ISO terminology and concepts for drug-device combinations
EfPIA	0	0	Multiple	Editorial comment.	There are numerous instances throughout the document where 'extractable/leachable' or 'extractable and leachable' are used despite the acronym E&L being defined early in the document. Utilize acronym in all instances for consistency.
EFPIA	0	0	N/A	General Comment - Regarding ophthalmic products, since these products are now considered medical devices by FDA, we recommend guidance be provided within this document to clarify whether safety risk assessments need to be performed twice, one following ISO 10993-17 (calculating TIs) and one following this document (calculating PDEs).	
EFPIA	0	0	N/A	General Comment - No guidance is provided regarding allowance for adjustment to factors, with appropriate rationale, to PDEs for intermittent dosing. We recommend this guideline include content to address this topic.	
EfPIA	0	0	Supporting Documentation - 4-tert-amyl-phenol	It says 4-tert-amylphenol is a known environmental endocrine disruptor, not human health… Unclear what this means and the data that supports this statement. Endocrine disruption is a very charged term in toxicology, and so this requires additional explanation.	Include information on what the effects were and why they are not relevant for human health or exclude from the monograph. Environmental effects in general should be excluded since leachables are intended for patient safety.
EfPIA	0	0	Supporting Documentation - BHT	BHT has in silico predictions, but with no reference to the model used or version. Also there is animal data (summarized in Health Council of the Netherlands. 2,6-Di-tert-butyl-p-cresol. (CAS No: 128-37-0). Health-based Reassessment of Administrative Occupational Exposure Limits. 2000/15OSH/101. 2004.) which shows oral absorption was 80-90% in rats, 85% in guinea pigs, and close to 100% in mice.	Use experimental data which is published instead of in silico predictions for BHT.
EfPIA	0	0	Supporting Documentation - Irganox 1310	For F6, it says the value based on physicochemical characteristics, however the text used in silico predictions. In addtion, the in silico model / version should be included when doing an in silico prediction.	Update F6 in table to include in silico and include model / version in text of the in silico prediction.
EfPIA	0	0	Supporting Documentation - Rubber Oligomer C21H40	For F6, it says the value based on physicochemical characteristics, however the text used in silico predictions. In addtion, the in silico model / version should be included when doing an in silico prediction.	Update F6 in table to include in silico and include model / version in text of the in silico prediction.
EfPIA	0	0	Table A.1.1	If a component is evaluated as low risk according to the principles outlined in Figure 2, it should be considered qualified for use without further assessment i.e. without extractables/leachables testing.	Add an additional scenario with the following text: A component is evaluated as low risk following the principles in Figure 2 and complies with relevant regional food and/or pharmaceutical grade requirements. Potential outcome: Components considered qualified without additional extractables or leachables testing.

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EfPIA	0	0		The guidance given in the guideline regarding the in-use leachables assessment and/or testing of Administration Materials is not clear. The guideline refers to delivery devices and related compounds but would benefit from definitions of what is considered a delivery device, administration material etc. and from more guidance on the in-use assessment/testing	Clarify expectations regarding assessment and testing of delivery devices and. administration materials, especially regarding in-use.
EfPIA	0	0		Both the terms "Extractable and Leachable studies" and "Extractables and Leachables studies" (with an "s") are used thoughout the document. For consistency reasons only one term should be used in the document (with an "s" or without"). I believe that the term "Extractable and Leachable studies" is not appropriate. "Extractable and leachable" are adjective and suggest that the studies themselves are extractable and leachable, i.e. can be extracted or leach...A compound can be "an extractable or leachable compound" because the suffix "able" refers to the "ability" of the compound to be extracted or leach. A study does not have the ability to be extracted or leach...Therefore, the correct term should be "Extractables and Leachables studies" with an "s"...	Use consistently throughout the document "Extractables studies, Leachables studies" (and not Extractable studies, leachable studies")
EfPIA	0	0		Various terms are used to address or define the same things, e.g. "Extractables study" and "Extraction study", or "simulated leachables study" , "simulated leaching study" and "simulation study". Harmonization of the terms would be wished to align on the vocabulary, which is probably relevant for an ICH guideline. At minimum, the glossary should include such "terms" that can be equally used for a same concept	Harmonize vocabulary throughout the entire document regardless of the sections. Update the glossary as needed.
EfPIA	0	0		The lack of clarity as to the basis of thresholds is a major concern, it is difficult to understand / support these values without publication of the data itself. Indeed in both ICH M7 (addendum) and ICH Q3D the basis for PDEs is provided	Publish as a minimum as an appendix the derivation of the QTs
EfPIA	0	0		For both parenteral and inhalation routes of administration the QT is in several instances lower than the TTC. Given the standing of the TTC, as the threshold of toxicological concern it is difficult to understand how a QT based on other toxicity end points can be lower than the TTC without a clear explanation as to the basis for this	Align with the TTC as the lowest safety threshold or provide a clear rationale for the basis of QTs lower than this.
EfPIA	0	0		Primary packaging and delivery devices are subject to different regulations and requirements, leading to uncertainty about applicable rules and necessary data. For instance, the ICHQ3E guideline does not address biological reactivity, ISO 10993, USP 661.2,...Sometimes, extractables are not requested for delivery devices,....	
EfPIA	0	0		What's are your expectation for assembly (SUS): do we need to calculate the risk level of the assembly or do we need to calculate the risk level item per item ?	
EfPIA	0	0		The USP 1663 and USP 1664 monographs describes "simulation studies" in the context of extraction studies. USP 1664.4, a new draft monograph for assessment of leachables in topical and transdermal drug products, section 4.1 describes "simulated-use extraction study on the assembled container closure system to produce an extraction profile representative of probable leachables". Simulated extraction studies are a valuable tool for E&L assessments of the container closure system.	Add "simulation extraction studies" to the ICH Q3E guidance as an option
EfPIA	0	0		Use of Oxford commas should be considered.	While not required, use of the Oxford comma in lists would provide clarity and avoid potential ambiguity, for example line 61.
EfPIA	0	0		It should be clearly stated that E&L data are not required for early stage development	
EfPIA	0	0		What does E&L correlation mean	Clarify the meaning of E&L correlation. Define if qulaitiative and/or quantitative? Should it be leachable correlation through extractables? Inferred through AETs? Less emphasis on the same lots of material E&L comparison is not feasible on a global manufacturing scale (surface area, composition and weight could be used).

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ELSIE	0	0	0	We note here a number of general key concepts and themes that are described in more detail in the specific comments: The guideline should emphasize and prioritize leachables as the main focus of risk and thus evaluation, e.g., refer to "leachables risk management" throughout the document. Discussion on the need for testing "multiple batches", should consider that the evaluation should focus on the components relevant to leachables, rather than other aspcets of the product The guideline should refer to methods being "fit for purpose" as done in other ICH guidelines, rather than focusing various recommendations on "qualification" and/or "validation" In line with the request for flexibility, we note that the term "extractables leachables correlation" should rather be a "leachables to extractables" correlation. Further, the meaning of "correlation" should be described in the glossary, and it should include qualitative comparison founded on risk-based approaches There are some areas in the guideline (which are noted below in the specific comments) that appear to reqest E&L evaluations without considering the quality risk management approaches that should be done, rather than using E&L testing to test quality into products. The guideline should make reference to the ICH quality management guidelines There should be flexibility in allowing sponsors to develop uncertainty factors that are suitable to the context methods used in an E&L evaluation. Please also include discussion and examples of uncertainty factor development in the training sessions	See details in the specific line item comments
ELSIE	0	0	0	The emphasis on scientifically founded decisions in the E&L analysis and assessment is missing; for example, the appropriate choice of solvents, predictive modeling.	Emphasize the use of scientifically sound principles, tools and models.
ELSIE	0	0	0	E&L assessment is important but it must be in proportion so that patients can receive treatment on time. It is well known that at very low concentrations, it is extremely difficult to identify E&Ls; and that for some E&Ls, there are no commercially available standards. At the same time, toxicological data are often scarce and the toxicological risk assessment is very conservative. Zero risk is simply not realistic. Example: in critical care, it is of utmost importance to save somebody's life rather than academically debating about a potential risk from a leachable arising after decades of daily treatment, which is not the case in critical care.	Accept risk where no further risk mitigation is possible where the treatment with the drug product is crucial to the patient's life.

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ELSIE	0	0	0	The language used in the document is overly complex, making it difficult to follow—especially for non-native English speakers. Additionally, the guideline lacks conciseness and contains unnecessary repetition.	Rewording throughout the guideline is needed. For example: Example 1: The repeated use of “manufacturing components/systems, packaging or delivery device components” could be simplified or defined once and referred to with a consistent term (e.g., “product-contact components”). Examnple 2: The explanation of the risk matrix and its multifactorial nature is repeated in both Section 3.2 and again in the summary of risk assessment steps. These could be merged or cross-referenced. Example 3: The list of lifecycle changes that may trigger re-evaluation of leachables is extensive and repeated in both Section 3.6 and the Documentation section. A single consolidated list with cross-references would improve clarity. Example 4: The flowchart in Section 6.3 is supported by text that repeats many of the same steps already described earlier in the section. Consider summarizing the flowchart steps briefly and referring to the visual for details.
ELSIE	0	0	0	Sterilization, namely by autoclave, is a huge driver for leachables migration, the document should include more details on the potential impact of different sterilization techniques on leachables profile.	Consider adding a section regarding sterilization impact
ELSIE	0	0	0	The words "extraction study" and "extractable study" are used interchangeably	Harmonize
ELSIE	0	0	0	The terms "manufacturing" and "fabrication" appear to be used inconsistently, which may lead to confusion.	Harmonize
ELSIE	0	0	0	Review the use of terms "quantitation" and "quantification" throughout the document	Harmonize
ELSIE	0	0	0	The guideline titled "Extractables and Leachables" contains a disproportionate amount of toxicological information, yet unfortunately provides very limited detail on E&L itself.	Balance the guideline text with more focus on E&L and less focus on toxicology
ELSIE	0	0	0	The content in the document jumps around fairly abruptly between drug container/delivery systems and manufacturing components/systems, which have different recommendations/requirements in some cases.	Consider better separating the assessment of manufacturing components/systems from drug delivery/container systems.

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ELSIE	0	0	0	As indicated in the scope, the guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope. Despite this, within the entire text there is a repetitive indication of ‘delivery device components‘, which actually belong to medical devices and not to pharmaceuticals as such. Due to this, a confusion / impression is created that this guideline applies also to medical devices, at least to delivery devices. And this should not be the case, since there are ISO 10993 series of standards that should be considered for the safety evaluation of medical devices, in particular, ISO 10993-18, ISO 10993-12 and ISO 10993-17 for chemical characterization and toxicological risk assessment of medical device constituents. Besides, there is ISO 21726, which gives a guidance on how to apply TTC for medical devices. Moreover, there are several new ISO TS/TR coming for medical devices to provide more guidance on the analytical procedures for E&L, and also for toxicological risk assessment of medical devices. This means that there are guidances already for medical devices and if the devices (delivery devices in particular) would be included also in the scope of ICH Q3E, this would create a confusion, which guidance should then be applied for devices. This becomes more critical, since there are certain requirements defined in ICH Q3E, which are in direct conflict with the requirements defined in the ISO standards. The most obvious difference is the QT that should be applied as Systemic Toxicity Threshold, especially in case of parenteral application. Since there is no Appendix to demonstrate how the QT thresholds are derived, it is not clear which chemicals are taken as a basis for the QT derivation. But it should be definitely considered that E&L for pharmaceuticals and medical devices, although having quie high similarities, have also significant differencies, e.g., E&L that can be observed for pharmaceuticals would never be observed for medical devices. There is a growing evidence for this (see, e.g., Masuda-Herrera et al., 2002: doi: 10.5731/pdajpst.2021.012693; Builee at el., 2025: https://doi.org/10.3389/ftox.2025.1600127). From these papers it can be seen that even higher 'QT' can be applied for medical devices. Another major difference is the analytical procedure. For medical devices a semi-quantitative analysis is performed most of the time and leachable study is very uncommon. When ICH Q3E is followed, then for the extractables identified above the AET a leachable study is always necessary. Therefore, current text in the guideline may cause confusion for manufactureres and for regulatory agencies with respect to which standards / guidances should be applied for medical devices (and delivery devices in particular).	Remove 'delivery device components' from the text of ICH Q3E, since medical devices are not in scope of ICH Q3E. As indicated in the scope of this guidance, the final DP should be in focus in its finished state and not the delivery device.
ELSIE	0	0	0	In general, there is a need to have the list of Non-mutagens/Predicted Non-Mutagens classified as Class 1, in order to be able to exclude them from the QT application. Currently, only 2 examples are included. And there is a need to have the lists of Non-mutagens/Predicted Non-Mutagens classified as Class 2, and also the Class 3 compounds, since without appropriate lists it becomes very challenging to make use of quaification thresholds suggested.	
ELSIE	0	0	0	In general, it would be very helpful to have an Appendix that would provide details (at least the list to start with) on how the QT thresholds are derived. Is it planned to add Monographs for all chemicals that were considered for the QT derivation?	
ELSIE	0	0	0	There seems to be a gap between pharmaceutical injectable products and medical devices when it comes to E&L. Comment: Add reference to guidance relevant for medical devices.	Guidelines between injectable drugs and medical devices vary greatly. Medical devices-specific guidelines (or something similar) should be referred to, to avoid the development of medical devices to fall under the very regulated umbrella of pharma injectable drugs.
ELSIE	0	0	0	The potential for interaction of leachables with the drug product can be challenging if not impossible -- for example, for drug products that have an unclear mode of action and/or whose mode of action is indirect (example human plasma for plasma exchange after a severe accident). During quality control, any relevant interactions that may alter the quality of the drug product would be captured. So, there is no need to assess every leachable (or extractable) in this regard.	Delete request for assessment of interaction, since this is already captured in quality control of the drug product and for some drug products, interactions are irrelevant.
ELSIE	0	0	Supporting Documentation: Class 3 Leachable Monograph page 19	In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively, why is an F6=10 used?	

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ELSIE (Extractables and Leachables Safety Information Exchange)	0	0	0	Given the range and variety of products and unique extractables and leachables challenges with each we encourage regulatory flexibility in allowing different science-based, risk-based, and fit for purpose approaches to be applied depending on the product and its application and use.	Provide text within the guideline noting this as part of the intent of this guideline
Ferring Pharmaceuticals	0	0		The document is in general very extensive for a guidance with many repeatings. Suggest to streamline the document to ease the use. Additionally there are many different terms used/introduced. Propose to extend the glossary to elaborate further to ensure correct interpretation of the guideline.	
Gedeon Richter Plc.	0	0	0	Throughout the text different terms are used with the same/comparable meaning (e.g. "packaging" vs. "container&closure system" vs. "Packaging components/systems" vs. "primary packaging" vs. "immediate packaging").	In the text only one term should be used consistently. Alternatively, these should be specified/defined in the "Glossary" section or should be claimed that these are used as synonyms.
Laboratoires Théa	0	0		How to deal with unknows compounds observed in the extractables study above the AET and above its toxicity threshold?	
Laboratoires Théa	0	0		Is it possible to have more details regarding the level of qualification/validation of the analytical methods used for extractables study, targeted leachables study and non-targeted leachables study? Can you please add in annex some examples of method validation?	
Lotus pharmaceutical company	0	0		If the extractables study does not identify any risk substances, is it still necessary to perform leachables testing at all time points during long-term stability studies? Can the leachables testing schedule be shortened or replaced by accelerated stability studies? Additionally, how many batches are required at minimum for leachables testing?	
Lotus pharmaceutical company	0	0		If the extractables study identifies degradation products originating from the API, excipients, or the finished product, should the E&L risk assessment report explain/investigate whether these are due to natural product degradation or migration from contact materials? Should the control limits for degradation products follow the qualification thresholds defined in ICH Q3A or ICH Q3B, or those defined in ICH Q3E?	
Luye Pharma	0	0	-	Why are class 1 monographs are listed in the core document whereas class 3 monographs are listed in supporting documentation.	Harmonise the listing of the leachable monographs.
Luye Pharma	0	0	page 21	The header indicates C12 to C22 acids, but the table additionally lists C8, C9, and C10 acids.	Harmonize header, tables and content
Medicines for Europe	0	0	3.3,3.4, 3.5	The guideline mentions that supplier extractables data can be leveraged but does not clarify: Whether confirmatory leachables testing by the finished product manufacturer is mandatory when supplier data (extractables) covers worst-case conditions and the relevant extractables are under the AET. What constitutes sufficient documentation from the vendor to support reliance on their data? To what extent a bridging justification between vendor data and the finished product conditions is acceptable? For instance if extractables are available from the vendor is it acceptable for the finished product manufacturer to only do leachables? This ambiguity creates uncertainty for applicants when designing E&L strategies and preparing regulatory submissions.	Add explicit guidance in Section 3.3 (Risk Assesment), 3.4 (Risk Control) and Section 3.5 (Documentation and Compliance) to: Define conditions under which supplier extractables data can be considered fully adequate without confirmatory leachables testing. In addition, conditions for relying on vendor's extractables' data to only do leachables. Provide minimum documentation requirements for vendor data (e.g., test conditions, solvents, analytical methods, AET application). Clarify criteria for bridging justification between supplier data and finished product conditions (e.g., pH, temperature, contact time comparability).
Medicines for Europe	0	0	-	It would be more consistent to list the leachable monographs in one document.	Include class 1 monographs in supporting documentation.
Medicines for Europe	0	0	page 21	Table header refers to C12 to C22 acids, but table comprises C8/C9/C10 acids as well	please bring in line
Octapharma	0	0	0	The emphasis on scientifically founded decisions in the E&L analysis and assessment is missing; for example, the appropriate choice of solvents, predictive modeling.	Emphasize the use of scientifically sound principles, tools and models.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Octapharma	0	0	0	E&L assessment is important but it must be in proportion so that patients can receive treatment on time. It is well known that at very low concentrations, it is hard to impossible to identify E&Ls; that for some E&Ls, there are no commercially available standards. At the same time, toxicological data are often scarce and the toxicological risk assessment is very conservative. Zero risk is simply not realistic. Example: in critical care, it is of utmost importance to save somebody's life rather than acedemically debating about a potential risk from a leachable arising after decades of daily treatment, which is not the case in critical care.	Accept risk where no further risk mitigation is possible where the treatment with the drug product is crucial to the patient's life.
Octapharma	0	0	0	Blood- and blood derived biopharmaceutical drug products should be out of scope, because human blood and plasma naturally contain chemicals form the donors' environments and lifestyles, which are hard to distinguish from leachables. Furthermore, the matrix is analytically very challenging and very low AETs are hardly achievable (due to a mix of matrix problems and high posology).	Blood- and blood derived biopharmaeutical drug products are out of scope.
Octapharma	0	0	0	The potential for interaction of E&L with the drug product can be challenging if not impossible for example, for drug products that have an unclear mode of action and/or whose mode of action is indirect (example human plasma for plasma exchange after a severe accident). During quality control, any relevant interactions that may alter the quality of the drug product would be captured. So, there is no need to assess every E&L in this regard.	Delete request for assessment of interaction, since this is already captured in quality control of the drug product and for some drug products, interactions are irrelevant.
POLPHARMA	0	0	General	We appreciate the proposed guideline with a holistic overview of the risk assessment and control of leachables. We also very much support that various approaches can be accepted ranging from compliance with relevant food-contact safety or pharmacopeial standards/regulations to more extensive E&L characterization and safety risk assessment, depending on the anticipated risk and prior knowledge.	N/A
Sartorius-Stedim Biotech GmbH	0	0	3.2	This risk-matrix does not consider that most SUS (filters, bags etc.) are already applied in hundreds of qualified process to manufcature DS and DP. From a "forward looking" guideline we would expect to propose also shortcuts for qualification of things, which are already qualified. In the current form we would need to re-qualify devices again and again - please ask yourselve: where is the benefit in such a repeated work?	
Sartorius-Stedim Biotech GmbH	0	0	3.2	The master variable for exposure calculations is the volume of a CCS and/or SU devices. In case of manufacturing devices we talk here about process volumes of several 100 if not 1000L, SUS sizes can be quite large (storage and mixing bags up to 1000L). Therefore reasonable scaling methods need to be proposed to scale extractables data into potential leachables - in particular for SUS. Please include this aspect appropriately whenever the guidelines refers to exposure.	Respective scaling methdodologies are provided in: (1) Dennis Jenke, Extractables and Leachables: Characterization of Drug Products, Packaging, Manufacturing and Delivery Systems, and Medical Devices. (John Wiley & Sons, Inc., 2022; (2) Hauk, A., et al.: Using Extractables Data of Single Use Components for Extrapolation to Process Equipment Related Leachables: The Toolbox and Justifications. Eur. J. Pharm. Sci. 163, 105841 (2021). (3) Hauk, A., et al.: R. From extractables to exposure data: Sensitivity analysis of extrapolation algorithms with focus on USP 〈665〉. Eur. J. Pharm. Sci. 207, 107026 (2025). Possible pitfalls with physically wrong scaling methodologies were published in: (4) Jenke, D. & Rabinow, B. E. Proper Accounting for Surface Area to Solution Volume Ratios in Exaggerated Extractions. PDA J. Pharm. Sci. Technol. 71, 225–233 (2017).
Sartorius-Stedim Biotech GmbH	0	0	Introduction	The guideline does not reasonably differentiate between container closure systems (CCS) and single use systems (SUS) used in manufacturing (see table on the right). This is a critical aspect, because the fate of leachables in CCS and in manufacturing are completely different. While one can imagine that leachables may reach an equilibrium concentration in a CCS after longer storage time, this is no longer true for SUS like perfused bioreactors, filters, chromatographic systems, UF/DF tangential-flow devices, tubes, etc. SUS are used in the dynamic environment of manufacturing, therefore the assumption that an equilibrium concentration may be reached during processing is misleading. Further we would like to highlight that the purpose of down stream operations is to enrich the DS and remove undesired impurities. Process equipment related leachables are just one class of undesired impurities, without having any common physical-chemical property, which would exclude them from removal . Therefore a reasonable assessment must explicitly include the "clearance" capacity of downstream processing.	Either the authors make a clear differetiation between CCS and SUS or SUS shall completely be removed from the text. An illustarive scheme concerning the fate of leachables in a downstreanm process is given on the right side.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sartorius-Stedim Biotech GmbH	0	0		With this guideline - if it will become offical without significant changes - ICH will hamper any future research and progress in the E&L field. The main problem is that the authors consider E&L anlysis as a kind of "forensic" analysis without taking the significant body of knowledge into accout which exists on E&L today. As an example, we from Sartorius conducted more than 150 extractables studies over the last 10 years and are today able to predict extractables profiles for our SUS and assemblies. We have a database and (KI like) algorithm developed, which help us identifying and predicting E&L profiles and allows an automatic safety assessment and equivalency evaluation after material changes. This is possible, becasue we know the typical substabce clusters in which E&L occur in extration experiments. To be honest, today a "forensic" style analysis is no longer required in the E&L field is it much more required to use and evaluate the already existing knowledge appropriately.	The guideline shall motivate the use of prior knowledge, IT tools (KI), modelling and not hamper their use. It is neccessary, that we overcome the repeated "forensic style"anlaysis and "worst case assessments" of E&L for SUS.
Sartorius-Stedim Biotech GmbH	0	0		Another weakness of the guideline is that it considers leachabels for CCS and SUS both as high risk for patients - for SUS this is not supported by our experince. Until today there was no published case, where a SUS related leachables caused a patient saftey risk. On the other hand, SUS related process leachabels may be detrimental to process performance and product quality - this is not adeqately elaborated in the draft.	Please consider, what Dennis Jenke wrote in his E&L textbook (Extractables and Leachables: Characterization of Drug Products, Packaging, Manufacturing and Delivery Systems, and Medical Devices. (John Wiley & Sons, Inc., 2022; page 217): "…experience, introspection, and experimentation has established that the chances of PERLs accumulating in finished drug products are negligibly low, especially for PERLs derived from the downstream manufacturing components."
Hikma			Leachable Monograph page 12	Is "in silico prediction" tool OECD QSAR Toolbox. Version 4.5 SP1.?	
Hikma			Leachable Monograph page 19	In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively, why a F6=10 was used?	
Luye Pharma			page 21	incorrect CAS for Lauric acid in the table	Change CAS of Lauric acid from ~~57-10-3~~ to 143-07-7
Luye Pharma			page 22-23	"A parenteral chronic class-specific value of 50 mg/day was proposed and considered applicable to multiple fatty acids exposure, including fatty acids lacking toxicity data. Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22 Based on endogenous and exogenous human exposure, as well as non-clinical exposure, fatty acids are considered to be of low acute and chronic toxicity. Aligned with product quality considerations, systemic exposure of ≤10 mg/day to one or more C8 to C22 fatty acids is acceptable without justification regardless of the administration route or exposure duration. Higher amounts may also be acceptable with appropriate justification."	- It is unclear which class the stricter exposure limit of ≤10 mg/day applies to. The term "monosaturated." may be corrected, as applicable. - The rationale for imposing a stricter limit (10 mg/day vs. 50 mg/day) appears unjustified, considering that the fatty acid group also includes essential fatty acids with substantially higher recommended daily intakes. - Exposure limits should not be applied unconditionally to essential fatty acids that have higher recommended daily doses.
Luye Pharma			page 23	"Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22" - It is possible that the term "monounsaturated acids" was intended instead of "monosaturated"?	Please clarify terminology.
Medicines for Europe			page 21	incorrect CAS for Lauric acid in the table	Change CAS of Lauric acid from ~~57-10-3~~ to 143-07-7
Medicines for Europe			page 22-23	"A parenteral chronic class-specific value of 50 mg/day was proposed and considered applicable to multiple fatty acids exposure, including fatty acids lacking toxicity data. Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22 Based on endogenous and exogenous human exposure, as well as non-clinical exposure, fatty acids are considered to be of low acute and chronic toxicity. Aligned with product quality considerations, systemic exposure of ≤10 mg/day to one or more C8 to C22 fatty acids is acceptable without justification regardless of the administration route or exposure duration. Higher amounts may also be acceptable with appropriate justification."	- It is unclear to which class the tighter exposure limit of ≤10 mg/day applies. Please be specific and clarify / correct the term monosaturated - The definition of a stricter limit (10 vs 50 mg/d) does not seem justified, as the fatty acids also include essential fatty acids with significantly higher recommended daily doses. - Limits shall not unconditionally apply to essential fatty acids with higher recommended daily doses.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe			page 23	"Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22"	Please clarify which fatty acids fall under the definition, i.e. maybe monoUNsaturted acids should have been phrased.
Pharmapol-Arzneimittelvertrieb-GmbH	0	0	0	It is clearly stated that the scope of the ICH Q3E Guideline is to improve the safety of new and approved drug products by minimizíng risks. Nevertheless, considering the time to identify and quantify possible extractables to be able to design and conduct a leachable study we kindly suggest to consider that, given the scope and duration of the required studies, this effort could lead to supply difficulties of authorised medicines being impaired due to limited flexibility. We primarily supply critical medicinal drug products, which can be found on the actual Union List of Critical Medicines, whose importance and availability have been recognized by EMA and different European Groups are working on the further regulations to secure supply like the ongoing Critical Medicines Act. For example for rarley used medicines like emergency medication or acute remidies, taking into account the rarely frequency of use of those products and therefore the limited exposure of patients in comparison to the benefits in life threatening emergency situation the question comes up if the proposed measures in the guideline are appropriate. The stringent requirements for studies in the event of potentially necessary components replacement and/ or changes in the container closure systems would restrict the flexibility of pharmaceutical companies too much to fulfil their task of avoiding shortages in the EU.	Exemption: For approved short-term medication like for example emergency products changes in the manufacturing process including components replacement and/ or changes in the container closure systems respectively the delivery device a paper-based safety assessment of possible extractables and leachables is acceptable, if available shelf-life studies demonstrate the stability and quality of the drug product after the implemenation of the described changes
PDA	0	0		The Product Quality Research Institute (PQRI) and the United States Pharmacopeia's Chapter <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and Chapter <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems define the Analytical Evaluation Threshold (AET) as "The concentration threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment." PDA proposes updating the statements in the guidance referencing the AET to align with other established industry definitions by modifiying the statments in this guidance to say that the AET is the threshold “at or above” which leachables should be characterized.	PDA recommends updating the statements on lines 152, 157, 164, 169, 366, 421, 447, 457, 538, 692, and 835 to say "at or above" in regards to the Analytical Evaluation Threshold (AET).
PDA	0	0		In alignment with PDA's other general comment, PDA recommends reviewing that the use of "AET" and "SCT" is used consistently throughout the document to ensure that the correct term is being used in the guidance to avoid reader confusion. SCT is a safety-based limit that defines what is toxicologically acceptable, while the AET is the analytical trigger derived from the SCT that dictates when test results require evaluation or control; they serve different purposes and are not interchangeable. In the cases where PDA feels "SCT" is more appropriate than "AET", specific comments to the line number have been provided for consideration.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PDA	0	0		As analytical technologies continue to advance, it is increasingly feasible for well-designed simulation or extractables studies to sufficiently support risk assessments, particularly for components located further upstream from the final container closure system. However, the language in Section 4.5 Simulated Leachable Study may be interpreted as emphasizing that drug product leachables studies are expected for all components—including single-use systems and other upstream, lower-risk materials—and that simulation/extractables studies are supplemental rather than potential alternatives. Additionally, statements such as those in lines 425–428, which reference the possibility of correlating leachables and extractables data to justify the use of routine extractables testing in place of routine leachables testing (e.g., for high-risk products, change control, or ongoing quality control), suggest potential advantages. Nonetheless, further clarification would be beneficial regarding the circumstances under which simulation or extractables studies may appropriately replace leachables studies, given the significant impact this could have on cost, timelines, and overall program efficiency. It is also unclear how "routine extractables testing" of components would practically be implemented and what level of correlation between extractables and leachables would be required to justify reducing or eliminating routine leachables testing. Additional guidance on the criteria, data expectations, and decision framework for determining when such correlation is sufficiently robust would help ensure consistent interpretation and application across the industry.	PDA encourages providing specific guidance for when simulation studies/extractables studies may be able to replace leachables studies.
Boehringer Ingelheim	0	498	6.1	Typo Add verb: is	As such, in addition to amount of exposure, the SCT **is** dependent on both route and duration of exposure
Boehringer Ingelheim	0	553	6.2	Typo Start new paragraph at "Subsequently…" as this relates to all leachables, and not only to the Class 1 leachables at the beginning of the paragraph.	
Boehringer Ingelheim	0	1079	Appendix 5	Typo ", if justified…": separate with ; or .	; if justified

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	1	61	1. 2. 3.1	The title of guideline is: GUIDELINE FOR EXTRACTABLES AND LEACHABLES, but in the scope of document apart from definition of extractables there is nothing more about them, all descriptions are related to leachables. As Extractables are potential leachables and further in the text there is a lot about them, worth to bind them together from the beginning.	line 45-47: The purpose of the guideline is to provide a holistic framework whereby leachables-associated risk (based on or including extractables data) can be identified, assessed, and controlled to protect the safety, efficacy, and quality attributes of the finished drug product
Sartorius-Stedim Biotech GmbH	1	6	Introduction	We recommend to add the term "process equipment realted leachabels (PERLs)" to enable a differentiation between "leachables" which may end up in a DS or DP (e.g. those relased from a CCS) and those which occur during processing, but are removed from the product stream	
Bio-Process Systems Alliance	2	2	1	The definition of leachables combines leachables from final drug product container with leachables from manufacturing systems. This ignores the development of the definition of Process Equipment Related Leachables (PERLs) in USP <665> & <1665> and sets up the entire Q3E to assess all leachables as if they will end up in the drug product.	Suggest to limit scope to final drug product primary packaging container and/or device only, or introduce definition for PERLs and revise Guidance with specific guidance for PERLs

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chiesi Farmaceutici	2	6	1	The definition of Leachables and potential source should be clearer, and not limited only to the migration of Extrctables to the drug product.	It is suggested to integrate by adding that the leaching process may be promoted by the drug product formulation (or components of it). Therefore, Leachables can be a subset of, or are directly/indirectly derived from Extractables. It is suggested to integrate the sentence as follows: "Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions. Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions and thus are potential leachables. More in details, as the leaching process may be promoted by the drug product formulation (or components of it), Leachables can be a subset of, or are directly/indirectly derived from Extractables."
EfPIA	2	3	1	Administration materials (such as infusion bags or lines) are not listed as such. They are not entirely covered by the term "delivery device components" . Clarification is wished.	Proposed wording/change: Leachables are chemical entities that migrate from manufacturing components/systems, packaging, administration materials and/or delivery device components. [...]"
EfPIA	2	42		Can we ask them to clarify scope. From reading the context of the article I would not expect this to be applied to medical devices like empty syringes that are filled with drug product at point of care, but a clarification on whether it applies in that case or not would be helpful.	
EfPIA	2	6	1	Clarify "delivery device components"—term is unclear and not standard. May refer to drug delivery systems, not standalone devices.	Define and clarify scope of "delivery device components" in glossary or replace with "drug delivery systems."
EfPIA	2	6	1	We believe that the wording of the guideline scope generates doubts on the medical device inclusion. Indeed, the wordings used across the documents, e.g. "drug delivery device components" or "drug delivery systems/devices" are not common and might cause confusion. This guideline should NOT be applicable to medical devices that are specifically regulated by other standards (ISO 10993 series for instance). Therefore we recommend to remove "delivery device components" from the text of ICH Q3E, while refer to"drug-device combination products", to make clearer that medical devices are not in scope of this document.	We recommend to remove "~~delivery device components~~" from the overall text of ICH Q3E, while refer to"drug-device combination products", to make clearer that medical devices are not in scope of this document.
EFPIA	2	3	1	Administration materials (such as infusion bags or lines) are not listed as such. They are not entirely covered by the term "delivery device components" . Clarification is wished.	Proposed wording/change: Leachables are chemical entities that migrate from manufacturing components/systems, packaging, administration materials and/or delivery device components. [...]"
ELSIE	2	6	1	"Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions. Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions and thus are potential leachables" • Clarity is required regarding the delivery device components in above lines - for example, whether they are separate parts of the drug product (e.g., a catheter) or can be integrated into the drug product (i.e., EVA release liner in a pouch). What is a "delivery device"? This term does not appear to be officially recognized. Is the document intending to refer to "drug delivery systems" or "drug delivery devices"? If the intention is to include auto-injectors, MDI, transdermal patches, etc., the appropriate terminology would be "drug delivery system" and not "device" since the latter (eg;. intrauterine device) are evaluated according to ISO 10993-18 and it falls outside the intended scope of ICH Q3E.	• We recommend that a definition of "delivery device components" be added to the glossary. Alternatively, the term "delivery device components" should be removed, or it can be replaced with a more suitable term. Any definition should clarify that what is being referred to are drug delivery systems and may be part of drug device combination products where the primary mode of action is the drug

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	2	3	1	Throughout the document it is not always clear, whether it is manufacturing items or primary packaging / device items or both.	Would it be possible to specify more clearly throughout the document, whether it is manufacturing items or primary packaging / device items?
Laboratoires Théa	2	6	1	Can you confirm that the E&Ls studies for the manufacturing components are now also mandatory for Europe	
Sanjay Desai (Cipla Ltd.)	2	4	1	The usage conditions are equally important in the determination of in-use leachable profile, as the leachables contribution from device components are majorly takes place during usage. Many devices are not in direct contact with drug products under normal storage conditions and coming in the contact of drug product and/or patient at the time of usage only. Hence, inclusion of in-use leachable profile determination is important from patient safety aspect.	Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing, labelled storage and usage conditions.
AESGP	3	5	1.	The term "delivery device" might lead to misinterpretation regarding medical devices	add a definition of what are 'delivery devices'
EfPIA	3	3	1	What is a "delivery device"? This term does not appear to be officially recognized. Is the document intending to refer to "drug delivery systems" or "drug delivery devices"? If the intention is to include auto-injectors, MDI, transdermal patches, etc., the appropriate terminology would be "drug delivery system" and not "device" since the latter (eg;. intrauterine device) are evaluated according to ISO 10993-18 and it falls outside the intended scope of ICH Q3E.	Leachables are chemical entities that migrate from manufacturing components/systems, packaging components into a drug product under the established manufacturing and labelled storage conditions.
EfPIA	3	5	1	Same remark as above	Proposed wording/change: Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging, administration materials and/or delivery device components [...]
EfPIA	3	3	1	Include reference to DS and DSI, DS mentioned at later stages of doc	Addressed elsewhere
Maven E&L Ltd	4	4	Section 1	I suggest the "labelled storage conditions" is replaced with monitored storage condition. Leachable storage may or may not directly reflect the labelling of a registered drug product and may include accelerating conditions	I suggest the "labelled storage conditions" is replaced with monitored storage condition.
AstraZeneca	4	4	Section 1	I suggest the "labelled storage conditions" is replaced with monitored storage condition. Leachable storage may or may not directly reflect the labelling of a registered drug product and may include accelerating conditions	I suggest the "labelled storage conditions" is replaced with monitored storage condition.
EfPIA	4	4	1	Should also mention use conditions	Proposed wording change: "...manufacturing and labelled storage and use conditions."
EfPIA	6	6	1	Extractables are not always potential leachables	and thus can be (or may be) potential leachables
AESGP	7	8	1 Introduction, page 1	Add the word 'potentially' before leachable as the leachable may or may not be realised under real use conditions.	add, 'potentially' to sentence, i.e. This guideline presents a holistic framework and process for the assessment and control of potentially leachable impurities
EfPIA	8	8	1	The term "leachable impurities" is not appropriate as it suggests that leachables are inherently impurities, which is definitely not correct from a scientific perspective. Indeed , leachables are in most cases primary leachables, originating from plastic or rubber materials, and correspond to additives, degradation products from additives, oligomers (I keep the list short), etc...and all these compounds (organic and inorganic) are not from a polymer/rubber perspective considered as impurities: they are inherent to those polymers/rubbers, and core constituants, i.e. not impurities. Secondary leachables may be regarded as drug impurities in this context, but the current wording brings confusion.	Delete "impurities" and keep the wording simple "[...] control of leachables to further expand the existing ICH guidelines, including [...]"

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AESGP	12	17	1. Introduction	Aim should also be to provide a risk based and proportionate framework for established medicinal products based on materials (i.e. compendial ingredients) and bioavailability/exposure.	While the guideline includes materials characterization and process understanding, its 'The' primary purpose 'of this guideline' is to protect patient safety and product quality through assessment and control of leachables in the drug product. 'The guideline provides a risk based and proportionate framework for established medicinal products based on consideration of manufacturing and packaging materials and bioavailability, considering the drug form and exposure of the drug product Solid Oral 'and topical' drug product's' manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements (See Section 3.2).'
AstraZeneca	13	14	Section 1	"...primary purpose to protect patient safety and product quality…" Guideline has significant focus on how to evaluate patient safety impact but evaluating the impact on product quality from leachables is not well defined.	Add details on how to evaluate leachables impact on product quality or refer reader to ICH Quality guideline.
EfPIA	13	14	1	Remove "product quality" as no quality-related testing is being performed. I agree that leachables can have an impact on product quality, but the purpose of e/l is patient safety. Product quality is assessed through compatibility testing that is performed under a different process.	Remove "and product quality" from the sentence. E&L is one part of the overall product quality assessment, soften product quality wording
EfPIA	14	14	1	Delete reference to Product Quality?	Addressed elsewhere
ELSIE	14	17	1	"Due to ongoing developments in materials engineering, device technologies, and manufacturing approaches, E&L assessments remain a critical component of ensuring drug product safety and quality." The concepts included in the guideline are not forward looking. While ICH Q3E represents a major step forward in global alignment and clarity for E&L evaluations, it primarily reflects current industry standards rather than introducing novel or forward-looking concepts.	Suggest removing sentence from section
EfPIA	16	17	1	Editorial comment.	Consider changing to read "…that are forward looking and adaptable within the scientific and regulatory landscape."

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Sartorius-Stedim Biotech GmbH	16	17	Introduction	We consider this draft guideline far away from being "forward looking", as it does not address the significant progress which was made in E&L research over the last few years. This includes methods for prediction of extractables (please consider the FDA homepage with the CHRIS model), modelling of the fate of leachabels in CCS and the fate of PERLs in process streams. Instead of beeing "forward looking" this guideline freezes the current way of E&L assessment, which is "forensic", "worst case" and is using physical assumptions which are not justified (e.g. in scaling of SU devices).	Please recongnize that there are a number of scientific publications which need to be considered. A few relevant publications are given below (if required we can provide more): (1) Li, K. et al. Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products. PDA J. Pharm. Sci. Technol. 69, 590–619 (2015). (2) Pahl, I. et al.: Using Extractables Data of Sterile Filter Components for Scaling Calculations. PDA J. Pharm. Sci. Technol. 73, 523–537 (2019). (3) Hauk, A. et al.: Using Extractables Data of Single Use Components for Extrapolation to Process Equipment Related Leachables: The Toolbox and Justifications. Eur. J. Pharm. Sci. 163, 105841 (2021). (4) Pahl, I., Hauk, A., Schosser, L. & von Orlikowski, S. Considerations on Performing Quality Risk Analysis for Production Processes with Single-Use Systems. in Single-Use Technology in Biopharmaceutical Manufacture 211–218 (John Wiley & Sons, Ltd, 2019). doi:https://doi.org/10.1002/9781119477891.ch17; (5) Piringer, O. G. & Baner, A. L. Plastic Packaging: Interactions with Food and Pharmaceuticals. (Wiley-VCH, 2008). doi:10.1002/9783527621422; (6) Saylor, D. M. & Young, J. A. Modeling extraction of medical device polymers for biocompatibility evaluation. Regul. Toxicol. Pharmacol. 141, 105405 (2023). (7) Heider, N. & Sobańtka, A. PredicDiffTM: a computational tool for the prediction of PERLs concentrations based on extractables data. Eur. J. Pharm. Sci. 210, 107108 (2025). (8) Hauk, A., Wildschütz, A., Pahl, I., Canton, D. & Menzel, R. From extractables to exposure data: Sensitivity analysis of extrapolation algorithms with focus on USP 〈665〉. Eur. J. Pharm. Sci. 207, 107026 (2025).
BioPhorum	18	42	2.0	General scope comment: The guidance does not differentiate between container closure systems and single use systems used in manufacturing, there are technical differences: in container closure systems, leachables can accumulate to equilibrium, whereas in single use manufacturing, impurities are removed and leachables typically do not end up in the product	Include separate guidance for container closure systems and single use systems used in manufacturing Clearly differentiate between extractables and leachables for container closure systems versus single use devices, noting that current standards and regulatory expectations differ significantly between these categories.
BioPhorum	18	42	2	Scope for Single-Use (and manufacturing components). The guideline scope claims to be a holistic (#7) framework for leachables assessment, and states (#208) this should be conducted on single-use and multi-use manufacturing components/systems. However, very little to no guidance is given for single-use (other than anecdotal risk considerations) and the guideline heavily focuses on applications around final container/product leachables, where significant additional rigor & testing requirements are expected to address the high risk. This creates unwarranted expectations for single-use that are either easily misinterpreted, or greatly impact the pharmaceutical manufacturing cost. - (#223) a leachables to extractables correlation would not be expected for all single-use items (undue expectations)	Either (i) remove single-use manufacturing systems from scope, focusing on equipment from final clearance step down, or (ii) expand the risk assessment section to provide guidance for what is expected for single-use assessments (e.g. USP <665 alignment).
BioPhorum	18	42	2.0	SCOPE: "Cell and gene therapy" are mentioned, but there is little specific guidance. As cell therapy products tend to have a clearance step at the end of the process with minimal volume carry-over, the risk is generally more focused on the impact to the cell itself. As such, perhaps the current guideline does not add much related to cell therapy, and it should be removed from scope. must differentiate b/w standard API and cell product . guideline does not adequately address the unique risks and assessment needs for cell and gene therapy products, where the primary risk is to the cells during processing rather than directly to the patient, and called for more specific guidance.	Suggestion not to emphasize 'cell therapy' as in scope.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chiesi Farmaceutici	18	42	2	The order of products in scope/not in scope and focus of the guideline is confused.	The suggested order is: products in scope, products not in scope, substances corresponding to the focus (in particular, the content of lines from 23 to 26 and from 30 to 31 should be reported at the end of the paragraph), as follows: "The guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope. Organic leachables are the primary focus of this guideline. Though recommended methodologies for elemental analysis are within the scope of this guideline, the safety assessment of elemental leachables are addressed by ICH Q3D and thus out of scope for this guideline. The guideline also applies to approved products for any changes that are likely to impact the leachable profile or patient exposure such as those relating to formulation, manufacturing, dosing, and/or container closure system (i.e., life cycle management). This guideline is not intended to apply to extrinsic, extraneous or foreign substances resulting from product contamination or adulteration. This guideline is not intended for herbal medicinal products and crude non-32 processed products of animal or plant origin. For these products in liquid dosage forms, regional expectations may apply.
Chiesi Farmaceutici	18	42	2	[Continued from above] The order of products in scope/not in scope and focus of the guideline is confused.	This guideline is not intended for products used during clinical research stages of development. However, in cases of high risk to the patient, principles of this guideline may be applicable to support clinical studies. Generally, radiopharmaceuticals are not considered in scope, unless there is a specific cause for concern. The guideline does not apply to systems used in the manufacture or storage of excipients. Refer to Section 3.4.1 for special considerations regarding packaging components for liquid or semiliquid active pharmaceutical ingredients (APIs). Organic leachables are the primary focus of this guideline. Though recommended methodologies for elemental analysis are within the scope of this guideline, the safety assessment of elemental leachables are addressed by ICH Q3D and thus out of scope for this guideline. This guideline is not intended to apply to extrinsic, extraneous or foreign substances resulting from product contamination or adulteration."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	18	42	2	Scope: Drug Substance	Suggest incorperating clarity on how its "in scope under speical considerations" and cummlative use? its mentioned 6 times in the the guidance document. Case study/Training material example using DS storage
BioPhorum	19	20	2	guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. What with liquid or semi-liquid drug substance?	in lines 183-185 there is reference to liquid or semi-liquid drug substance storage containers - see proposal for adjusting description for line 40-42 in section 2
EfPIA	19	24	2	The scope description is not aligned with the document title. It is, rightly, focussed on leachable assessment and does not mention extractables.	
EfPIA	19	31	2	The guideline is applicable to new drug products and to legacy products undergoing change control.	Move lines 27-31 after line 22 to ensure scope clarity.
EfPIA	19	20	2	Why mention cell and gene therapies specifically and not other modalities?	The guideline should clearly define the scope
EfPIA	19	22	2	Historically, some guidelines –although broadly applicable to all drug products including biological/biotechnological – may not included vaccines within their scope. As a result, vaccine-specific considerations might have been insufficiently addressed.	It is proposed to adapt "The guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope." to "The guideline applies to the risk assessment and control of leachables in new drug products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological/biotechnological products (including vaccines, cell and gene therapy products) are also in scope."
EFPIA	19	22	2	The current scope of this guidance is as follows: "The guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope." However, medical devices are not clearly stated as out of scope of this guideline. Section 2 defines the scope to include new drug products and drug-device combination products. We recommend to clarify and clearly state that medical devices are not in the scope of the document since devices are mentioned in various contexts throughout the document.	We recommend the following revision to the text of the guideline, "The guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope. Medical devices are outside the scope of this guideline."
ELSIE	19	22	2	The scope is defined to include new drug products and drug-device combination products.	It would be helpful to clarify and state clearly that medical devices are not in the scope of the document since devices are mentioned in various contexts throughout the document.
ELSIE	19	31	2	The guideline is applicable to new drug products and to legacy products undergoing change control.	Move lines 27-31 after line 22 to ensure scope clarity.
Merck KGaA, Darmstadt, Germany	19	20	2	It is not clear why "cell and gene therapy products" are additionally mentioned. These are drug products as well. If CGT are called out in particular, a rationale why CGT are specifically mentioned should be added.	The guideline applies to the risk assessment and control of leachables in new drug products~~, including cell and gene therapy products~~.
AstraZeneca	20	21	Section 2	The phrase : meets the definition of pharmaceutical or biological products is used - yet there in no reference as to where / how this is defined	Add a reference
BioPhorum	20	22	2.	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	Propose to align with Figure 5 and e.g., lines 822-823 to clarify scope. Clearly separate medical devices from ccs. confusion regarding the classification of drug delivery devices versus primary packaging, advocate for clearer separation and reference to relevant device and packaging regulations.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	20	22	2.	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	Propose to align with Figure 5 and e.g., lines 822-823 to clarify scope.
EfPIA	20	22	2	Drug-device combination products should not be in scope. The device component is expected to be addressed according to ISO requirements (more requirements than only biocomp & E/L). ISO 10993-18 contains significantly more information on E/L assessment than this current draft. The tox assessment of a device component is assessed according to ISO 10993-17. It cannot be supported that devices become part of the scope of the ICH Q series, as they are not in scope of the other Q guidance documents.	Strongly encourage limiting this guidance only to drug products. Devices cannot be supported in the ICH Q framework where ISO is the most appropriate regulatory guidance framework. Introducing duplication/divergent guidance cannot be supported by industry as it is not helpful.
EfPIA	20	22	2	Drug-device combination products should be evaluated in accordance with the ISO 10993 series. For example, the leachables profile of an implantable drug-device product cannot be adequately characterized using ICH Q3E, as worst-case release scenarios require exhaustive extractions, which are not addressed in this guideline.	Remove sentence from section
EfPIA	20	21	2 Scope	Drug-device combination products: pharma part is in the scope, device part perhaps not.	Device components are mentioned in all occations when listing what are related to E&L. Delivery devices in the scope are missleading when medical devices are not clearly excluded. Should mention in the document that for medical devices see relevant guidelines ISO & FDA interpretation about that.
EfPIA	20	20	2	Editorical comment.	Consider adding "the fluid path in contact with drug product in" in front of the "Drug-device combination products".
EFPIA	20	22	2 Scope	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well	align with Figure 5 and e.g. lines 822-823 to clarify scope
ELSIE	20	22	2	"Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope." • The lines state that scope of the guideline includes drug-device combination products; however the definition of leachables and extractables differs significantly between the definitions for medical device and a drug product. Drug-device combination products: pharma part is in the scope, device part perhaps not. Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	• We recommend that definitions of "extractables" and "leachables" be added to the glossary. • We recommend including example case studies involving API-loaded implants and patches to enhance clarity. This term "drug device combination products" needs to be defined. Using search, it is the only time this term in used throughout the document. Recommend it be defined with a reference for the term. Device components are mentioned in all occations when listing what are related to E&L. Delivery devices in the scope are missleading when medical devices are not clearly excluded. Should mention in the document that for medical devices see relevant guidelines ISO & FDA interpretation about that. Or clearly define "drug device combination products" in the context of the scope of this guideline. Propose to align with Figure 5 and, e.g., lines 822-823 to clarify scope.
IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)	20	22	2.	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	Propose to align with Figure 5 and e.g., lines 822-823 to clarify scope.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sartorius-Stedim Biotech GmbH	20	20	Scope	The statement, that this guideline is applicable to ATMP products is from our point of view missleading if not wrong, as it gives no advice how to assess potetial effects of PERLs on therapeutic cells. Patient safety in ATMP is a result of not only the leachables in the final product but much more on the integrity of the therapeutic cells. Please consider that the cells are in close contact with the devices over quite some time.	Please consider the discussion in the whitepaper from BPSA: M. Aysola, D. Clarke, R.H. Colton, P. Cummings, J. Grebin, A. Hauk, E. Heintz, T. Kapp, L. Brendan, R. McDermott, P. Hernan, J.P. St. Laurent, BPSA - Extractables/Leachables Considerations for Cell & Gene Therapy Drug Product Development, Bio-Process Syst. Alliance (2020) 17. https://bpsalliance.org/pdf-download-form-el-cgt/.
EfPIA	21	23	1	This makes reference to marketing authorisations that meet the definition of of a pharmaceutical or biological product	Consider reference to how this is defined
Maven E&L Ltd	23	26	Section 2	ICH Q3D safety assessment of elemental impurities provides PDEs for some elemental impurities but not others e.g. Iron or Calcium. Can ICH Q3E clarify how these types of elements should be assessed? Should they be treated like a Class 3 organic leachable? This classification is missing from ICH Q3D and hence it is not clear how elementally leachables should be assessed. Additionally, what modifying factors are relevant as the method described in ICH Q3D is different to that described in ICH Q3E. Perhaps an additional section on inorganic leachables should be incorporated?	Add a new section on inorganic leachables
AstraZeneca	23	26	Section 2	ICH Q3D safety assessment of elemental impurities provides PDEs for some elemental impurities but not others e.g. Iron or Calcium. Can ICH Q3E clarify how these types of elements should be assessed? Should they be treated like a Class 3 organic leachable? This classification is missing from ICH Q3D and hence it is not clear how elementally leachables should be assessed. Additionally, what modifying factors are relevant as the method described in ICH Q3D is different to that described in ICH Q3E. Perhaps an additional section on inorganic leachables should be incorporated?	Add a new section on inorganic leachables
EfPIA	23	26	2	ICH Q3D is not only about safety assessment of elemental impurities, it is also about risk assessment and control. However the current wording specifies only that "safety assessment of elemental leachables are addressed by ICH Q3D and thus out of scope", i.e. suggests that the risk assessment for elemental impurities may be in scope of ICH Q3E. I would seek for more clarity - see proposal.	Proposed wording/change: "Organic leachables are the primary focus of this guideline. Though recommended methodologies for elemental analysis are within the scope of this guideline, the safety assessment as well as the risk assessment and control of elemental leachables are addressed by ICH Q3D and thus out of scope for this guideline".
EfPIA	23	26	2	We understand and agree that elemental impurities are managed through ICH Q3D, however there is still a gap for those elemental impurities that are not included in the ICH Q3D/don't have a PDE. We propose to at least mention them, refreing to a toxicologist evaluation.	Though recommended methodologies for elemental analysis are within the scope of this guideline, the safety assessment of elemental leachables are addressed by ICH Q3D and thus out of scope for this guideline. Importantly, for elemental impurities that are frequently determined as E&L but that are not included in the ICH Q3D specific PDEs can be established with expert advise of a Toxicologist.
EfPIA	23	26	2	Bracketing paragraphs start with " The guideline applies…", which makes this paragraph sound out of place.	Suggest rewording the first sentence in line 23 to "This guideline is primarily focused on organic leachables." or something similar. Alternatively, this paragraph could be merged in with the preceding paragraph: "The guidline applies to the risk assessment and control of leahcables, with a primary focus on organic leachables, in new... Suggest flipping first 2 paragraphs

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	23	26	2	The guideline states that “organic leachables are the primary focus of this guideline and the safety assessment of elemental leachables is addressed by ICH Q3D and thus out of scope for this guideline.” However, Section 4.3 of the guideline (Extractables Study) indicates that analytical procedures should include both organic extractables and elemental extractables. This appears to create ambiguity regarding the expectation for inclusion of elemental impurities testing within extractable and leachable (E&L) studies thus, it is requested that the guidance be harmonized to ensure consistent interpretation between the general scope statement and Section 4.3, particularly regarding the treatment of elemental extractables and leachables inlcuding Q3D and other additional elements.	Clarify if extractable/leachable analysis is required for ICH Q3D class 1/2/3 leachables only or for ICH Q3D "other elemental impurities" as well.
EfPIA	24	26	2	Editorial comment.	Change to "…the safety assessment of elemental leachables is addressed…".
AstraZeneca	25	26	Section 2	Elemental impurities are out of scope because they're addressed in ICH Q3D but cell/gene therapies and vaccines are out of scope of Q3D and in scope of Q3E	Update ICH Q3D or explicitly state this discrepancy in Q3E and how Q3D should be used for cell/gene therapy and vaccines.
EfPIA	27	29	2	The sentence *"The guideline also applies to approved products for any changes that are likely to impact the leachable profile or patient exposure such as those relating to formulation, manufacturing, dosing, and/or container closure system (i.e., life cycle management)."* is too vague. A clear guidance should be given what extend of additional testing is proposed.	It would be helpful to provide more concrete guidance, such as: A detailed list of examples of changes that fall under this category. A stepwise approach or decision tree to determine whether a change necessitates re-evaluation of the leachable profile. Clarification of acceptable thresholds for changes and when these would trigger further studies.
GUERBET	27	29	2	The current working plan aims to have the Q3E guideline applicable for JUL-2027 (step 4) : what will be acceptable delay of implementation for existing Drug Products ?	Include the delay of implementation in the draft guideline
Hikma	27	29	2	Is the expectation to apply this guideline retrospectively, to approved products which dossiers do not have any extractable and leachables data?	Clarify on the scope if the recommendations on this guideline are to be applicable only when changes to the approved dossier are being filed.
EfPIA	31	32	2	Editorial comment.	Add a space break between lines 31 and 32
AESGP	32	34	2. Scope	It is unclear why the second sentence mentions liquid dosage forms of herbal medicinal products. Should the comment apply to all dosage forms. Also, 'regional expectations' may always apply so suggest this text is not required.	Add clarifying text AND, delete, 'For these products in liquid dosage forms, regional expectations may apply'
Medicines for Europe	32	33	2	The guideline specifies that it does not apply to herbal medicinal products and crude non-processed products (lines 32-34). Consider outlining the rationale for these exclusions and any potential overlap with established guidelines. Further clarification on how regional expectations for these products may vary would be valuable.	It would also be useful to outline the rationale for these exclusions and any potential overlap with established guidelines when assessing leachables in herbal products.
Maven E&L Ltd	35	37	Section 2	How would a high risk to patients be determined during clinical phases. Consider giving further guidance on situations where this might occur	
AESGP	35	37	2	This paragraph might mislead. E&L studies should usually be performed during R&D stages of development. If only used during approval phases, it will be significantly difficult to implement changes. Also chapter 3.1 refers to "product development considerations" - phrases might need adaption to not be contradictory	Text might be changed to: This guideline does not necessarily need to be applied during clinical stages of development. However, principles of this guidelines may be helpful and applicable to support the product development.
AstraZeneca	35	37	Section 2	How would a high risk to patients be determined during clinical phases. Consider giving further guidance on situations where this might occur	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	35	39	2.0	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definition of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/
EfPIA	35	39	2.	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definiton of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/
EfPIA	35	39	2	Recommendations for clinical development and radiopharmaceuticals are unclear. What is understood under ''specific cause for concern''?	
EfPIA	35	37	2. Scope	*35 This guideline is not intended for products used during clinical research stages of development.* *36 However, in cases of high risk to the patient, principles of this guideline may be applicable to* *37 support clinical studies.* The draft excludes clinical-stage products; however, in some cases, high-risk scenarios may warrant their inclusion.	Please clarify exactly when clinical-stage products are included or excluded. Under what specific product types or risk conditions does the guideline expect an extractables and leachables (E&L) study to be conducted during early clinical phases?
EfPIA	35	35	2	Why are clinical phases out of scope of this ICHQ3E? At least, clinical phase 3 would have to be part of this scope as per regulatory expectations and potential safety risk associated to these studies (could be thousand of people involved in the clinical study phase 3)	Include that the principles of ICH Q3E may be at least applied prospectively to materials and components used in late-stage clinical development (e.g., Phase III or PPQ) when these are expected to be part of the commercial process for example.
EfPIA	35	37	2. Scope	Regarding "This guideline is not intended for products used during clinical research stages of development. However, in cases of high risk to the patient, principles of this guideline may be applicable to support clinical studies", could you please clarify the case of high risk?	Could you please add the example into the sentense as shown below? "This guideline is not intended for products used during clinical research stages of development. However, in cases of high risk to the patient (e.g.XXXXXX), principles of this guideline may be applicable to support clinical studies."
EfPIA	35	35	2	The wording " clinical research stage of development" is not common, we propose to use the term "early clinical stage" with refrence to clinical phases I and II.	This guideline is not intended for products used during early clinical development , such as Phase I and Phase II clinical trials~~ clinical research stages of development~~.
EfPIA	35	37	2	The current guideline's scope appears primarily focused on commercial drug products, yet the phrase "in cases of high risk to patient" creates ambiguity. If an extractables and leachables (E&L) issue is designated as 'high risk,' it logically implies the necessity of full quality requirements, including those for clinical applications. Therefore, clarification of the guideline's intended use during clinical research stages is required to prevent the premature application of commercial-stage requirements.	
EFPIA	35	36	2 Scope	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A definiton of "high risk to patient" would be helpful	clarification recommended
ELSIE	35	39	2.	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definiton of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/
EUCOPE	35	35	2.	Although the guideline indicates that products in clinical development are out of scope, could its principles be applied to evaluate the safety of E&L in formulations during clinical development using a less than lifetime exposure approach	
IPAC-RS	35	39	2.	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definiton of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Merck KGaA, Darmstadt, Germany	35	35	2	More clarity should be provided for "products used during clinical research stages of development". - It is not clear which stages of drug development are in scope - "Clinical research stages of development" implicates Phase I and II - There should be guidance on expectations to ensure the intended use of polymeric materials in clinical phases, e.g. "prior knowledge"	"This guideline is not intended for products used during the clinical development stages of Phase I and II, where prior knowledge (see section 4.1) is deemed sufficient to support the intended use."
BioPhorum	36	37	3.1.	Sentence is somewhat unclear on requirements for products in clinical trials. unclear why late clinical materials have been excluded. Clarity on what is considered high risk- what are the limits (pre PPQ/after PPQ)	need more guidance on high risk applications and clinical studies
EfPIA	36	39	2	The exclusions are conditional without adding any clarification. What would define "high risk to patient" or "specific cause for concern"?	Suggest removing the these conditional phrases from the document scope.
EfPIA	36	36	2	How can you determine if the material poses a high risk to the patient when these guidelines do not apply to the clinical phase and no E&L risk assessment has been done?	
EfPIA	36	37	2	Need to better define what is considered 'high risk to patient'.	Consider referencing Figure 2 and/or providing an example defining 'high risk'. E.g., advanced cancer, life treatening, etc
EfPIA	36	37	2	Harmonization of the wording with line 35	However, in cases of high risk to the patient, principles of this guideline may be applicable to early clinical development ~~support clinical studies~~.
EFPIA	36	37	2	The guidance states the following: "This guideline is not intended for products used during clinical research stages of development. However, in cases of high risk to the patient, principles of this guideline may be applicable to support clinical studies." However, the guideline does not state or clarify whether it can be applied for products in Phase 3 studies. Additionally, further definition of "high risk to patient" would be helpful to clarify, e.g., type of application, treatment, indications, etc.	We recommend the guideline clarify or explicitly state whether it can apply to products in Phase 3 studies, as this is not currently clear. Additionally, we recommend the guideline provide additional definition of "high risk to patient", e.g., type of application, treatment, indications, etc. to clarify how the guideline should be applied.
Merck KGaA, Darmstadt, Germany	36	37	2	Minor edits to clarify the guidelines support of potential leachables assessment instead of support of clinical studies. More clarity on "high risk cases" would be needed. Examples of "high risk cases" during clinical development phases would help.	"However, in cases of high risk to the patient, principles of this guideline may be applicable to support potential leachables evaluation during clinical studies. [Please add examples of high risk cases]"
Maven E&L Ltd	38	39	Section 2	Why are radiopharmaceuticals not included in scope? As with clinical phase scope. How would it be determined when specific cause for concern? In other ICH guidance there is more justification including; The justification is their unique characteristics — very short shelf-lives, single or limited-dose use, and impurity concerns (radiochemical/radionuclidic) that differ from conventional drugs. It would seem that may not be reason to differentiate them from leachable controls as these concerns also exist in other doses forms which would be in scope	
AstraZeneca	38	39	Section 2	Why are radiopharmaceuticals not included in scope? As with clinical phase scope. How would it be determined when specific cause for concern? In other ICH guidance there is more justification including; The justification is their unique characteristics — very short shelf-lives, single or limited-dose use, and impurity concerns (radiochemical/radionuclidic) that differ from conventional drugs. It would seem that may not be reason to differentiate them from leachable controls as these concerns also exist in other doses forms which would be in scope	
AstraZeneca	38	39	Section 2	Consistent with other Q3 guidance, radiopharmaceuticals are out of scope, but here this is caviated with the phrase unless there is cause for concern. This is a very open ended term without any context or example	Remove the phrase cause for concern
BioPhorum	38	39	2	Generally, radiopharmaceuticals are not considered in scope, unless there is a specific cause for concern. The examples of specific cause for concern worth to mention to have the same / good understanding when guideline should be implemented	need clarity on radiopharma. Justification for them in scope

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	38	39	2	The sentence "*Generally* , radiopharmaceuticals *are not considered* in scope, *unless* ..." is unclear and too vague. It is difficult to understand when it is in scope or not. It would be better to maybe delete "Generally" and/or add examples of "specific cause of concern" or follow a similar wording as for products in development	This guideline is not intended for radiopharmaceuticals. However, in cases of specific risk to the patient, principles of this guideline may be applicable to support radiopharmaceuticals
EfPIA	38	38	2	Clarity on radiopharmaceuticals - if they are out of scope this means there is no expectation of an E&L assessment? What about in-use? Or what would be the requirements for a cold precursor product (with a long shelf life)?	Clarify what is in/out of scope
EIGA	38	39	2 Scope	EIGA (European Industrial Gases Association, www.eiga.eu), on behalf of the medicinal gas industry, submits this position in response to the public consultation on the draft ICH Q3E Guideline. We support the guideline's risk-based principles. However, a rigorous application of these same principles demonstrates that the scientific and mechanistic basis for E&L, as defined by the guideline, is not applicable to medicinal gases (e.g., medicinal oxygen, nitrous oxide, carbon dioxide, nitrogen) or their container closure systems (CCS). The rationale for this position is based on the unique physical state of gases, the inert nature of their high-pressure metallic CCS, and the fact that existing guidelines (notably ICH Q3D) already address the only relevant potential risks. We therefore formally request the explicit exclusion of medicinal gases from the scope of the final ICH Q3E guideline. 2. Risk-Based Justification Our justification aligns with the guideline's focus on risk, materials, and patient exposure. 2.1. Scope and Nature of Medicinal Gas Products The draft guideline appears to target new drug products or those with complex formulations. Medicinal gases do not fit this profile. Well-Established Status: All currently approved medicinal gases are well-established products with decades of safe use, supported by extensive pharmacopoeial monographs. Simple Formulation & Physical State: Medicinal gases are inorganic simple molecules or combinations of. Critically, they are delivered without liquid excipients or solvent mediums. The absence of a liquid phase eliminates the	Generally, radiopharmaceuticals and medicinal gases are not considered in scope, unless there is a specific cause for concern

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EIGA	38	39	2 Scope	[Continued from above] 2.2. Inapplicability of E&L Framework to CCS Materials The ICH Q3E guideline's primary focus is on organic leachables (e.g., plasticizers, additives, oligomers) migrating from polymeric and elastomeric components. The CCS for medicinal gases is fundamentally different. Dominance of Metallic Materials: The CCS for medicinal gases consists of high-pressure cylinders or cryogenic vessels (high-strength steel or aluminum alloys) and valves (brass or stainless steel) which are in direct contact with the medicinal gas. These are inert metallic materials, not the complex organic polymers ICH Q3E targets. Existing Controls for Metallics: The only potential leachables from these dominant metallic materials are elemental leachables. These are already comprehensively addressed and controlled by the ICH Q3D guideline and associated risk assessments. See also EIGA Doc 216 (www.eiga.eu), demonstrating that the stablished manufacturing and supplied systems are in control and ensure that the levels of potential elemental impurities in all medicinal gases are maintained well below their 30% limit of the respective permitted daily exposure. Minority Components: The only non-metallic materials (e.g., gaskets, O-rings) are used for sealing. Their contact surface area is negligible, and they are in contact with a non-solvent (the gas), under conditions (see 2.3) that do not promote extraction.	Generally, radiopharmaceuticals and medicinal gases are not considered in scope, unless there is a specific cause for concern
EIGA	38	39	2 Scope	[Continued from above] 2.3. Absence of Leaching Mechanisms and Stability to Change The guideline's concern for changes affecting the leachable profile is not scientifically relevant to medicinal gas systems. Absence of Mechanism: As stated in 2.1, the lack of a liquid solvent phase prevents the extraction mechanism. Stability to Change: The potential for changes (manufacturing, CCS) to impact a leachable profile is severely restricted: Manufacturing: The extreme temperatures and pressures used in gas manufacturing, combined with the intrinsic properties of the gases, severely restrict the palette of compatible materials. CCS: The materials for high-pressure cylinders have been in use for decades. Fundamental changes are rare and subject to extensive performance and compatibility testing under global standards (e.g., ISO). Exposure: The dosing and administration of these well-established gases are fixed, limiting any change in patient exposure. 3. Conclusion and Formal Recommendation Based on the established nature of medicinal gases, their simple, solvent-free formulation, the dominance of metallic contact materials controlled under ICH Q3D, and the fundamental absence of the physical mechanisms for organic extraction and leaching, the ICH Q3E guideline is not applicable to medicinal gases. To prevent future regulatory ambiguity and misapplication of the guideline, we formally and respectfully recommend that the final ICH Q3E guideline include a specific clause for medicinal gases, similar to radiopharmaceuticals, explicitly stating, " Generally, medicinal gases are not considered in scope unless there is a specific cause for concern”	Generally, radiopharmaceuticals and medicinal gases are not considered in scope, unless there is a specific cause for concern

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	38	39	2	We are curious as to why radiopharmaceuticals are considered out of scope of this document. Wouldn't such drugs be no different from any other drug as far as patient leachable risk that is within the scope of this document? The only difference is that the mechanism of action relies on the radioactive aspect of the drug; otherwise, the patient leachable risk will be the same for any other non-radioactive drug administered in the same fashion.	If there is not a good reason as to why radiopharmaceuticals should be excluded from the scope of ICH Q3E, then we would recommend removing this statement and considering them in-scope.
Axplora - Novasep	40	42	1	Does the entire guideline apply to liquid and semi-liquid APIs?	
BioPhorum	40	42	2	The guideline does not apply to systems used in the manufacture or storage of excipients. Refer to Section 3.4.1 for special considerations regarding packaging components for liquid or semiliquid active pharmaceutical ingredients (APIs).	The guideline does not apply to systems used in the manufacturing or storage of excipients. The guideline also applies to packaging components for liquid or semiliquid active pharmaceutical ingredients (API), refer to Section 3.4.1
EfPIA	40	40	2	The guideline states that it "does not apply to systems in the manufacture or storage of excipients", however it does not refine the scope of other situations, such as diluents in vials or pre-filled syringes (to be used for dilution or reconstitution of concentrated or lyophilized drug products). This needs to be clarified.	Please consider clarifying with examples which components are considered out of scope.
EfPIA	40	40	2. Scope	The guideline excludes excipient manufacture and storage. Wouldn't similar considerations be applicable as extractables and leachables arising from excipient components impact the drug product? The onus would not necessarily be on the excipient manufacturer to perform E&L assessments but the DP manufacturer should factor in the contribution from excipients.	Please provide clarification on why excipients are excluded.
Sartorius-Stedim Biotech GmbH	40	40	Scope	Why does it not apply to "storage of excipients"? Please consider the last steps of a mAb production: in UF/DF, the production buffer is exchanged with a patient compatible buffer system containing also excipients. In UF/DF most PERLs from production are removed, but the PERLs in the exchange buffer/excipient preparation remain in the product. So obviuosly the excipients and other application buffer preparation steps are relevant.	
EFPIA	43	260	3.2 Risk assessment	Add a subsection within Section 3 (Risk Assessment) or Section 4 (Chemical Testing) discussing how the specific function of the device component (e.g., mechanical stress during injection, heat generation, specific flow paths) might influence the E&L profile differently than passive container closure systems.	Rationale: Device functions can create unique physical or chemical stresses not typical for standard packaging, potentially altering leachable profiles.
Bio-Process Systems Alliance	44	61	3.1	Scope-The draft guideline does not clearly delineate the boundary between extractables derived from materials of construction directly contacting the drug product and those introduced via upstream manufacturing equipment.	Clarify whether materials used in manufacturing systems (e.g., single-use bioprocess components) fall within Q3E scope when they contact drug substances or intermediates intended for further processing. A consistent demarcation would aid both manufacturers and regulators.
AESGP	45	45	3.1	Sentence limited to leachables but extractables as potential leachables should be included	"… wherby (potential) leachables-associated…"
EfPIA	45	47	3	This sentence reads like it is adding to the scope previously discussed.	Should this sentence be included in Section 2 and removed here, or is there an alternaitve wording that does not seem like it is adding to the scope already discussed.
AstraZeneca	46	46	Section 3.1	Introduce "efficacy" as a leachables risk to be identified, assessed, and controlled but no guidance is given on how to do this	Add details on how to evaluate leachables impact on efficacy or refer reader to existing ICH guideline
AstraZeneca	48	48	Section 3.1	Missing "risk" in reference to continuous quality "risk" management	Add "risk"
ELSIE	50	54	Figure 1	It would be nice to have a definition of "hazard".	Include Hazard in the Glossary or add a redirect in the text to Section 3.3/ln 106 where it is explained.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	51	51	Figure 1	Risk Control Measures to effectively control risk of potential leachables in materials, process, finished DP	Risk Control Measures to effectively control risk of potential leachables in materials, process, finished Drug Product. (The abbreviation DP in line 51 was not introduced until line 84 and hence, is unclear for the reader). Or could consider including in definitions/glossary
AstraZeneca	52	52	Figure 1	Figure 1 title is referred to as the "typical" risk management process in ICH Q9. Q3E implies this is THE process.	Align title with ICH Q9 language
BioPhorum	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment". Overall: requires improvements in the sequence of risk assessment steps, need clarification of the role of quality risk management versus patient safety.	Propose to adapt Figure 1 accordingly remove "quality" and advise using most appropriate risk management
EfPIA	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment".	Propose to adapt Figure 1 accordingly
EfPIA	52	52	3.1	Add "quality" before Risk management Process in title Fig 1	qualifty risk management is what is described in the figure and in the paragraph below
EfPIA	52	53	Figure 1	A risk asseement decision tree is proposed : Hazard Identification > Risk Analysis > Integrated Risk Evalution. What constitutes adequate data, and how should uncertainty be addressed?	Add more specificity regarding the minimal data requirements necessary to consider the dataset adequate.
EfPIA	52	54	Figure 1	Chemical characterization which is applied in ISO 10993 standard series is used in the figure	Medical devices are not in the scope, so this is missleading unless ICH Q3E is not proposing this term to be general. It refers to wider content than only E&L.
EfPIA	52	53	4.3	There are several Figure 1s	Update figure numbers
ELSIE	52	54	Figure 1	Chemical characterization which is applied in ISO 10993 standard series is used in the figure	Medical devices are not in the scope, so this is missleading unless ICH Q3E is not proposing this term to be general. It refers to wider content than only E&L.
ELSIE	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment".	Propose to adapt Figure 1 accordingly
IPAC-RS	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment".	Propose to adapt Figure 1 accordingly

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Maven E&L Ltd	53	54	Section 3.1	Figure 1: It is unclear how 1. Chemical characterisation 2. Safety risk 3. Quality risk are linked to the risk assessment process and why they are considered separate items or indeed if they are process steps. I would suggest safety risk is an output from the risk assessment, as is quality risk. However, chemical characterisation is a process within those The assumption being that chemical characterisation might inform both a safety risk or a quality risk. This also relates to Figure 2, where quality considerations and safety considerations appear to be listed (See comment below). The terms defined (Hazard Identification), Risk Analysis, Risk Evaluation do not appear to follow the definition within ICH Q9 and are not correctly defined elsewhere (See Comment Line 106-117, Section 3.3. The suggestion is that is need to be done.	
Maven E&L Ltd	53	54	Section 3.1	Figure 1: Under Risk Control, Risk Reduction is placed prior to Risk Acceptance. This would indicate that Risk Acceptance cannot proceed before Risk Reduction. This makes an assumption that risk assessment will conclude all risk need risk reduction. This seems a fundamental error in a risk based approach. Some risk might will be marked as acceptable under Risk Assessment and thus could proceed directly to Risk Acceptance or indeed some risk might be impossible to reduce and would proceed to risk acceptance to be risk controlled closely via for example discrete specification on leachables. I would suggest then than Figure 1 is redrafted to correct the arrow and place risk acceptance and risk reduction as a parallel sub-process within risk control. I appreciate this would mark this different from ICH Q9 graphic but would align in to the corresponding ISO standard on which ICH Q9 is based. risk acceptance being defined as being an informed decision to take a particular risk, and risk acceptance can occur without risk treatment, or during the process of risk treatment. Accepted risk being subject to monitoring Source ISO guide 73:2009 Risk management -vocabulary, Section 3.7.1.6 and ISO 31000:2009: Risk management - principles and guidelines	
AstraZeneca	53	54	Section 3.1	Figure 1: It is unclear how 1. Chemical characterisation 2. Safety risk 3. Quality risk are linked to the risk assessment process and why they are considered separate items or indeed if they are process steps. I would suggest safety risk is an output from the risk assessment, as is quality risk. However, chemical characterisation is a process within those The assumption being that chemical characterisation might inform both a safety risk or a quality risk. This also relates to Figure 2, where quality considerations and safety considerations appear to be listed (See comment below). The terms defined (Hazard Identification), Risk Analysis, Risk Evaluation do not appear to follow the definition within ICH Q9 and are not correctly defined elsewhere (See Comment Line 106-117, Section 3.3. The suggestion is that is need to be done.	
AstraZeneca	53	54	Section 3.1	Figure 1: Under Risk Control, Risk Reduction is placed prior to Risk Acceptance. This would indicate that Risk Acceptance cannot proceed before Risk Reduction. This makes an assumption that risk assessment will conclude all risk need risk reduction. This seems a fundamental error in a risk based approach. Some risk might will be marked as acceptable under Risk Assessment and thus could proceed directly to Risk Acceptance or indeed some risk might be impossible to reduce and would proceed to risk acceptance to be risk controlled closely via for example discrete specification on leachables. I would suggest then than Figure 1 is redrafted to correct the arrow and place risk acceptance and risk reduction as a parallel sub-process within risk control. I appreciate this would mark this different from ICH Q9 graphic but would align in to the corresponding ISO standard on which ICH Q9 is based. risk acceptance being defined as being an informed decision to take a particular risk, and risk acceptance can occur without risk treatment, or during the process of risk treatment. Accepted risk being subject to monitoring Source ISO guide 73:2009 Risk management -vocabulary, Section 3.7.1.6 and ISO 31000:2009: Risk management - principles and guidelines	
EfPIA	53	54	3.1	DP not defined in Figure 1	Include defintion /glossary cross-reference
EfPIA	53	54	3.1	It is unclear what is the "quality risk" mentioned in Figure 1. Risk assessment includes the chemical characterization followed by the safety risk (or TRA) but it is unclear what the "quality risk" is and how is performed/documented.	Remove "quality" from "quality risk"
EfPIA	53	54	3.1	In the hazard identification step, it is mentioned "Identify E&L of concern" but during this step, one cannot identifiy both E&L. At best, extractables and/or potential leachbales but not extractables AND leachables	extractables and/or leachables
EfPIA	53	54	3.1	Remove stop sign after regulators	
EfPIA	53	54	3	Before E&L identification, shouldn't there be an assessment of the severity of the risk from each material? Not all materials require thorough E&L studies	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	53	54	3.1	Structure of "Integrated Risk Evaluation" box doesn't align with other boxes in the figure.	Remove "of" so heading of box doesn't merge with clarifiers below as in the other boxes. Oxford comma
EfPIA	53	61	3	A risk assessment is performed to address Lecheable Risks. In this chapter, including the figure and throughout the test, the term "Leachable Risk Assessment" is the overall goal. Extractables and other aspects do inform the risk but the risk to the patient is based on the leachable profile.	Update the document to reflect leachable risk assessment (not E&L Risk Assessment)
ELSIE	53	54	3.1	Will there be a more detailed explanation of the risk assessment process shown in Figure 1? There appears to be no appendix with such information, and it is not really well-explained in the text. Looking at this flow chart, its hard to understand what each step requires or pertains to. One could make guesses and assumptions, but since this is a critical aspect of this document, it should be definitively explained somewhere.	Add a more detailed explanation of the inputs and outputs of each step of the flow chart in an appendix or as appropriate.
ELSIE	53	54	3.1	A material risk assessment is missing in Figure 1; the risk management process starts right away with chemical characterization.	Include material risk assessment in Figure 1 and perform chemical characterization only for high risk materials
ELSIE	53	54	3.1	It is unclear what is the "quality risk" mentioned in Figure 1. Risk assessment includes the chemical characterization followed by the safety risk (or TRA) but it is unclear what the "quality risk" is and how is performed/documented.	Remove "quality" from "quality risk"
ELSIE	53	54	3.1	In the hazard identification step, it is mentioned "Identify E&L of concern" but during this step, one cannot identifiy both E&L. At best, extractables and/or potential leachables but not extractables AND leachables	extractables and/or leachables
EUCOPE	53	54	3.1	The Risk Control in Figure 1 indicates that the risk of potential leachables in materials, process and finished DP should be controlled. Does it mean that leachables analysis should always be done?	Indicate if this risk control should always be done or if it's a step necessary only in certains circumtances; if this is the case, privinding examples may be useful.
Octapharma	53	54	3.1	A material risk assessment is missing in Figure 1; the risk management process starts right away with chemical characterization.	Include material risk assessment in Figure 1 and perform chemical characterization only for high risk materials
EfPIA	55	55	3	Give some examples of prior knowledge and reference further discussion on prior knowledge later in Sect. X	Examples provided in training materials
AstraZeneca	58	58	Section 3.1	Close collaboration with suppliers should also be noted. Supplier engagement can be pivitol in design, executing and summarizing E&L studies. Interaction w/ suppliers as part of knowledge sharing is stressed in other key E&L recommendations.	Highlight engagemnt with suppliers as a critical element to knowledgeshare and understanding. Maybe best addressed Sec. 4.1/4.2
Ferring Pharmaceuticals	58	60	3	Analytical chemists and safety experts are specified, but 'manufacturing', 'primary packaing' and 'device' specialists are also involved as they know the manufacturing processes and the items used and how primary pack/device items are constructed and pre-treated.	Propose to rephrase to take this info into account by e.g. referring to subject matter expert as a general instead.
EfPIA	60	61	3.1.	Sentence is somewhat unclear on requirements for products in clinical trainls	Propose to add " for approved products"
EfPIA	60	60	3.1	Every product or just new products and legacy products that undergo change control? Clarification required as it changes considerably the scope of the guideline and contradicts section 2.	
EfPIA	60	61	3.1	According to Figure 1, the Quality Risk Management process includes two main steps (Risk Assessment >> Risk Control) and the Risk Management process (overarching process) includes the Quality Risk Management process combined with the Lifecycle Management. In this context, the sentence "A Quality Risk Management Process should be initiated with every product, each with its own Risk Assessment, Risk Control and Lifecycle Management process" is confusing or not aligned with Figure 1. Is it not the Risk Management process which should be initiated with every product ? Additional comment: what is meant in this sentence with "product"? Drug product or material?	Proposed wording/change: "A Risk Management Process should be initiated for every (drug) product covering Quality Risk Management (with own Risk Assessment and Risk Control) and Lifecycle Management process"
EfPIA	60	61	3.1	When stating that a "Quality Risk Management Process should be initiated with every product…", it implies that a full QRM process should be conducted on all products, even in the case of different strengths or different packaging configurations for the same product. Data or assessment from similar products should be be acceptable as part of a new QRM process.	Please consider clarifying the acceptability of using a bracketing/matrixing QRM approach for similar products e.g. multiple strengths.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	60	61	3.1.	"A Quality risk Management process should be initiadted with every product….., ….each with its onw Risk assessment-> Comment: this seems plausible, but this does not necessarily mean additional analytical evaluation for "each product" in the case comparabiltiy to similar product is available and risk management would justify comparable risk.	
ELSIE	60	60	3.1	"A Quality Risk Management Process should be initiated with every product...." Every product or just new products and legacy products that undergo change control? Clarification required as it changes considerably the scope of the guideline and contradicts section 2. Note that the Scope states "new drug products" are in scope, not "every product."	Clarify that "new drug products" is meant here.
ELSIE	60	61	3.1	Please clarify Quality Risk Management Process: are you expecting a new document? Or can companies rely on their existing procedures?	Clarification of expectation of a Quality Risk Management Process
ELSIE	60	61	3.1.	Sentence is somewhat unclear on requirements for products in clinical trainls	Propose to add " for approved products"
ELSIE	60	61	3.1	Individual products may share the same risk factor (only vary by final volume or weight) or they could be entirely unique. There should be flexibility in the language for similar products (more closely related than discusison of abreviated packages (Ln 166-174).	
ELSIE	60	61	3.1	A Quality Risk Management Process should be initiated with every product, each with its own Risk Assessment, Risk Control and Lifecycle Management process.	Does this mean that grouping of similar products is not possible?
EUCOPE	60	61		EUCOPE suggests a possibility to use also the worst case approach in creating the Quality Risk Management Process, when applicable. For example in a case where several strengths of a drug product exist with same manufacturing process and primary packaging material it is not reasonable to perform leachables studies for all strengths, but rather only with the strength considered as the worst case strength for the drug product.	
IPAC-RS	60	61	3.1.	Sentence is somewhat unclear on requirements for products in clinical trainls	Propose to add " for approved products"
Lotus pharmaceutical company	60	61		ICH Q3E guidelines state that all products must undergo E&L (Extractables and Leachables) risk assessment, control, and lifecycle maintenance. For oral dosage forms with low E&L risk, is it expected to submit an E&L risk assessment report at the registration stage?	
Octapharma	60	61	3.1	Please clarify Quality Risk Management Process: are you expecting a new document? Or can companies rely on their existing procedures?	Clarification of expectation of a Quality Risk Management Process
BioPhorum	62	100	3.2	Scope for Materials Upstream of final clearance step: Whereas the guideline mentions (#52) Risk Management, (#55) holistic strategies, risk drivers (#66, #68, #70 ... includes clearance steps, #73, #83/Figure 2) , the emphasis of the guideline is primarily on rigorous testing strategies around final containers. By mentioning lower risk applications, the reader feels this guideline covers their scope, but in reality little to no guidance is provided for what level of testing may be suitable for these applications. Hence, the guideline drives high level, fully quantitative data or leachables expectations for many bioprocess materials far upstream of the final container and away from the patient.	Suggest to focus scope of Q3E on container closure, or materials downstream of the final bioprocess clearance step. Alternatively, it should be clear that lower risk materials may require studies aligned to the appropriate level of risk, but that the specific recommendations are out of scope at least the present version of Q3E. Clarify section title - should it read risk assessment to align with line 63. reconsider use of "matrix" throughout
EfPIA	62	81	3.2	Being sterilization, namely by autoclave, a huge driver for leachables migration, the document should include more details on the potential impact of different sterilization techniques on leachables profile.	Consider adding a section regarding sterilization impact
EfPIA	62	81	3.2	Complex language/phrasing. The use of the word "dimensions" is unecessary. The section will be difficult to interpret by a non-native English speaker. Significantly simplify.	Delete whole first sentence and replace with "Quality and safety aspects are considered in the risk assessment of leachables. The following factors are applicable:", and proceed with the bulleted list.
EfPIA	62	100	3.2	Could you please explain the methodology used to assess the risk level as low, moderate, or high?	
EFPIA	62	100	3.2 Risk Matrix	Enhance Section 3.2 (Risk Matrix) to specifically highlight the drug-device interface as a critical area where unique interactions (e.g., adsorption, degradation, new adduct formation) might occur and affect the leachable profile.	Rationale: The interface is often a unique chemical and physical environment in DDCPs compared to standard drug product containers.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	62	81	3.2	The age of the materiel is not considered as an important dimension. It may be (see section 4.6 E&L correlation); this is especially valid for gamma radiated components due to the long lasting effect and impact on depolymerization.	Add a section to encourage companies to take in consideration the age of the material in the risk assessment/studies design.
Laboratoires Théa	62	100	3.2	Can you please add in annex an example of risk assessment for packaging material?	
Laboratoires Théa	62	78	3.2	For manufacturing components, can you confirm that the risk assessment can be based on UPS <665> and USP <1665>?	
Maven E&L Ltd	63	78	Section 3.2	The definition of Quality risk and Safety risk has been separated but in the descriptions of Quality risk given it would also include a safety component in that patients receiving the drug product are affected based on the nature of the risk. There is no clear definition of why quality risk is presented separately from safety risk and how this might be reflected in any scoring during risk analysis. I suggest here would be to provide further example (perhaps a Appendix) where risk assessment process (Hazard identification, Risk Analysis and Risk Evaluation) is illustrated. This also influences figure 2 as it is unclear why "Quality Considerations" are not also contributing factors to the assessment of leachable safety risk . It is suggested that this passage might be re-written to more clearly recognise that leachable risk must be defined from a clear detailing of the cause and effect of the risk event so that identified risk can be analysed and evaluated. A suggestion that that takes the form, "Because of (cause)...there is a risk that (risk event)...leachable are...(the effect)	
AstraZeneca	63	78	Section 3.2	The definition of Quality risk and Safety risk has been separated but in the descriptions of Quality risk given it would also include a safety component in that patients receiving the drug product are affected based on the nature of the risk. There is no clear definition of why quality risk is presented separately from safety risk and how this might be reflected in any scoring during risk analysis. I suggest here would be to provide further example (perhaps a Appendix) where risk assessment process (Hazard identification, Risk Analysis and Risk Evaluation) is illustrated. This also influences figure 2 as it is unclear why "Quality Considerations" are not also contributing factors to the assessment of leachable safety risk . It is suggested that this passage might be re-written to more clearly recognise that leachable risk must be defined from a clear detailing of the cause and effect of the risk event so that identified risk can be analysed and evaluated. A suggestion that that takes the form, "Because of (cause)...there is a risk that (risk event)...leachable are...(the effect)	
EfPIA	63	63	3.2	Simplification required in "overall risk assessment" - superfluous.	Remove "For the overall risk assessment and control of leachables" and start the sentence at " it is important"
ELSIE	63	63	3.2	Simplification required in "overall risk assessment" - superfluous.	Remove "For the overall risk assessment and control of leachables" and start the sentence at " it is important"
EfPIA	64	64	3.2	The bullets following this paragraph are not pharmaceutical quality attributes (i.e, attributes that impact specifications, ergo quality). They are pharmaceutical - or better yet, formulation - aspects	Change sentence to ". . ., entailing both pharmaceutical and safety aspects."
AESGP	66	81	3.2 Risk Matrix	Consideration of manufacture process risks alone as a contributor to E and L should also be risk based. For - simple oral dose forms especially in the solid state, topical cream products for skin application and nasal preparations, which are made by or simple manufacture processes that do not include polymeric materials (e.g. all equipment of stainless steel construction) and where equipment product contact is of short duration should also be regarded as minimal risk. This text should also be consistent with Table A.1.1	Between line 74 and 75 add, "For simple oral dose forms especially in the solid state, topical cream products for skin application and nasal preparations, made by simple manufacture processes that do not include polymeric materials and where equipment product contact is of short duration should also be regarded as minimal risk."
AstraZeneca	66	74	Section 3.2	Bullet point 1 seems to address compatibility risk. Risk of leachables from formulation interactions is addressed in bullet points 3 and 4.	Delete bullet point 1 or rephrase.
Chiesi Farmaceutici	66	67	3.2	In the first point delivery devices/device constituent parts are not directly mentioned but it is important to specify them among items/materials that could go in direct contact with fomulation and so interact with it, as reported in other relevant parts of the guideline (as for example Figure 2).	It is suggested to modify the first point as follows: "The potential for interaction between manufacturing equipment or packaging/*delivery device* components and the formulation"
ELSIE	66	67	3.2	"The potential for interaction between manufacturing equipment or packaging component and the formulation" • Coatings, such as PTFE have the capability to inhibit leaching and therefore not all surfaces of components are equivalent	• We recommend including 'coatings' as they may be impactful in inhibiting potential interactions; "The potential for interaction between manufacturing equipment or packaging component and the formulation, with considerations to addition of coatings to surfaces, which may inhibit the leaching process"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	66	73	3.2	Line 68: Pretreatment prior to use; Would be interesting to provide further details on pretreatment for the risk assessment exercise and support risk ratings	Provide further details on pretreatments: washing/rinsing, sterilization, type of sterilization (steam or gamma).
GUERBET	66	67	3.2	How should be presented the difference of criticality between the different material in contact with the drug product, i.e. tubing less critical than filters ? Is it acceptable to have no study for the less critical ones (tubing, gaskets…) ?	Explain more in detail the way the different materials in contact with the drug product should be managed.
Sanjay Desai (Cipla Ltd.)	66	67	3.2	For the overall risk assessment and control of leachables, it is important to consider the risk of leachables contributed from delivery device in addition to manufacturing equipments and packaging components to ensure pharmaceutical quality and safety.	The potential for interaction between manufacturing equipment, packaging component or delivery device and the formulation
Bio-Process Systems Alliance	70	72	3.2	Important dimensions of risk are introduced here, which suggests that scaling of extractables data and / or estimation of downstream removal steps is an appropriate approach, yet no guidance is offered anywhere else in the Guidance on how to perform this.	Suggest to limit scope to final drug product primary packaging container and/or device only or revise Guidance to include guidance on scaling via surface area or equilibrium and guidance on the estimation of leachables removal capacity of downstream steps.
ELSIE	70	72	3.2	Surface to volume ratio is taken into account, which we welcome but stands in contrast to USP 665. We encourage this step, however USP (and FDA) should take into consideration to also harmonize USP 665 accordingly.	USP (and FDA) should to take into considereation to also harmonise USP 665 accordingly
Sanjay Desai (Cipla Ltd.)	70	70	3.2	For the overall risk assessment and control of leachables, it is important to consider the risk of leachables contributed from delivery device in addition to manufacturing equipments and packaging components to ensure pharmaceutical quality and safety.	The manufacturing, storage and usage conditions,
Sartorius-Stedim Biotech GmbH	72	72	3.2	This formulation is too vage - downstream processing can remove almost all PERLs.	see graphic above
ALK (GFLUS)	73	74	3.2	Should this section include either specifics regarding allergenic products (same extraction sovents but different allergen species) or provide justification for matrixing different product species that utilize the same solvent matrix?	N/A
ELSIE	73	74	3.2	"The leaching propensity of the formulation, including but not limited to API, pH, organic co-solvents and surfactant/chelating agents" • Viscosity and molecular weight of the solvent (drug product) directly impact diffusion based on the Stoke-Einstein equation. Lower molecular weight solvents (e.g., ethanol) diffuse more rapidly and can penetrate polymer matrices more easily. Higher molecular weight solvents (e.g., PEGs) diffuse more slowly, reducing their ability to extract leachables.	• We recommend including "viscosity and molecular weight" of the vehicle to the list of factors impacting leaching propensity: "The leaching propensity of the formulation, including but not limited to API, pH, viscosity, molecular weight, organic co-solvents and surfactant/chelating agents"
Ferring Pharmaceuticals	73	74	4	The fourth bullet says …API, pH,organic co-solvent…" and it is not clear what property of API is meant here. Is it organic nature?	Propose to rephrase with specific properties
Rentschler Biopharma SE	73	74	3.2	The prediction of the leaching propensity of the API (especially for monoclonal antibodies) requires a comprehensive understanding of physical and chemical properties of the molecule itself, the drug product formulation, the identity of the contacting material and contact conditions such as pH, temperature etc, and will have to be based on experimental studies.	Could you please provide examples here, especially for biomolecules? Can a procedure as in USP<1665> be applied (risk level depending on protein content)?
AESGP	75	78	3.2 Risk Matrix	Add a reference to the physical form of the product	Physical form of product (liquid, semi-solid etc)
AESGP	75	78	3.2	Quality risk provided as explanatory list of bullet points but safety dimensions as plain text.	For readability purposes, an alignment of formatting for these dimensions might be helpful
EfPIA	75	78	3.2	Complex language/phrasing. The use of the word "dimensions" is unecessary. The section will be difficult to interpret by a non-native English speaker. Significantly simplify.	Reword to state that "The following exposure related factors impact the safety assessment of leachables:" and proceed with the current list.
EfPIA	76	77	3.2	What is meant by "pertininet patient populations"? These assessments are all dose based and inherently relevant to the "pertninent patients".	Omit the "pertininet patient populations" from the list.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	77	78	Sectiion 3.2	aling terminiolgy "maximal dosing" and "maximum potential treatment duration in a lifetime with tha of ICH M7	Seek consistency with udnerlying guidelines. ICH M7 refers to max daily dosing and duration of exposure
EfPIA	77	77	2	Any changes in formulation, manufacturing, dosing, container closure system, is the scope of "any changes" too wide?	Reword it to make the scope not too wide
EfPIA	79	81	3.2	Complex language/phrasing. The use of the word "dimensions" is unecessary. The section will be difficult to interpret by a non-native English speaker. Significantly simplify.	Simply state that "Figure 2 provides an overview of the risk factors to consider in a leachable risk assessment"
Ferring Pharmaceuticals	80	80	3.2	"...all those..." is contradictonary to the previous line (79) which specify "...(not all inclusive)..."	Propose rephrasing
EfPIA	82	156	3.4	Concistency in wording across guideline Comment: Several phrases covering the same? manufacturing equipment versus manufacturing components/systems versus manufacturing materials Rationale: the use of several phrases for the same can create confusion.	Recommend to choose and use one phrase consistently across the guideline
BioPhorum	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as “small parts”—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.
EfPIA	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as “small parts”—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.
EfPIA	83	85	3.2	Comment: Figure 2 Manufacturing conditions: The conditions mentioned should include dosage form or state during manufacturing, where liquids have a higher risk compared to solid states. Rationale: Liquids have a higher probability of interaction with the surfaces of the manufacturing materials compared to pharmaceutical formulations in solid state. Maybe it should be included in "Leaching propensity of DP formulation"?	Figure 2 Manufacturing conditions: Lower risk Mild: short duration, low pressure/temperature, solid Higher risk High: lipophilic and/or high pressure/temperature, liquid
EFPIA	83	85	3.2. Risk assessment, Figure 2 Overview on Aspects to Consider for Risk Matrix	Consider adding device-specific factors to the Risk Matrix (Figure 2, Section 3.2), such as "Complexity of Delivery Mechanism," "Device Material Type" (beyond typical pharma packaging), or "Duration/Nature of Device-Tissue Contact."	Rationale: Explicitly including device-related risk factors makes the matrix more directly applicable and comprehensive for DDCPs.
ELSIE	83	85	3.2 Figure 2	Not very clear. There seems to be an arrow line missing between DP stored frozen and low quantity of extractables. In addition, low quantity of extractables doesn't mean lower risk. Risk is dependent on the level and toxicological evaluation. Same for high quantity extractables, e.g., extractables can all be below AET and have low risk.	Figure 2 needs updating and clearification

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as "small parts"—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.
EUCOPE	83	85	Figure 2	Manufacturing conditions considerations in the risk assessment should include Process Step (proximity to DS/DP) and Contact Surface Area.	Propose adding Process Step and Contact Surface Area as considerations to the Risk Matrix.
IPAC-RS	83	85	3.2	Figure 2. Not very clear. There seems to be an arrow line missing between DP stored frozen and Low quantity of extractables. In addition, low quantity of extractables doesn't mean lower risk. Risk is dependent on the level and toxicological evaluation. Same for high quantity extractables, i.e., extractables can all be below AET and have low risk.	Figure 2 needs updating and clearification
IPAC-RS	83	83	3.2	Figure title requires adjusting due to typo - suggested amendment in red text	Figure 2: Overview ~~on~~ of Aspects to Consider for Risk Matrix
IPAC-RS	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as "small parts"—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.
AESGP	84	85	Fig. 2	the intraperitoneal route of administration is missing.	to be added. Perhaps for future alignment, similar to performing an FMEA, a scheme with a point system would help to score the different risks
AESGP	84	85	Figure 2	Some scanrios are 'low' risk rather than 'lower'. For example, solid dose forms in plastic packaging the is pharmacopoeal grade is agreed as low risk by EMA and there is no justifiable reason	change 'lower risk' to 'low risk' in the figure.
BioPhorum	84	84	fig 2	Risk table does not provide guidance for items outside final drug product container closure, lower risk items should require less rigorous assessments	Provide clarity on lower risk items
BioPhorum	84	84	fig 2	exposure time is a critical factor in container closure system studies, requiring tailored justifications, whereas for single use devices, standardized methods such as USP 665 are typically used.	update fig 2 to explicitly mention exposure or contact time. Update arrow 3 to "manufacturing and/or contact conditions", ensuring applicability to delivery devices and packaging.
EfPIA	84	84	3.2	Based on the figure2, how do you combine the different level of risk to have a final one that seems raisonnable to the patient? Ex: A product not aggressive could be consider as low risk, but the risk could be more important for intravenal products.	
EfPIA	84	84	3.2	Could you please clarify what you consider to be a short duration for the manufacturing process? For example, does this refer to 24 hours or just a few minutes? Additionally, could you specify the value used to define low pressure? I would also appreciate if you could indicate where the lyophilized product is represented in this figure, as its placement is not entirely clear.	
EfPIA	84	84	3.2	The risk matrix addresses safety risk as a whole. The "safety assessment" refers to toxicological evaluation, while "pharmaceutical quality considerations" reflect different risk factors. The term "pharmaceutical quality considerations" is not synonymous with "risk factors"; a definition of this term may be needed.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	84	86	3	Please provide an explanation of the position “topical dermal” in relation to “oral” in figure 2 under the Toxicological considerations for Route of administration. The safety risk of topical dermal drug delivery depends among other things on the integrity and area of the skin being treated and the local tolerability of the drug product; but generally, topical dermal drug delivery represents a lower risk for systemic toxicity compared to oral drug delivery.	Provide an explanation.
ELSIE	84	85	3.2	Should consideration be included in this figure for the known presence of Class 1 compounds	
ELSIE	84	85	3.2	Low to high risk for treatment duration is presented.	More clarity on the treatment duration classifications would be helpful since options exist that are not presented in the diagram.
ELSIE	84	85	3.2	Low to high risk for leaching propensity of drug product formulation is presented.	Add "low pH" to the diagram under high risk. Leaching propensity at either pH extreme presents a high risk.
IPAC-RS	84	85	3.2	Should consideration be included in this figure for the known presence of Class 1 compounds	
Sanjay Desai (Cipla Ltd.)	84	85	3.2	As per "Modified FDA/CDER/CBER Risk based approach to consideration of leachables" in USP<1664>, the "likelihood of interaction with packaging/delivery device component", the risk is higher in inhalation aerosols and spays than the liquid dosage forms (injections/injectable suspensions/inhalation solutions). An appropriate and harmonised modification is recommended.	An appropriate and harmonised modification is recommended.
EfPIA	85	85	3.2	Exposure time is deemed a relevant factor to be considered in the risk matrix. Suggest to add exposure time to Figure 2, e.g., for a fluid path of a medical device	e.g. for a fluid path of a medical device; short / long contact time
EfPIA	85	85	3.2	Duration of contact is missing from Figure 2.	add Duration of contact to Figure 2
EFPIA	85	85	3.2. Risk Matrix as a Multifactorial Concept	Exposure time is deemed a relevant factor to be considered in the risk matrix.	e.g. for a fluid path of a medical device (top arrow)
ELSIE	85	86	3.2	Figure 2 is not very clear.	A higher quality, possibly color figure is needed.
ELSIE	85	85	3.2	"Figure 2: Overview on Aspects to Consider for Risk Matrix" • 1 PQC: "Likelihood of interaction with packing/delivery device component" • 2 PQC: "Manufacturing or packaging/delivery device material atributes" - one of the parameters 'quantity of extractables'; however, at risk assessment stage number of extractables may not be known. Clarification is needed how this parameter should be estimated or handled before testing results are available. • 4 PQC: " Leaching propensity of drug product formulation" - pH and surfactants are listed under high leaching propensity; however, pH will have greater impact on elemental impurities. Surfactants are not as strong as organic solvents such as ethanol • 4 SAC: "Patient population/Underlying conditions" - clarification is needed on whetheher the thresholds stated in ICH Q3E are protective of all populations.	• We recommend adding viscosity under the 1PQC setting, categorizing low viscosity as high risk and high viscosity as lower risk • We recommend under POC moving "pH and surfactants" to the mid-spectrum of risk, and assigning "organic solvents" to the higher risk category •We recommend replacing "patient population" under 4SAC with "life expectancy" to more accurately describe the associated risk
ELSIE	85	85	3.2	Exposure time is deemed a relevant factor to be considered in the risk matrix. Suggest to add exposure time to Figure 2, e.g., for a fluid path of a medical device	e.g. for a fluid path of a medical device; short / long contact time Additionally, make sure that "medical device" components that are in scope are included in definitions or otherwise clearly defined within the context of the guideline
IPAC-RS	85	85	3.2	Exposure time is deemed a relevant factor to be considered in the risk matrix. Suggest to add exposure time to Figure 2, e.g., for a fluid path of a medical device	e.g. for a fluid path of a medical device; short / long contact time
Medicines for Europe	85	85	3.2	In Figure 2, "Leaching Propensity of the drug product", should low pH also be listed in the high risk category, as we have observed a greater amount of compounds extracted at low pH (e.g. 2) compared to high pH (e.g. 11)	list low pH and high pH, or cite extreme pH

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Qualimetrix SA	85	85	3.2	Within the concept of pharmaceuticals discrimination as per “patient population/ underlying conditions” seems of low consequence – plus it begs the question: “How are the different conditions and patient groups distributed from low risk to high risk? Even more so in a manner that is not wholly open to debate by the regulatory authorities.”	
Qualimetrix SA	85	85	3.2	Where are highly porous/surface lyophilizates placed within the leaching propensity gradient of the table?	
Qualimetrix SA	85	85	3.2	The figure could be refined to place characteristic cases somewhere within the risk gradient – otherwise a lot of choices become open to debate against the respective reviewer.	
Rentschler Biopharma SE	85	85	3.2	Figure 2 describes several risk dimensions to be considered to determine the overall drug product risk. Whilst the upper seven dimensions are easy to understand and practical, it remains unclear in which way the patient population should be considered for the risk matrix. In addition, for the safety assessment there are no individual thresholds stipulated for e.g. neonates, children or elderly. Usually, the dose considers the weight of a patient which is the most practical way forward to assess the safety of a drug product (as it is done e.g. regarding bacterial endotoxins).	Recommend to delete the dimension of patient population from figure 2 risk matrix or please provide clear guidance.
Maven E&L Ltd	86	100	Section 3.2	No where in this text does it clear outline what risk assessment process show in Figure 1 might achieve. That is what are the potential outputs from the process. Figure seems to indicate only the following; communication with the regulators, a review event (during lifecycle management) or another risk assessment (because risk reduction was "unacceptable". I would suggest that Figure 1 and the text in this section can be revised to clearly show that through the process of risk management risks can be identified and then resolved to a point where risk is accepted (controlled) since all identified risks are demonstrated either low initially or low after risk reduction by consideration of a clearly defined set of attributes / requirements	
AstraZeneca	86	86	Section 3.2	It is encouraging to see reference to the potential use of prior knowledge as part of the risk assessment process, however while reference is made to food-contact safety standards and pharmacopoiel standards, no reference is made to existing approved products and their assocaited CCS	Consider adding a reference to the use of information from approved products as a valuable source of prior knowledge
AstraZeneca	86	100	Section 3.2	No where in this text does it clear outline what risk assessment process show in Figure 1 might achieve. That is what are the potential outputs from the process. Figure seems to indicate only the following; communication with the regulators, a review event (during lifecycle management) or another risk assessment (because risk reduction was "unacceptable". I would suggest that Figure 1 and the text in this section can be revised to clearly show that through the process of risk management risks can be identified and then resolved to a point where risk is accepted (controlled) since all identified risks are demonstrated either low initially or low after risk reduction by consideration of a clearly defined set of attributes / requirements	
EfPIA	86	88	3.2	While unambiguous reference is made to the leverage of prior knowledge, as currently written it suggests this is somewhat limited in scope to food standard - pharmacopeial standards. This is very narrow and takes no account of often the most useful data derived from equivalent packaging / manufacturing systems	Expand definition to include utilisation of surrogate data from related packaging / manufacturing equipment.
EfPIA	86	87	3.2	Sentence is a bit vague, assume it should say that there are various risk assessment approaches? Or various approaches for safety assessments?	Maybe change sentence to, ". . . Knowledge, various approaches for safety assessments can be adopted . . ."
Luye Pharma	86	96	3.2	"For oral drug products, compliance with relevant regional food-contact safety regulations may be sufficient to support the safety and quality … For all other drug products, ..., extractable/leachable assessments are typically warranted."	Adherence to food regulations shall also be an option for other than oral forms; provided appropriate justification is given.
BioPhorum	88	88	3.2	add additional references to standards and guidance's providing guidance for lower risk applications. Applies to text, "standards/regulations to more extensive E&L characterization and safety risk assessment (See 89 Appendix 1). For oral drug products, compliance…"	Add to read as follows… standards/regulations (e.g., USP <1665>, “Biophorum Leachables Best practice (2018)” (see Table 1)) to an appropriate risk based level of more or less extensive E&L characterization and safety risk assessment (See 89 Appendix 1). For oral drug products, Note: if direct reference to local documents like USP 665 is not possible, the guideline should still acknowledge the existence of such documents to guide low-risk scenarios.

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EfPIA	88	89	3.2	Specify cross reference	Table A.1.1.
ELSIE	88	89	3.2	Specify cross reference	Table A.1.1.
AESGP	89	94	3.2 Risk Matrix as a Multifactorial Concept	When desribing the general requirements, separate the discussion on 'manufacturing' and 'container closure sytem 'packaging' into separate sentences so it is clear for the reader. For manufacturing, in the non-prescription medicine realm (oral, topical and nasal preparations), due to the GMP criteria and other elements (very short contact time, often in stainless steel (or equivalent), at non-elevated temperatures) with low bioavailabilities (very small doses for nasal preparations, low bioavailability for dermal, the risk for E&L through manufacturing is low and in general studies are not required. Considering the container closure context, add topical drug products to the example as systemic exposure from drug products is lower than from oral drug products, so the same logic applies. In addition, add nasal preparations as systemic exposure would be negligible as the drug volumes administerd to the patient are very small and not respired into the deep lung. A large proportion of the small volume is expelled out the nose (following patient blowing the nose) and/or swallowed and, therefore, absorption across the mucosal membrane in the nasal cavity is minimal and toxicological risk from a leachable is not realised. Also, make the text on compendial grade documentation for packaging consistent with the table A.1.2.	For oral ', preparations (which includes solutions, sprays and drops intended for nasal administration) and topical' drug products, compliance 'manufactured using equipment components compliant with relevant 'Good Manufacturing Practice (GMP) standards are sufficient to support the safety without additional extractables or leachables testing' with relevant regional food-contact safety regulations 'and or compendial requirements' may be sufficient to support the safety and quality of polymeric manufacturing equipment/systems. For all other drug products, or for oral products that do not comply with the regulations for food contact in terms of composition, specification, and in-use limitations, extractable/leachable assessments are typically warranted. For oral drug products, nasal preparations and topical drug products compliance with relevant regional food-contact safetyregulations may be sufficient to support the safety and quality of polymeric manufacturing equipment/systems and container closure systems if adequately justified (e.g., proposed use is consistent with regional regulations for food contact use 'or compendial standards including composition and specifications', the leaching propensity of the drug product is similar or less than those listed in a referenced regional regulation, and all specified testing results meet acceptance criteria). For all other drug products, or for drug products that do not comply with the regulations for food contact 'use or compendial standards' in terms of composition, specification, and in-use limitations, extractable/leachable assessments are typically warranted.
AESGP	89	96	3.2. Risk Matrix	For oral topical creams for skin application and nasal preparations, products should also address the case where polymeric components are not used in manufacture (E and L not required). And compendial grade should be given equal prominence with food contact grade	For oral drug products 'both liquid and solid', topical creams for skin, and nasal preparations, compliance with relevant regional food-contact safety regulations 'and/orcompendial standards' may be sufficient to support the safety and quality of polymeric manufacturing equipment/systems and container closure systems if adequately justified (e.g., proposed use is consistent with regional regulations for food contact use 'and/or compendial standards', the leaching propensity of the drug product is similar or less than those listed in a referenced regional regulation, and all specified testing results meet acceptance criteria).
AstraZeneca	89	89	Sectiion 3.2	specify Oral "solid" DP if suggesting food compliance statements are acceptable and E&L testing is not necessary	Oral liquids present an increased risk that requires add'n info above and beyond oral solids, potentially including E&L testing.

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BioPhorum	89	96	3.2	As for oral drug products, the risk for topical other than ophthalmic administration is regarded low both in the EMA Guideline for plastic immediate packaging materials and the FDA Guidance on Container Closure Systems for Packaging Human Drugs and Biologics. In both guideline requirements for safety are the same as for oral DP. Emphasize that different levels of testing may be appropriate based on the level of risk. ….	Propose to add topical other than ophthalmic, not only oral DP For all other drug products (including oral and topical, but not ophthalmic), or for oral products that do not comply with the regulations for food contact in terms of composition, specification, and in-use limitations, an initial process based risk assessment should be conducted to determine that extractables or leachables data are required.
EfPIA	89	96	3.2	As for oral drug products, the risk for topical other than ophthalmic administration is regarded low both in the EMA Guideline for plastic immediate packaging matierials and the FDA Guidance on Container Closure Systems for Packaging Human Drugs and Biologics. In both guideline requirements for safety are the same as for oral DP.	Propose to add topical other than ophthalmic, not only oral DP
EfPIA	89	91	3.2	Qualifying a polymeric manufacturing component with only food contact safety compliance is not aligned with USP <665>	
EfPIA	89	96	3.2	The requirement for oral products is now unclear. Does this mean food regulations suffice for all polymeric materials, regardless of risk level? This contradicts USP 665. Additionally, for primary packaging, food standards are insufficient (see FDA guidelines and USP1664).	
ELSIE	89	96	3.2	As for oral drug products, the risk for topical other than ophthalmic administration is regarded low both in the EMA Guideline for plastic immediate packaging matierials and the FDA Guidance on Container Closure Systems for Packaging Human Drugs and Biologics. In both guideline requirements for safety are the same as for oral DP.	Propose to add topical other than ophthalmic, not only oral DP
EUCOPE	89	94	3.2	Does it mean that, in case of oral drug products, a food-contact compliant container may be sufficient, avoiding any risk assessment as well as any testing?	To be clearly what "may be sufficient" means.
IPAC-RS	89	94	3.2	Why restrict this statement to "polymeric" manuf. and CCS. Why not include glass or other materials?	Consider other materials to be included in this statement.
Lotus pharmaceutical company	89	94		According to ICH Q3E, polymer-based process systems may use a food safety statement to support E&L testing exemption. For process systems that are not composed of polymers, is it acceptable to use a food safety statement to exempt E&L testing?	
Medicines for Europe	89	96	3.2	The draft guideline states that compliance with food regulationns may be sufficient for oral drug products, while all other drugs the extractable/leachable assessments are typically warranted. We propose to clearly state that food regulation should not be exclusively limited to oral drugs, when appropiately justified.	Compliance to food regulation shall not be limited exclusively to oral forms, but shall still be a feasible approach for other dosage forms as well, if justified.
Medicines for Europe	89	91	3.2	The guideline mentions that for oral durg products, food-contact safety regulations may be sufficient to support the safety and quality of polymeric manufacturing equipment/systems and container closure systems if adequately justified. Is this aplicable to all oral drug products including solid dosage forms, oral solutions/susspensions?	Clarification to be added specifying dosage forms.
AESGP	90	90	Figure 2	Nasal preparations (which includes solutions, sprays and drops intended for nasal administration) and topical creams and ointments for skin appllication should be added as they do not pose risk to patients due to exposure to leachables. This is because the manufacturing process involves very short contact time, often in stainless steel (or equivalent), at non-elevated temperatures. In addition systemic exposure would be negligible as the drug volumes of nasal preparations administerd to the patient are very small and not respired into the deep lung. A large proportion of the small volume is expelled out the nose (following patient blowing the nose) and/or swallowed and, therefore, absorption across the mucosal membrane in the nasal cavity is minimal and toxicological risk from a leachable is negligible. For topical creams and ointments for skin appllication there is minimal systemic exposure as the skin acts as a barrier. Also, add 'compendial grade requirements' to regional contact material regulation compliance	For oral drug products, 'nasal preparations and topical creams and ointments applied to skin' compliance with relevant regional food-contact safety regulations 'and/or compendial grade requirements'may be sufficient...

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	90	90	3	LEO Pharma has interpretated that the draft guideline ICHQ3E requires extraction studies to be conducted for all topical products regardless of the compliance status of the packaging materials. LEO Pharma believe this is an unnecessary strengthening of current regulatory requirements to topical drug products. Currently, EMA Guideline on Plastic Immediate Packaging Materials (section 4 and appendix II) states that extraction studies are not necessary for topicals if materials are described in the European Pharmacopoeia (or in a pharmacopoeia of a member state) or approved for use in food packaging (comply with foodstuff legislation). LEO Pharma proposes to exclude topicals with low safety risk (reference is given to l. 84-86) from the requirement on extraction studies in the cases where component materials meet either the pharmacopoeial standard or the foodstuff compliance criteria which further add to the low safety risk.	Add "and topicals" to the text, i.e. "For oral and topical drug products, … "
EfPIA	90	90	3.2	We are not assessing quality in this work stream	Remove "and quality" for this line
EfPIA	92	93	3.2	How can one demonstrate that "the leaching propensity of the drug product is similar or less than those listed in a referenced regional regulation"? Also, the leaching proposensity relates to the material and not the DP	Clarification needed
ELSIE	92	93	3.2	How can the one demonstrate that "the leaching propensity of the drug product is similar or less than those listed in a referenced regional regulation"?	Clarification needed
AESGP	94	96	3.2 Risk Matrix	It should be addressed to the container closure complying to food contact, not the drug product	For all other drug products, or for oral products that 'where the container closure materials' do not comply with the regulations for food contact 'and/or compendial standards' in terms of composition 'and' specification, and in-use limitations, extractable/leachable assessments are typically warranted.
BioPhorum	96	96	3.2	Follows up on Table 2 in text, to emphasize different levels of testing may be appropriate based on the level of risk. …. "For all other drug products, or for oral products that do not comply with the regulations for food contact in terms of composition, specification, and in-use limitations, extractable/leachable assessments are typically warranted. An initial process based risk assessment should be conducted to determine that extractables or leachables data are required."	An initial process based risk assessment should be conducted to determine that extractables or leachables data are required.
EfPIA	96	96	3.2	extractable/leachable	E&L
ELSIE	96	96	3.2	extractable/leachable	E&L
ELSIE	99	99	3.2	Understanding the respective risk level of the corresponding factors is part of the risk assessment process and may inform manufacturing and packaging components selection as well as the development of an overall risk assessment/control strategy.	Understanding the respective risk level of the corresponding factors is part of the risk assessment process and may impact manufacturing and packaging components selection as well as the development of an overall risk assessment/control strategy.
Ferring Pharmaceuticals	99	99	3.2	"...may inform..." - is 'inform' the wright word?	Is "...may include..." what is meant?
ELSIE	100	100	3.2	"overall" is unnecessary and can be removed to improve clarity.	Remove the word
ELSIE	101	117	3.3	Risk' paradigm presented here seems to only be self-referential and over simplistic. For instance 'Risk Analysis' is actually a means of 'Exposure Assessment' defining occurance and patient exposure to identified leachables.	In addition, to nomenclature revisions it may be worthwhile to stratify the traditional toxicological risk assessment components (Haz ID, Dose Response, Exposure Assessment, Risk Characterization) either within this framework or as a separate workflow.
Ferring Pharmaceuticals	101	101	3.3	How does this assessment fit into BPOG's approach for evaluation of E&L originating from manufacturing items?	Would it be possible to align with BPOG's approach and with the approach outlined in USP 665/ USP 1665?
EfPIA	102	103	3.3	What is the need to capitzalize "Risk Management Process", "Multidimensional Risk Matrix" and "Typical Workflows"? "Multdimensional " is unnecessary as risk matrices consider all dimensions	At least multidimensional should not be capitalized and removed. It does not correspond to the caption of Figure 2.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	102	103	3.3	What is the need to capitalize "Risk Management Process", "Multidimensional Risk Matrix" and "Typical Workflows"? "Multdimensional " is unnecessary as risk matrices consider all dimensions	At least multidimensional should not be capitalized and removed. It does not correspond to the caption of Figure 2.
Ferring Pharmaceuticals	104	104	3.3	The caption for Figure 3 is stating "Figure 1"	The captions for the figures and tables should be updated.
EfPIA	105	106	3.3	As above (lines 53-54), initial step to identify whether risk of leachables from the material is significant (e.g. E&L studies generally not performed on stainless steel components)	
Maven E&L Ltd	106	111	Section 3.3	ICH Q9 Definition: Hazard identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Hazard identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process. ICH Q3E definition is too literal: "Identify potential leachables..." Rather it should consider both processes and practices which answer the question what might produce leachable exposure for a patient using the drug product"	should consider both processes and practices which answer the question what might produce leachable exposure for a patient using the drug product"
AESGP	106	117	3.3	The risk assessment steps align with 1.) Extractables testing, 2.) Leachables testing, 3.) Toxicological assessment	Perhaps the usual terms as mentioned in column F might be added
AstraZeneca	106	111	Section 3.3	ICH Q9 Definition: Hazard identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Hazard identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process. ICH Q3E definition is too literal: "Identify potential leachables..." Rather it should consider both processes and practices which answer the question what might produce leachable exposure for a patient using the drug product"	should consider both processes and practices which answer the question what might produce leachable exposure for a patient using the drug product"
BioPhorum	106	111	3.3	Step 1 - Hazard identification for manufacturing components/systems, container/closure systems can be done as well based on supplier / vendor E&L data	Proposal to add information in line 110:based upon prior knowledge (experience with component, prior testing, supplier E&L data etc.)
EfPIA	106	117	3.3	Hazard Identification is understanding the safety hazards (i.e., relevant toxicology data). What is described in Step 1 /2 is exposure assessment.	Change to: Step 1: Hazard assessment - Identify E&Ls and understand their toxicological hazards. Step 2: Risk Analysis: Quantitate exposure and compare to relevant hazards of E&Ls
EfPIA	106	107	3.3	Implies that ALL potential leachables need to be identified, but only potential leachables above the appropriate SCT/TTC would require ID	Modify sentence to, "Identify potential leachables that may migrate into the drug product at levels above the appropriate SCT/TTC from direct . . . "
ELSIE	106	111	3.3	The risk matrix, as presented in Figure 1 and described in section 3.3, points to the identification of leachable exposure based on leachables present in the material that may migrate into the product/therapy. Knowledge of the full leachable profile at the risk assessment stage is often not possible. This section does note that this may be best on prior extractable/leachable testing; however, it is often the case that risk is assessed prior to the execution of testing and thus this type of data is typically not available at the risk assessment stage. Similarly, risk assessments are used to show that the component/system in question is low risk and thus testing is not required.	Improve and clarify description of the sequence of events in the risk assessment process as described in the document and shown in figure 1. Specifically, when and how hazard identification is done and how it relates to when E&L testing is performed instead of implying that such testing would be done before hazard identification is assessed (which is typically not the order these assessments are performed in).
EfPIA	108	109	3.3	Regarding the identification of potential leachables (step 1), "secondary pacakging" may not be compliant with the "relevant regional food-contact safety regulations" discussed in lines 89 to 91, this seems to imply that this should that this should be discussed in all cases, even for solid oral dosage forms. The circumstances around which the assessment of secondary packaging should be conducted needs to be clarified.	Please consider specifying under which circumstances assessment of secondary packaging is required and remove ambiguity. Consider providing a listing of examples.
ELSIE	108	108	3.3	• Typo correction: "...and delivery devices components) or indirect (e.g., secondary ….."	"...and delivery devices components) or indirect (e.g., secondary …"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	110	111	3.3. Risk Assessment	"….based upon prior knowledge (experience with component, prior testing, etc.= and /or….."--> would be also help full to rely on prio supplier knowledge, because sometimes it is supplier intelectual property.	"….based upon prior knowledge (experience with component, prior testing, supplier prior kwowledge, etc.
EfPIA	111	111	3.3	extractables and leachables	E&L
ELSIE	111	111	3.3	extractables and leachables	E&L
Maven E&L Ltd	112	113	Section 3.3	Same point as above does not follow ICH Q9 definition: Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. ICH Q3E definition does not mention a consideration of severity of the hazard from leachables, rather only focus is "...on occurrence of leachable..". Not considering both severity of hazard and probability of harm (occurrence) does not fully consider and score the risk accurately	
AstraZeneca	112	113	Section 3.3	What is meant by the phrase quantitate the potential occurance of leachables ? do this mean or indeed risk, the need for actual analytical data ?	Consider clarifying what is meant by this term
AstraZeneca	112	113	Section 3.3	Same point as above does not follow ICH Q9 definition: Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. ICH Q3E definition does not mention a consideration of severity of the hazard from leachables, rather only focus is "...on occurrence of leachable..". Not considering both severity of hazard and probability of harm (occurrence) does not fully consider and score the risk accurately	
Bio-Process Systems Alliance	112	113	3.3	The requirement is to quantitate the potential occurrence of leachables in the drug product, with no guidance for PERLs, scaling and downstream removal	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device only or revise Guidance to include explicit guidance on scaling via surface area or equilibrium and guidance on the estimation of leachables removal capacity of downstream steps.
EfPIA	112	112	3.3	The occurence of leachables should be determined or estimated but not "quantitated"	Rewording
EfPIA	112	113	3.3	Step 2 - this simply defines the need to quantitate the potential occurence of leachables but provides no advice on the basis of how this can be done	The extent of risk could be defined in many ways from green / amber/ red to actual numerical data. It could also be based on in silico tools that predict purge within a manufacturing sytem
EfPIA	112	113	3.3	Quantitatively assess the likelihood and extent of leachables in the drug product and the resulting patient exposure. How in practice?	
ELSIE	112	112	3.3	The occurence of leachables should be determined or estimated but not "quantitated". This section feels unnecessarily complex. Wouldn't it be clearer to simply state: "Quantitate leachables in the drug product and assess patient exposure"? Quantifying the potential occurrence seems redundant—if leachables are present, they must be quantified.	Reword for clarity
Sartorius-Stedim Biotech GmbH	112	112	3.3	Correct, but please propose reasonable and physically correct methodologies for exposure calculations. Including methodologies to evaluate combination of devices (e.g. assemblies unsed in manufacturing)	Examples of valid algorithm for scaling and combination of devices were published (see above)
Maven E&L Ltd	114	117	Section 3.3	Same point as above does not follow ICH Q9 definition: Risk Evaluation compares the identified risk against a risk criteria. That is risk analysis scored the risk. Risk evaluation considers the consequence of the score derived. The current wording in ICH Q3 discusses qualification for intended use without any guidance on what constitutes qualification. This should be more careful worded to craft a risk criteria in terms relevant to the management of leachable risk. Perhaps this should then be leachables are not a safety risk (and add definitions) or leachables are not a quality risk (alignment with product specification requirement - leachables as a CQA - product meets specification, or leachable not required as a CQA and product meets specification)	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	114	117	Section 3.3	Same point as above does not follow ICH Q9 definition: Risk Evaluation compares the identified risk against a risk criteria. That is risk analysis scored the risk. Risk evaluation considers the consequence of the score derived. The current wording in ICH Q3 discusses qualification for intended use without any guidance on what constitutes qualification. This should be more careful worded to craft a risk criteria in terms relevant to the management of leachable risk. Perhaps this should then be leachables are not a safety risk (and add definitions) or leachables are not a quality risk (alignment with product specification requirement - leachables as a CQA - product meets specification, or leachable not required as a CQA and product meets specification)	
EfPIA	114	117	3.3	In practice, how is an "integrated risk evaluation" documented besides a toxicological safety assessment?	Clarification needed
EfPIA	114	117	3.3	In Step 3 - Integrated Risk Evaluation, the sentence does not include delivery devices components, while in Step 1 - Hazard Identification, delivery devices components are mentioned. For consistency reasons delivery devices components shall be added to step 3, too.	Proposed wording/change: "•Step 3 – Integrated Risk Evaluation: Evaluate the potential risk to impact product quality, safety and efficacy to determine if the selected manufacturing components/systems, container/closure systems and delivery devices components are considered qualified for the intended use."
EFPIA	114	117	3.3	In Step 3 - Integrated Risk Evaluation, the sentence does not include delivery devices components, while in Step 1 - Hazard Identification, delivery devices components are mentioned. For consistency reasons delivery devices components shall be added to step 3, too. The guideline currently states that in step 3 of the risk assessment, you must "evaluate the potential risk to impact product quality, safety and efficacy to determine if the selected manufacturing components/systems and container/closure systems are considered qualified for the intended use." Comment: According to Step 3, "Integrated Risk Evaluation", potential risks from extractables and leachables (E&L) must not only be assessed in terms of safety but also regarding quality and efficacy of the drug product. However, the quality and efficacy of each drug product is already routinely assessed during the manufacturing process and prior to release. Leachables are typically present in very low concentrations that rarely affect the quality and the efficacy of drug products. An individual assessment of every potential leachable (=extractable) and confirmed leachable bears no proportion in relation to the actual risk and it is already captured in routine QC measurements.	Proposed wording/change: "•Step 3 – Integrated Risk Evaluation: Evaluate the potential risk to impact product quality, safety and efficacy to determine if the selected manufacturing components/systems, container/closure systems and delivery devices components are considered qualified for the intended use."
ELSIE	114	117	3.3	In practice, how is an "integrated risk evaluation" documented besides a toxicological safety assessment?	Clarification needed. It would be helpful to include brief examples or a general description of what is included in an integrated risk evaluation
ELSIE	114	117	3.3	According to Step 3 integrated risk evaluation, potential risks from E&L must not only be assessed in terms of safety but also regarding quality and efficacy of the drug product. However, the quality and efficacy of each drug product is already routinely assessed during the manufacturing process and prior to release. Leachables are typically present in very low concentrations that rarely affect the quality and the efficacy of drug products. An individual assessment of every potential leachable (=extractable) and confirmed leachable bears no proportion in relation to the actual risk and it is already captured in routine QC measurements.	Reduce E&L assessment to the safety risk only. State "leachables are typically present in extremely low concentration and potential impact on the drug product's quality and efficacy (which are routinely assessed during QC testing) is highly unlikely."
Octapharma	114	117	3.3	According to Step 3 integrated risk evaluation, potential risks from E&L must not only be assessed in terms of safety but also regarding quality and efficacy of the drug product. However, the quality and efficacy of each drug product is already routinely assessed during the manufacturing process and prior to release. Leachables are typically present in very low concentrations that rarely affect the quality and the efficacy of drug products. An individual assessment of every potential leachable (=extractable) and confirmed leachable bears no proportion in relation to the actual risk and it is already captured in routine QC measurements.	Reduce E&L assessment to the safety risk only. State "leachables are typically present in extremely low concentration and potential impact on the drug product's quality and efficacy (which are routinely assessed during QC testing) is highly unlikely."
EfPIA	115	115	3.3	E/L is an assessment a safety, quality and efficacy are assessed through a separate process stream.	Remove, "quality" and "efficacy". Compatibility (i.e., assessment against specifications - quality and efficacy) is a separate process stream.
EfPIA	116	124	3.4	Potentially expand on the " qualified" components Terminiology ...for intended use and what those requirements are looks like	Potentially a cross reference to the figure and table A.1.1

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Maven E&L Ltd	118	123	Section 3.4	It would appear to suggest on line 123 that only extractable or leachable testing can achieve low risk. Thus, testing must be done in all cases. That seems not to align with statements made elsewhere in this document for example in Appendix 1, low risk scenarios are given and the suggestion is that these would avoid testing if compliance data is available. For example, if risk assessment identifies a gap in understanding on level of risk (uncertainty) which might be filled by additional information from non testing, why would this not be acceptable? Such as might be obtained from a suitable model or a set of documentation which covers the risk.	
AstraZeneca	118	123	Section 3.4	It would appear to suggest on line 123 that only extractable or leachable testing can achieve low risk. Thus, testing must be done in all cases. That seems not to align with statements made elsewhere in this document for example in Appendix 1, low risk scenarios are given and the suggestion is that these would avoid testing if compliance data is available. For example, if risk assessment identifies a gap in understanding on level of risk (uncertainty) which might be filled by additional information from non testing, why would this not be acceptable? Such as might be obtained from a suitable model or a set of documentation which covers the risk.	
Bio-Process Systems Alliance	118	197	3.4	Quantification Without Reference Standards-Many extractables lack reference standards, yet quantification is required for comparison to thresholds.	Acknowledge and permit use of surrogate response factors, internal standards, or class-specific correction factors, with illustrative examples. This will harmonize expectations across laboratories. For line #163, 'if authentic reference standards do not exist, compounds with responses believed to be lower than the extractables in question should be employed.'
Bio-Process Systems Alliance	118	197	3.4	Mixture and Cumulative Effects-The guideline treats compounds individually, without addressing cumulative exposure from multiple leachables below thresholds.	Include a note recommending summation of structurally related compounds (e.g., phthalates) when cumulative exposure could exceed thresholds, or guidance on when mixture assessment is scientifically justified.
EfPIA	119	119	3.4	"comprehenshive" is unnecessary in this sentence	Remove word
EfPIA	119	119	3.4	The concept of "comprehensive" risk assessment is introduced, but is not explained. The term "comprehensive" is also not mentioned in the section dedicated to risk assessment (3.3). Suggestion is to be consistent throughout the entire document	Proposed wording/change: "If the risk assessment indicates risk mitigation is needed, measures may [...]"
ELSIE	119	119	3.4	"comprehenshive" is unnecessary in this sentence	Remove word
EUCOPE	121	123	3.4	When the risk assessment determines that mitigation measures are necessary as a risk control strategy, the guideline specifies that additional extractable & leachable studies should be conducted to verify the effectiveness of those measures. Can the sponsor present alternative approaches, other than retesting, supporting the adequacy of the risk control strategy?	
Sartorius-Stedim Biotech GmbH	121	123	3.4	In principle correct, but please consider: why shall one "validate" mitigation in E&L studies? It is absolutely sufficent to qualify a "clearance" step with generic stuides, in particular in cases where they can be justified with physical principles. The approach to validate any mitigation with E&L studies would produce an endless studing of already approved mitigation concepts.	Please make a differenciation between mitigation, which is based on empirical consideration (where indeed a qualification may be neccessary) and such based on generic physical principles, where a validation is not adequate.
Maven E&L Ltd	124	132	Section 3.4	This text implies that all components (without exception) require a qualification linked to acceptance criteria and testing. Risk control should include low risk items which can be qualified without this requirement. This should be made clear. There is no clear statement in this section of this type and it should be added. Perhaps a sentence of the style, "The level of qualification needed for risk control should be commensurate with the level of risk defined during risk assessment. Risk Control requirements of low risks being lower than high risks"	The level of qualification needed for risk control should be commensurate with the level of risk defined during risk assessment. Risk Control requirements of low risks being lower than high risks
AESGP	124	126	3.4	Usually, only leachables but not extractables studies are performed in a GMP-setup. This part might lead to the conclusion that e.g. packaging parts need to be investigated for extractables ahead of using them in e.g. a delivery device. This can be established by a target QC testing but should only be performed if a major risk is expected from that specific part.	Perhaps rephrasing the part with focus on leachables testing or excluding (as far as possible) a QC extractables testing will help to streamline the process

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	124	132	Section 3.4	This text implies that all components (without exception) require a qualification linked to acceptance criteria and testing. Risk control should include low risk items which can be qualified without this requirement. This should be made clear. There is no clear statement in this section of this type and it should be added. Perhaps a sentence of the style, "The level of qualification needed for risk control should be commensurate with the level of risk defined during risk assessment. Risk Control requirements of low risks being lower than high risks"	The level of qualification needed for risk control should be commensurate with the level of risk defined during risk assessment. Risk Control requirements of low risks being lower than high risks
EfPIA	124	128	3.4	It is not clear of the proposal is for all high risk components, even if it has been demonstrated no leachable risk in final container closure or just the ones where there might be residual risk despite all controls in place. Leachable study for container closure will be executed over the SL of the product, wouldn't that capture any leachable risks?	Add clarity is sampling, testing is expected for in-process samples on regular basis or just the first time for high risk components
ELSIE	124	131	3.4	Quality control and supplier qualification including quality agreement are already routinely in place for materials. Are you suggesting batchwise testing of E&L in quality control of materials? E&L testing for materials as part of quality conrol would severly delay production. At the same time, the benefit of such testing is questionable, because of batch-to-batch and lab variability. There is no benefit in comparison to today's testing and re-testing if the material changes in a way that could impact the E&L profile.	Risk control should be reduced to E&L testing of high risk materials (see material risk assessment) if the material changes in a way that could impact its E&L profile.
ELSIE	124	125	3.4	"Once the components are qualified for the intended use, a control strategy should be implemented" • Clarification is necessary on what "qualified components" refers to. • Clarification is necessary as to why a control strategy ('acceptance criteria, analytical procedures and sampling for components') is required beyond the specified quality agreements, if the components are not found to impact on the critical quality attributes (i.e. no leachables are observed)	• We recommend that definition of "qualified components for intended use" be added to the glossary. • We strongly recommend that supplier release testing be allowed and referenced within the guidline
Octapharma	124	131	3.4	Quality control and supplier qualification including quality agreement are already routinely in place for materials. Are you suggesting batchwise testing of E&L in quality control of materials? E&L testing for materials as part of quality conrol would severly delay production. At the same time, the benefit of such testing is questionable, because of batch-to-batch and lab variability. There is no benefit in comparison to today's testing and re-testing if the material changes in a way that could impact the E&L profile.	Risk control should be reduced to E&L testing of high risk materials (see material risk assessment) if the material changes in a way that could impact its E&L profile.
EfPIA	125	125	3.4	Editorial comment.	Defined acronym GMP for clarity.
EfPIA	125	125	3.4	comma location incorrect	Comma after "limited" should be moved to after "to".
EfPIA	126	128	3.4	The general requierment of quality control is not aligned with the practice we believe that to pursue the risk based approach, systematic testing should be limited for high risk component and for a specific identified leachable only.	Once the components are qualified for the intended use, a control strategy should be implemented. This comprises, but is not limited, to routine GMP practices which are imperative for component quality controls. A control strategy should be in place to: • For high risk component and for a specific identified leachable only, establish adequate ~~acceptance~~ ~~quality~~ control including acceptance criteria, analytical procedures, and sampling plan for components as appropriate
EfPIA	128	128	3.4	Why only "components" and not container closure system or final finished packaged products?	Clarification needed
ELSIE	128	128	3.4	Why only "components" and not container closure system or final finished packaged products?	Clarification needed
EfPIA	129	129	3.4	Replace "vender" with supplier since "supplier" is used elsehwere in the document	Rewording
EfPIA	129	129	3.4	Editorial comment.	Vendor is misspelled. Change to 'vender' to 'vendor'.
EfPIA	129	129	3.4	Spelling error: "vender" is spelled "vendors"	Change "venders" into "vendors"
ELSIE	129	129	3.4	replace "vender" with supplier since "supplier" is used elsewhere in the document	Reword -- just make sure whatever term is used, is used consistently throughout

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	129	129	3.4	• Editing correction/typo: "Establish appropriate quality agreement with component venders including component"	• "Establish appropriate quality agreement with component vendeors including component". (Use "o" rather than "e")
Medicines for Europe	129	129	3.4	correct spelling of "venders"	"vendors"
EfPIA	132	137	3.4	As written this sets the expectation that irrespective of the factors described in Figure 2 ,that extractables and leachables studies are expected and that other approaches are the exception	the tone of this paragraph is not aligned with Figure 2.
EFPIA	132	137	3.4	This section suggests that extractables and leachables studies are expected in all cases (for primary packaging and delivery device) and that other approaches such as material based approach (e.g. for delivery devices components or administration materials) or any other "prior knowledge" based approaches are not possible. This is not in line with Figure 2 but also with an overall risk assessment approach that would consider extractables and leachables testing only when significant risks are identified (e.g. moderate/high risks)	Align the content of this paragraph with Figure 2 i.e. clarify whether other approaches than extractables and leachables testing are considered applicable depending on the level of risk.
ELSIE	132	134	3.4	Information in this sentence is already mentioned and is redundant	Remove sentence
Ferring Pharmaceuticals	132	132	3.4	Consider relocation of the workflow in core text	Will facilitate the reading
EfPIA	133	151	3	Suggest adding (Tables A.1.1 and A.1.2) at the end of l. 138, after the sentence "under certain circumstances alternative approaches may be proposed with proper justification" to make it clear and lead the reader to find some examples of what the certain circumstances can be.	End of l. 138: Add "Table A.1.1 and A.1.2".
EfPIA	133	133	3.4	The word "venders" is to be corrected to "vendors".	The word "venders" is to be corrected to "vendors".
Maven E&L Ltd	134	135	Section 3.4	This again makes an assumption that all risks require testing. I would suggest a revision to say. "Where risks are initially marked as high, the risk level should be tested for its accuracy with the relevant testing linked to risk description, through either extractable or leachable investigation aligned to the risk to confirm the risk rating. Low risks might avoid testing. High risk can then be rated low on completion of testing which demonstrates a low risk"	Where risks are initially marked as high, the risk level should be tested for its accuracy with the relevant testing linked to risk description, through either extractable or leachable investigation aligned to the risk to confirm the risk rating. Low risks might avoid testing. High risk can then be rated low on completion of testing which demonstrates a low risk"
AESGP	134	135	3.4	Manufacturing equipment not listed here - cross reference lines 138 and below?	Depending on the scope of this document to cover any manufacturing equipment - see remark above.
AESGP	134	135	3.4 Risk Control	The guideline should acknowledge directly that E&L studies may not be required.	'If required,' Typically, extractable and leachable studies should be conducted for packaging and delivery device components.
AstraZeneca	134	135	Section 3.4	This again makes an assumption that all risks require testing. I would suggest a revision to say. "Where risks are initially marked as high, the risk level should be tested for its accuracy with the relevant testing linked to risk description, through either extractable or leachable investigation aligned to the risk to confirm the risk rating. Low risks might avoid testing. High risk can then be rated low on completion of testing which demonstrates a low risk"	Where risks are initially marked as high, the risk level should be tested for its accuracy with the relevant testing linked to risk description, through either extractable or leachable investigation aligned to the risk to confirm the risk rating. Low risks might avoid testing. High risk can then be rated low on completion of testing which demonstrates a low risk"
EFPIA	134	137	3.4	Typically, extractable and leachable studies should be conducted for packaging and delivery device components. Under certain circumstances alternative approaches may be proposed with proper justifications. The guideline is unclear as to what meant by "alternative approaches". Additionally, it is not clear which situations would fall "under certain circumstances alternative approaches may be proposed with proper justifications".	We recommend the guideline include additional clarification and/or examples of would could be considered as "alternative approaches", as well as examples of situations that would fall under "certain circumstances" where "alternative approaches may be proposed with proper justifications".
EfPIA	136	137	3.4	It is not clear which situations would fall "Under certain circumstances alternative approaches may be proposed with proper justifications"	Include examples
EfPIA	136	136	3	Examples of alt approaches	Examples provided in training materials

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	136	137	3.4	…alternative approaches may be proposed with proper justifications.” Need clarity regarding what is meant by “alternative approaches	
ELSIE	136	137	3.4	"Typically, extractable and leachable studies should be conducted for packaging and delivery deice components. Under certain circumstances alternative approaches may be proposed with proper justifications." What is meant by 'alternative approaches?' It is not clear which situations would fall "Under certain circumstances alternative approaches may be proposed with proper justifications"	More clarification needed on which alternative approaches are acceptable. Inclusion of examples would be helpful
AESGP	138	165	3.4	These paragraphs are not fully clear. In general these should aim on an alternative process to leachables studies because these are rarely possible / performed for manufacturing equipment.	Text should be rephrased with a step-by-step description for risk analysis in manufactirung as alternative to leachables testing
EfPIA	138	141	3.4	Lack of clarity on scope and limits. It could be read as packaging requirements have to be applied to all process equipments, which is unrealistic…	
Sartorius-Stedim Biotech GmbH	138	150	3.4	Correct, but please consider: why should extractables conditions for SUS be justified? With beginning of next year we will have USP 665, a standard methodology, which provides all neccessary information about extraction conditions for dedicated device components.	Better differentiate between CCS (final containers used to bring DP to the market) and SUS used in manufacturing.
AESGP	140	142	3.4 Risk Control	Manufacture equipment materials such as polymeric materials should be defined. Contact time should also be addessed e.g below 24 hours is not significant	Insert a sentence in 141, 'For very short contact durations of less than 24 hours, this should be regarded as non-significant'
EfPIA	141	143	3.4	Pressure is typically not considered when designing an extractables study; could you explain further?	
EfPIA	141	143	3.4	Extractables studies should therefore be designed to represent the worst-case scenario of the manufacturing conditions (e.g., smallest scale with longest contact durations, highest temperature and pressure).	pre treatment and solvent selection should be considered

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	141	142	3.4	" Extractables studies should therefore be designed to represent the worst-case scenario of the manufacturing conditions (e.g., smallest scale with longest contact durations, highest temperature and pressure)." • Rationale: An extractable study performed using aggressive extraction mechanism such as reflux has the potential to generate an unrealistic profile of potential leachables, and this should be highlighted within the guidance. These guidline's lines detail the manufacturing process; however, it states that extractables studies should be designed to represent the worst-case scenario of the manufacturing conditions. That said, 'manufacturing condition' is not applicable when considering the countainer closure system (CCS), as typical extractables studies are not performed under manufacturing conditions. • Rationale: Given the batch size relative to the manufacturing component, it is impossible to truly replicate the processing ratio of batch size to equipment, as suggested within lines 141 and 142.	• Extractables studies should therefore be designed to represent the worst-case scenario to identify potential leachables. However, we recommend referncing in this guidline that applicants should be mindful that the use of aggressive extraction method, such as reflux, may generate unrealistic and unrepresentative profile of extractables. • Extractables studies are not capable of truly representing manufacturing conditions; however, the conditions should be representative of batch manufacture in order to achieve the require AET based on similar parameters/conditions (e.g., highest temperature, similar solvents and pressure). We recommend text chage following rationale: " Extractables studies should therefore be designed to represent the worst-case scenario of the manufacturing conditions (e.g., smallest scale with longest contact durations, highest temperature and pressure) the expected worst case scenario with regards to potential extractables. However, the conditions of extraction must be balanced to provide a realistic and representative extractables profile but not so aggressive as to chemically degrade, deform or artifically generate extractables from the material to give an unrealistic representation of the extractables profile. With regards to manufacturing processing equipment, extractables studies should be representative of the worst-case scenario (e.g., smallest scale with longest contact durations, highest temperature and pressure), but analytically feasible of achieving the AET (this may require modification of solvent to equipment stoichiometry."
Maven E&L Ltd	142	150	Section 3.4	Opportunity to add that testing of extractables and study design should be aligned to risk description. Also consideration of type of extraction study for parts and types of packaging where no liquids are present such as dry powder inhalers or investigation of semi-permeable systems with no liquid present such that solvent extractions might be replaced with more aligned conditions such as thermal desorption	
AstraZeneca	142	150	Section 3.4	Opportunity to add that testing of extractables and study design should be aligned to risk description. Also consideration of type of extraction study for parts and types of packaging where no liquids are present such as dry powder inhalers or investigation of semi-permeable systems with no liquid present such that solvent extractions might be replaced with more aligned conditions such as thermal desorption	
ELSIE	142	142	3.4	The description of the smallest scale as the worst case scenario is not always correct.	Please update to reflect that the surface area to volume ratio should be considered to determine worst case.
EUCOPE	142	142	3.4	Smallest scale is typically associated with worst-case Surface Area to Volume ratio.	Propose specifying why smallest scale is considered worst case by addition of SA:V ratio (i.e., ratio is greatest at smallest scale).
Qualimetrix SA	143	146	3.4	It is debatable in the case of filters. It appears quite relevant to more “rigid” parts (where the phenomenon is diffusion-regulated to a high extent), but the membranes of a filter are (by design) fully permeable. The larger volume of distribution does apply, but is it “a given fact” that production lines incorporate a “pooling vessel” at the end of the filtration step? The example of line 880, assumes uniform distribution – what would an example for a tubing at the filling point look like?	This could be addressed by placing the filter at different section of the risk gradient “leaching potential” – again example placements would be helpful to establish where we stand.
EfPIA	145	145	3.4	Editorial comment.	Change 'contacting' to 'contact'.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	146	150	Section 3.4	As worded this would seem to suggest that a risk assessment study is needed for both biologics and small molecules, the latter has long been considered low risk and effectively out of scope. this wording and possible interpretation is at odds line 195-197	Why has the scope effectively changed ? (the scope section does not expressively define the nature of the material nor its origin. If small molecule DS manufacture is now in scope have the implications of this and the scale of work been properly considered ?
ELSIE	146	150	3.4	"Leachables introduced in upstream manufacturing process steps might be able to be purged through downstream steps, e.g. purification/polish, lowering the risk for leachables ending up in the final drug product. These factors should be taken into consideration for manufacturing equipment selection and qualification, as well as quality investigations". • Not clear how to incorporate this into the study design, as previous line 141 stated "Extractables studies should therefore be designed to represent the worst-case scenario of the manufacturing conditions". Clarification is needed to ensure that extractables studies generate a realistic and representative extractables profile; representative of leachables in the product Question: Is it possible to include "discard volume" as a "purging step"? For the case where a product is passed through a sterile filter and then directly filled into e.g. vials, exponentially decreasing leachables can be removed by defining a discard volume. This option should be also taken up as a type of "purging step".	Clarify text to ensure that extractables studies generate a realistic and representative extractables profile, representative of leachables in the product Could also consider the following revision: "…in the final drug product. This could also involve a scientifically justified discard volume taken at the start of after an interruption of the filling process. These factors should be taken into consideration …"
Maven E&L Ltd	151	152	Section 3.4	Perhaps there is opportunity here to change sentence to read, "...may be considered minimal and qualified when all extractables are at or below AET…."	...may be considered minimal and qualified when all extractables are at or below AET…
AstraZeneca	151	152	Section 3.4	Perhaps there is opportunity here to change sentence to read, "...may be considered minimal and qualified when all extractables are at or below AET…."	...may be considered minimal and qualified when all extractables are at or below AET…
EfPIA	151	153	3.4	In the sentence "For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed", is there any confusion between extractables and leachables ? If the first part of the sentence specifies "extractables" (logically as it makes the link to USP<665> which primarily relies on extractables assessment), the second part of the sentence should also specify "extractables" and not "leachables". If not, guidance or clarification should be provided. Or "leachables" should be replaced by "compounds"	Proposed wording/change: "For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 extractables *(or compounds)* are observed"
ELSIE	151	153	3.4, 5 and 4.3	"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5). The analytical procedures used in extraction studies should comply with the criteria provided in Section 4.3." The risk is considered as minimal when all extractables are under the AET. This seems to not be applicable for class 1 but what about other compounds where the PDE can be lower than the AET. • Clarification is needed on the necessity of further assessment of leachables when extractables peaks exceed the AET, and whether a low safety concern would justify not performing further assessment, even if the AET is exceeded. • Sentence implies that testing for Class 1 leachables is required regardless of risk. Since this section discussed risk control, the reference to the Class 1 leachables should be the risk of it. • We recommend referencing in the guidline that leachables risk may be considered minimal and acceptable when all extractables peaks identified as greater than the Analytical Evaluation Threshold (AET) have been found to pose negligible safety concerns	•"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5)" OR •"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product (see Section 5) and no Class 1 leachables are observed when testing Class 1 leachables is considerd apropriate as directed by risk assessment (see Section 5)." Consider also making the revsion: "...no Class I leachables (leachables to be avoided) are observed...."
IPAC-RS	151	155	3.4	"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5). The analytical procedures used in extraction studies should comply with the criteria provided in Section 4.3." Can this be clarified?	Provide clearer explanation; consider clarifying in this section as well as Section 5 and Section 4.3

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Laboratoires Théa	151	165	3.4	Can you confirm that a leachables study (non-targeted included) is not required for manufacturing components when no extractables above the AET is observed?	
Rentschler Biopharma SE	151	153	3.4	Rentschler is a CDMO for biopharmaceuticals and therefore applies a wide variety of polymer-based manufacutring components/systems in a broad spectrum of manufacturing processes. Therefore, for the evaluation of polymer-based manufacturing components/systems which were assessed as relevant for a more extensive E&L characterization, Rentschler has so far used extractables data provided by manufacturers of these manufacturing components. Applying thresholds as stipulated by ICH M7 (1.5 µg/person/day or application of ICH M7 staged approach for less than lifetime application), the extractables are usually below the AET and no further studies are required. However, many extractables in the studies provided by manufacturers of polymer-based production materials are listed as "unknowns". Information on polymer formulations and additives used in the production of these polymer-based materials are usually not available from manufacturers as they consider these their intellectual property and as trade secrets. It therefore cannot be excluded, that there are Class 1 extractables amongst the unknown extractables listed in manufacturers' extractables data. Following the current ICH Q3E draft guideline, this would mean, that Rentschler (or its customers, respectively) would need to perform extractables studies for a large number of production materials and identify all extractables found. Conducting additional extractables studies involves significant financial investment and demands considerable time and resources, which can pose a challenge for many organizations. Despite these efforts, the actual risk to patient safety associated with the polymer-based manufacturing components in question is typically not high. Therefore, while diligence in identifying potential extractables is essential, it is important to balance the cost and effort with the realistic assessment of risk to optimize resource allocation effectively.	Recommendation: It should be in the responsibility of manufacturers of polymer-based materials used in (bio-)pharmaceutical manufacturing and packaging to prove that no Class 1 extractables/leachables are released from their polymer-based materials. In case this cannot be excluded, manufacturers should be obliged to identify the Class 1 extractables which may potentially leach from the respective material. Proof should be provided with certifications based on knowledge of the polymer formulation and additives and/or extensive extractables studies.
Sartorius-Stedim Biotech GmbH	151	155	3.4	Appling USP 665 does not require to elaborate an AET	
Medicines for Europe	152	154	3.4	This strategy ignores potential leachables which are not evidenced in the extractables study. (i.e., residues which may be introduced through the actual manufacturing process not evidenced in controlled, component-level extractables studies).	Consider removing this text and mandating justification for using component extractables in lieu of product leachables.
EfPIA	153	153	3.4	I so not see the relevance of the phrase, ". . . and no Class 1 leachables are observed ". At this point, only compounds above the AET might be identified and Class 1 are special case compounds that would generally have thresholds well BELOW typical e/l AETs	Suggest to re-word it like, ". . . and no Class 1 compounds are expected from the associated material (see Section 4.3)." Lines 315-319.
ELSIE	153	153	3.4	For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5).	What are the targeted compounds to be analysed? It is to know the analytical limit for such compounds.
Qualimetrix SA	154	155	3.4	how are the acceptance criteria (i.e. AET) set regarding the manufacturing materials that are placed after mixing/ collecting vessels i.e. tubing for the filling needles?	
Maven E&L Ltd	156	160	Section 3.4	Suggestion to revise the wording to, "as long as the quantification of extractables is performed against appropriate reference standards with demonstrated response and identity comparable to observed extractable…"	as long as the quantification of extractables is performed against appropriate reference standards with demonstrated response and identity comparable to observed extractable…
AstraZeneca	156	160	Section 3.4	Suggestion to revise the wording to, "as long as the quantification of extractables is performed against appropriate reference standards with demonstrated response and identity comparable to observed extractable…"	as long as the quantification of extractables is performed against appropriate reference standards with demonstrated response and identity comparable to observed extractable…
ELSIE	156	165	3.4	A quantitative E-Study should be omitted, if the PDE of an extractable > AET is essentially (e.g. factor of 100) higher than the semi-quantitatively determined concentration. Rationale: Uncertainty factors are generally in the range of 2-4 and can be individually estimated for an identified compound based on the chemical structure. If the margin of safety for such a compound is essentially higher than the semi-quantitatively determined concentration, there is no added value in development and qualification of a specific method for this compound.	Include exception for quantitative extractables studies, if justified by a high margine of safety.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	156	160	3.4	"In cases where manufacturing components/systems extractables are observed in concentrations above the AET, an identification of those extractables and quantification of the concentrations may be conducted to mitigate the leachables risk as long as the quantification of extractables is performed against appropriate reference standards of the same identity as the identified extractables" • The guidline lines state that when extractables are over the AET, extractables need to be quantified regardless of identification and safety assessment. • The wording "of the concentration" is confusing within this context, we suggest to remove it.	• We recommend removal of requirement to quantify when extractables are identified and considered safe and removal of "of the concentration" : "In cases where manufacturing components/systems extractables are observed in concentrations above the AET, an identification of those extractables and quantification of the concentrations may be conducted to mitigate the leachables risk as long as the quantification of extractables is performed using analytical procedures which are suitably qualified. against appropriate reference standards of the same identity as the identified extractable "
IPAC-RS	158	158	3.4	"an identification of those extractables and quantification of the concentrations may be conducted to mitigate the leachables risk…" Revise "may" to "must," as without identification the risk cannot be mitigated.	Change the "may" to "must"
ELSIE	159	160	3.4	This section assumes a reference standard is readily available for most extractables, which is not always the case.	Discuss surrogate compound selection alternatives.
ELSIE	159	160	3.4	(Additional Lines: 368; 475; 479) Focus on availablity of reference standard is limiting and would create complications with identifying any source of reference standard or having only one source of a reference standard.	Change “Reference Standard” to “Suitably Characterized Material"
EfPIA	160	161	3.4	Even in the case where no commercially available standards exist, it is impossible to know if the response factor of the extractable in the test article is similar to the surrogate standard use for semi-quantification	Reword "However, if authentic reference standards do not exist, compounds with similar physicochemical properties can be employed."
EfPIA	160	161	3.4	Rationale: About the use of surrogate compounds is not only a matter of analytical response but also phisico-chemical characteristics/retention time. Suggest to use a compound with similar structural related properties.	"However, if authentic reference standards do not exist, compounds with a similar phisico-chemical properties and similar analytical response can be employed.
EfPIA	160	161	3.4	Reliance on semi-quantitative extractables data and surrogate standards above AET. Common FDA/EMA Query on if this approach provides sufficient rigor.	~~However, if~~ Surrogate standards may be used only when levels are at or below the AET; for peaks above AET, authentic reference standards should be used whenever available. ~~do not exist, compounds with a similar analytical response can be employed~~
ELSIE	160	161	3.4	"However, if authentic reference standards do not exist, compounds with a similar analytical response can be employed" • Rationale: In addition to the use of compounds with a smilar analytical response, include allowance for the use of reference standards not of the same identity as the extractable quantified and with a response which is not similar to the analytical response of the extractable quantified if the difference in analytical response is established, demonstrated to be precise and used to adjust the amount of the extractable determined. (e.g., For the quantification of formaldehyde using the Hantzsch reaction for its derivatisation it is established that one mole of hexamethylenetetramine used as a reference standard provides a response equivalent to the response of 6 moles of formaldehyde). "compounds with a similar analytical response can be employed". If no authentic reference standard exists, you don't know the response of the extractable/leachable. Suggest to use a compound with similar structural related properties. Even in the case where no commercially available standards exist, it is impossible to know if the response factor of the extractable in the test article is similar to the surrogate standard use for semi-quantification	• We recommend to remove sentence: "However, if authentic reference standards do not exist, compounds with a similar analytical response can be employed" Reword: "...similar compounds with, e.g., similar physico-chemical properties, can be employed, with scientific justification"
IPAC-RS	160	161	3.4	"compounds with a similar analytical response can be employed". If no authentic reference standard existh, you don't know the response of the extractable/leachable. Suggets to use a compound with similar structural related properties.	"similar compound with structural related properties can be employed"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	160	163	3.4	The guideline states that if authentic reference standards do not exist, compounds with a similar analytical response can be employed. The lack of more specific requirements can lead to different interpretation and implementation by the applicants and by the authorities.	Limit of quantification and criteria to be more elaborated for better understanding and alignment. Analytical uncertainty factor may be included.
Qualimetrix SA	160	161	3.4	How can a "similar analytical response" be established / justified among two species, when one compound is not commercially available?	
ELSIE	161	165	3.4	It is difficult to understand the directive here, which states that if a leachable is below the safety level described in section 6 than it is safe, or alternatively a safety assessment may be performed. Isn't the determination of a safety level in section 6 and its application to the extractable a safety assessment? If not, how does a safety assessment, as alluded to here, differ from the safety level as described in section 6?	Clarify the differences between assessment of the extractable against the safety level established in section 6 versus its assessment via a safety assessment.
ELSIE	161	163	3.4	" If extractables concentrations quantified in this manner are below the relevant acceptable safety level (see Section 6), then the safety concern associated with leachables risk is considered negligible. "	• The number, quantity and amount of extractables can vary based on a number of factors. Therefore, we propose allowing the option to test leachables as they represent the actual risk to patient safety.
Luye Pharma	161	163	3.4	"If extractables concentrations quantified in this manner are below the relevant acceptable safety level (see Section 6), then the safety concern associated with leachables risk is considered negligible." This indicates that leachables testing may be unnecessary when extractables from the manufacturing equipment remain below the safety concern threshold (AET). Consequently, the same principle should apply to extractables originating from packaging materials or device components.	include "If extractables concentrations quantified are below the relevant acceptable safety level (see Section 6), then the safety concern associated with leachables risk is considered negligible." for packaging material and device components (for instance below line 172). The guideline should also include the possibility of waiving leachables testing when these criteria are met. This is justified because an extractables profile without safety concern cannot lead to leachables that create a safety concern in the final product (see lines 419–421: "leachables are a subgroup of extractables").
Medicines for Europe	162	164	3.4	This strategy ignores potential leachables which are not evidenced in the extractables study. (i.e., residues which may be introduced through the actual manufacturing process not evidenced in controlled, component-level extractables studies).	Consider removing this text and mandating justification for using component extractables in lieu of product leachables.
EfPIA	163	165	3.4	The intention behind the statement "As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed." appears to suggest that a TRA based on a leachables study could superseed a TRA based on an extractables study.	Clarification needed
EFPIA	163	165	3.4	The guideline currently states, "As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed." Comment: The guideline states that leachables need to be performed for manufacturing equipment. Clarification is needed on whether the guideline requires leachables testing to be performed directly on the manufacturing equipment, or if it refers to testing the finished product. Additionally, this sentence should be clarified. As currently written, the sentence appears to suggest a leachables study is to be performed. It is unclear whether the author intended to propose a safety assessment of extractables as potential leachables instead.	
ELSIE	163	165	NA	"As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed." To be clarified	Provide clearer explanation
ELSIE	163	165	3.4	The intention behind the statement "As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed." appears to suggest that a TRA based on a leachables study could superseed a TRA based on an extractables study.	Clarification needed

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	163	164	3.4	"As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed. " • The guidline says that leachables need to be performed for manufacturing equipment. Clarification is needed on whether the guideline requires leachables testing to be performed directly on the manufacturing equipment, or if it refers to testing the finished product. • Clarification is needed, as the sentence as written appears to suggest a leachables study. It is unclear whether the author intended to propose a safety assessment of extractables as potential leachables instead	• We recommend text change based on the rationale: "As an alternative to quantification qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of extractables observed leachables may be performed. If a safety concern is identified from the extractables study, an additional leachables study may be warrantied."
IPAC-RS	163	165	3.4	"As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed."To be clarified	Provide clearer explanation
Laboratoires Théa	163	165	3.4	For manufacturing components, if the safety assessment demonstrates that the concentration of the extractables (above the AET) presents no patient safety risk, there is no need to perform a leachables study, is that correct?	
EfPIA	164	164	3.4	Compounds identified (level above the AET) must required a safety assessment if the actual level is above the relevant SCT established by the toxicologist expert.	It is proposed to adapt "As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed." to "As an alternative to qualification of extractables from manufacturing equipment at concentrations above the SCT, a safety assessment of leachables may be performed.
EfPIA	164	165	3.4	Expand options when extractables exceed AET to include simulated leachables studies - closer to reality as worse-case than leachables, but not as worst-case as extractables.	Modify to: ". . . Above the AET, simulated leachables study(ies) or a safety assessment . . ."
Maven E&L Ltd	166	174	Section 3.4	It would be better to give examples of what prior knowledge addresses what attribute. An expansion of Table A.1.2. might be useful	
AstraZeneca	166	174	Section 3.4	It would be better to give examples of what prior knowledge addresses what attribute. An expansion of Table A.1.2. might be useful	
BioPhorum	166	172	3.4	This is an example for an abbreviated data package: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Appendix 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Appendix 1, Figure 5
Chiesi Farmaceutici	166	170	3.4	Delivery device components are not mentioned. They should be mentioned together with packaging components as they could be in direct contact with the formulation as well.	It is suggested to modify the sentence as follows: "For a packaging/delivery device component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6)."
EfPIA	166	172	3.4	This is an example for an abbreviated data package: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
EfPIA	166	166	3.4	First time that "abbreviated data package" is showing up in the text.	Cross-reference to Table A.1.2 to help the reader understand what could coonstitute an "abbreviated data package" as it is unclear

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	166	172	3.4 and Table A.1.2 (Appendix 1)	"Abbreviated data package" is undefined. Clarify what it includes and when it's appropriate.	Define term and add cross-reference to Table A.1.2. Align and clarify where to find the safety evaluation terminology.
EfPIA	166	172	3.4	Reference Section 4.6.	Proposed wording: For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation (See Section 4.6), similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6).
EfPIA	166	166	3	Suggest that E&L for topical and oral low risk products equipment is handled under GMP i.e. not a part of the regulatory dossier.	L. 166 after full stop: Add "For oral and topical low risk products E&L for equipment is handled under GMP and is not a part of the regulatory dossier".
EFPIA	166	172	3.4	The guideline currently states, "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6). Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification." Comment: This is the first time the terms "abbreviated data package" is stated in the guideline text. This term is not described/defined in the glossary, nor is it in line with the safety evaluation/assessment described in the previous paragraph.	We recommend clarifying and defining the term "abbreviated data package" in the guideline glossary so the reader has clear understanding of the expected requirements.
ELSIE	166	172	3.4 and Table A.1.2 (Appendix 1)	"For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6). Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification." Please clarify what it is meant by abbreviated data package; First time that "abbreviated data package" is showing up in the text. This paragraph refers to an abbreviated "data package". This is not a term described in the glossary, nor is it in line with the safety evaluation/assessment described in the previous paragraph.	Provide clearer explanation Cross-reference to Table A.1.2 to help the reader understand what could constitute an "abbreviated data package" as it is unclear Define and align, as needed, the terminology here.
ELSIE	166	174	3.4	Would it be possible to explore the extension of the option to include an abbreviated data package not only for the final DP content but also for the DS final manufacturer or even the manufacturing system, where technical justification based on similarities with other studies can be provided? RATIONAL: If technically feasible, this approach could offer greater flexibility and ensure alignment across different manufacturing steps, fostering consistency and efficiency in the overall process.	
ELSIE	166	170	3.4	"For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge,(e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6) " • The guidline refers to an established extractables/leachables correlation; however, this can only be demonstrated when leachables are detected above the AET. In many cases, especially with aqueous drug products, there may be no leachables present to correlate. • Based on our experience, agencies expect leachables data to be provided for the actual finished product.	• We recommend text change: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge,(e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6) "

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	166	172	3.4	This is an example for an abbreviated data package: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5 Also provide a definition/explanation in the glossary of what is included in a leachables to extractables correlation; such correlation should allow for general comparisons, qualitative comparisons where feasible.
EUCOPE	166	174	3.4	The guideline allows for consideration of an abbreviated data package for a packaging or component system. Could you provide illustrative case studies? One of the criteria for applying an abbreviated data package is the availability of prior knowledge on a similar drug product. How should this similarity be demonstrated? Can we propose simulation studies?	
IPAC-RS	166	172	3.4	"For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6). Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification." Please clarify what it is meant by abbreviated data package	Provide clearer explanation of "abbreviated data package"
IPAC-RS	166	174	3.4	COMMENT: Would it be possible to explore the extension of the option to include an abbreviated data package not only for the final drug product content but also for the drug substance final manufacturer or even the manufacturing system, where technical justification based on similarities with other studies can be provided? RATIONAL: If technically feasible, this approach could offer greater flexibility and ensure alignment across different manufacturing steps, fostering consistency and efficiency in the overall process.	
IPAC-RS	166	172	3.4	This is an example for an abbreviated data package: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
Medicines for Europe	166	179	3.4	Can an abbreviated data package be submitted for lyophilized or liquid injection products that have similar organic composition and pH profiles as it has not been clearly specified in examples tabulated in Table A.1.2.	Give example for "prior knowledge" and parameters required to justify similarity of products (pH, …) in training materials
Medicines for Europe	166	179	3.4	The draft guideline introduces an option to submit an abbreviated data package for packaging components in E&L assessments, including the possibility to omit leachable data. While the intent to streamline documentation is acknowledged, this approach raises significant concerns regarding regulatory acceptability. Based on prior regulatory experience, even in cases where extractables are fully identified and evaluated, or no substances above the AET are detected, authorities consistently expect leachable studies to confirm the absence of harmful substances under actual product storage and use conditions. The guideline should clarify if leachable data remains a key component of all health authorities expectation in E&L assessments or clearly indicate regional differences.	
Qualimetrix SA	166	166	3.4	What are the minimum “contents” of an abbreviated data package? Can this be predefined?	
Sanjay Desai (Cipla Ltd.)	166	166	3.4	For the overall risk assessment and control of leachables, it is important to consider the risk of leachables contributed from delivery device in addition to manufacturing equipments and packaging components to ensure pharmaceutical quality and safety.	For a packaging component/system and delivery device component/system,

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	167	168	3.4	established extractable/leachable correlation	Perhaps rephrasing to leachables -> extractables correlation and add explanation on what the expectation for such a comparison would be
Qualimetrix SA	168	169	3.4	The notion of pharmaceutical product similarity is not well established. Which physicochemical properties should, at a minimum, be addressed?	
EfPIA	169	169	3.4	"No" and "few" extractables assume different risk levels. One can have only one compound above the AET that might be toxic, so the concept that just a few extractables might justify an abbreviated data package is not scientifically sound	Remove "few"
ELSIE	169	169	3.4	"No" and "few" extractables assume different risk levels. One can have only one compound above the AET that might be toxic, so the concept that just a few extractables might justify an abbreviated data package is not scientifically sound	Remove "few"
ELSIE	170	171	3.4	"Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification" • Rationale: Table A.1.2 provided examples where overall risk is low; however, further examples should be provided which have not be covered by other guidance documents.	• We recommend adding examples of overall mid- and high- risk, such as topic creams and patches, which have not been addressed in other guidance documents.
ELSIE	170	170	3.3	(such as Class 3 leachables; see section 6)	(such as Class 3 leachables, leachables with relatively low toxic potential; see section 6)
EfPIA	172	172		Here correlation is described as "extractable/leachable correlation" is is not in aligment with section 4.6 which describes "leachables to extractables correlation"	Change wording to "leachables to extratables correlation"
Medicines for Europe	172	172	3.4	Lines 161-163 imply that leachable studies might be skipped if no extractables are derived from manufacturing equipment above safety concern threshold (or AET). In consequence it is proposed that this should also apply to extractables originating from packaging materials or device components. Given that the origin of the extractable (potential leachable) shall not matter, and if safety can be concluded from extractables study for manufacturing equipment, the same shall be allowed for packaging and /or medical device components.	include "If extractables concentrations quantified are below the relevant acceptable safety level (see Section 6), then the safety concern associated with leachables risk is considered negligible." for packaging material and device components (e.g. under line 172). In addition the possibility to waive leachable testing under the mentioned conditions should be incorporated into the guideline. This is justified as an extractables profile without safety concern cannot trigger a safety concern derived from leachables in the finished product (refer to line 419-421 of the guideline "leachables are a subgroup of extractables").
ELSIE	173	174	3.4	• Editorial correction: "When an abbreviated data package is proposed, communications with relevant regional Regulatory Agency/Health Authority is recommended to align on approach"	• "When an abbreviated data package is proposed, communications with relevant regional Regulatory Agency/Health Authority is recommended to align on approach."
Maven E&L Ltd	175	179	Section 3.4	Suggestion to make this a risk based statement, "If a risk of chemical transformation via degradation or interaction of identified extractables has been identified as part of the risk assessment process then risk control should proposal should include relevant specific testing to evaluate and control this risk". This might include a leachable study to establish the leachable risk	If a risk of chemical transformation via degradation or interaction of identified extractables has been identified as part of the risk assessment process then risk control should proposal should include relevant specific testing to evaluate and control this risk". This might include a leachable study to establish the leachable risk
AESGP	175	176	3.4	Extractable transformation is mentioned - how to prove or argument that the compounds are not prone to degradation / reaction if these candidates are not fully literature studied?	Perhaps add: if compounds are known to degrade
AstraZeneca	175	179	Section 3.4	Suggestion to make this a risk based statement, "If a risk of chemical transformation via degradation or interaction of identified extractables has been identified as part of the risk assessment process then risk control should proposal should include relevant specific testing to evaluate and control this risk". This might include a leachable study to establish the leachable risk	If a risk of chemical transformation via degradation or interaction of identified extractables has been identified as part of the risk assessment process then risk control should proposal should include relevant specific testing to evaluate and control this risk". This might include a leachable study to establish the leachable risk

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	175	177	3.4	Identifying compounds that may degrade and pose a risk to patients is complex and, in some cases, may be impossible to predict due to unexpected reactions during sterilization, storage, and other conditions.	Remove "If identified extractables are likely to chemically transform into compounds with a higher safety risk (i.e. through chemical degradation and/or interaction with formulation components to generate compounds with a higher safety risk), or"
EfPIA	175	179	3.4	This paragraph states basically that Leachables testing for packaging component/system may be omitted in case the Extractables data package and related safety assessment is sufficiently strong - without indication of the route or drug type (e.g. Biologics). This is not very much aligned with HA who expect that applicants provide extractables/leachables correlation, and also not aligned with other regulatory chapters (e.g. for parenterals>.	When "all extractable peaks above the applicable AET can be adequately identified and/or quantified" , clarify whether/when a leachables study can be skipped
EfPIA	175	179	3.4	Simulations study could also be used (not only a leachable study) in case where not all the extractable peaks above AET can be adequately identified.	add simulation studies
EfPIA	175	179		Consistency with terminology for unknowns (if not all extractable peaks above the applicable AET can be adequately identified and/or quantified)	consistency of referencing unknowns throughout document
ELSIE	175	177	3.4	Identifying compounds that may degrade and pose a risk to patients is complex and, in some cases, may be impossible to predict due to unexpected reactions during sterilization, storage, and other conditions.	Remove "If identified extractables are likely to chemically transform into compounds with a higher safety risk (i.e. through chemical degradation and/or interaction with formulation components to generate compounds with a higher safety risk), or"
ELSIE	175	179	3.4	A leachables study is recommended in cases where degradation is expected or all extractable compounds cannot be adequately identified.	1. Please clarify that these two scenarios are not the only two scenarios where leachabes testing is expected. 2. Pleae clarify if any adaptations to the leachables testing strategy needed or expected when these specific scenarios arise.
ELSIE	175	179	3.4	"If identified extractables are likely to chemically transform into compounds with a higher safety risk (i.e. through chemical degradation and/or interaction with formulation components to generate compounds with a higher safety risk), or if not all extractable peaks above the applicable AET can be adequately identified and/or quantified, a leachable study should be conducted to address these concerns and demonstrate acceptability of the components" • Leachables should be prioritised over extractables testing as this is the final risk to the patient.	• We recommend the addition of sentence from the line 435- 436 before line 175: "it is the leachables profile that ultimately drives patient safety risk evaluations and component acceptability. If identified extractables are likely to chemically transform into compounds with a higher safety risk (i.e. through chemical degradation and/or interaction with formulation components to generate compounds with a higher safety risk), or if not all extractable peaks above the applicable AET can be adequately identified and/or quantified, a leachable study should be conducted to address these concerns and demonstrate acceptability of the components"
Ferring Pharmaceuticals	175	177	3.4	Should it be based on litterature search performed by a synthesis chemist or how should this be evaluated in practice? Some extractables have very complex chemical structure.	Suggest rephrasing
ELSIE	177	179	3.4	It is common to receive extraction profiles from the suppliers for which all of the extractables have not been identified. Suppliers use a broader range of solvents and lower reporting thresholds than an end user would in an effort to address all the potential applications. However, some of the solvents may not be relevant to a given drug product. In such cases, it seems wasteful to identify all of the extractables.	Recommend adding a caveat that the extractables in the clinically relevant solvents be identified.
Maven E&L Ltd	180	180	Section 3.4.1	Consider renaming this section to: Risk Based Considerations as they all seem depend on risk assessment process to identify. Perhaps include an introductory text such as, "The risk assessment conducted should guide the necessity for additional study which align to the identified risk"	Risk Based Considerations The risk assessment conducted should guide the necessity for additional study which align to the identified risk
AstraZeneca	180	180	Section 3.4.1	Consider renaming this section to: Risk Based Considerations as they all seem depend on risk assessment process to identify. Perhaps include an introductory text such as, "The risk assessment conducted should guide the necessity for additional study which align to the identified risk"	Risk Based Considerations The risk assessment conducted should guide the necessity for additional study which align to the identified risk

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	180	180	3.4.1	Probably don't need this heading as there is no 3.4.2. This might be more of a technicality on formatting. It makes sense to call special attention to it, though.	Remove heading and just provide the text.
ELSIE	180	197	3.4.1	•Components that are not in continuous contact with the drug formulation—such as MDI actuators, nasal applicators, and similar items—are generally considered to pose a low risk. As such, a higher threshold may be applied when developing an extractables profile to evaluate material-related risks. For components with transient contact, a threshold of 20 µg/g is recommended. Given their limited interaction with the drug product, routine extractables testing of these transient-contact components is typically not required unless a specific safety concern is identified during the extractables evaluation	
Medicines for Europe	180	180	3.4.1	chapter 3.4.1 - there is no subsequent subchapter 3.4.2	Adjust chapter numbering
Medicines for Europe	180	197	3.4.1	Consider alinging here with FDA Guidance for Chemical Characterization and ISO 10993-18 in which standardization around use of terms for compound identification are proposed.	Present and define terms: unknown, tentative, confident, confirme.
Merck KGaA, Darmstadt, Germany	180	187	3.4.1	Though indicated in line 40-43, Section 3.4.1 "Special Considerations" does not address the risk assessment for extractables and leachables for active pharmaceutical ingredients (APIs) that are precursors to non-biologic and non-biopharmaceutical DPs and/or are produced by chemical processes. This section considers "biological and biotechnology-derived products", and misses clarity for liquid or semi-liquid APIs, which are of biological or non-biotechnologically origin, such as chemically produced APIs. Suggest adding clarity in line by considering to use language in with USP <665>.	Suggest adding after line 187: Active pharmaceutical ingredients (APIs) that are the precursors to non-biologic and non-biotechnology derived products and/or are produced by chemical processes (as opposed to microbiological processes) are out of scope as these APIs are well-characterized substances that result from manufacturing processes that include multiple, highly effective purification processes.
Sartorius-Stedim Biotech GmbH	180	182	3.4.1.	The wording "cummulative" in this context is missleading. In the dynamic environment of manufacturing, the probability that PERLs may "accumulate" is almost zero. Downstream processing removes impurites, and the process flow dilutes impurites. Please reconsider the request for the assessment of "accumulation" for processes, where they obviously cannot occur.	Whenever using the wording of "cumulation" please consider whether it is correct: For CCS it must read: "accumulation until phase equilibrium is reached"; for SU storage devices one can use this phrasing as well, but not for devcies which are used in a dynamic process environment, where the liquid flow is continously diluting the PERLs.
Maven E&L Ltd	181	182	Section 3.4.1	Again, consider rewriting in format of risk statement, " The risk of a common leachable from multiple sources should be considered during the conducted risk assessment. The magnitude of the risk being linked to both nature of the leachable considered and any mitigating factors such as a purge point which reduces the risk"	The risk of a common leachable from multiple sources should be considered during the conducted risk assessment. The magnitude of the risk being linked to both nature of the leachable considered and any mitigating factors such as a purge point which reduces the risk"
AstraZeneca	181	182	Section 3.4.1	Again, consider rewriting in format of risk statement, " The risk of a common leachable from multiple sources should be considered during the conducted risk assessment. The magnitude of the risk being linked to both nature of the leachable considered and any mitigating factors such as a purge point which reduces the risk"	The risk of a common leachable from multiple sources should be considered during the conducted risk assessment. The magnitude of the risk being linked to both nature of the leachable considered and any mitigating factors such as a purge point which reduces the risk"
AstraZeneca	181	182	Section 3.4.1	Suggestion to include options beyond the cumulative leachable risk assessment.	Adding an option to test finished products.
BioPhorum	181		3.4.1	The statement "multiple manufacturing components … cumulative leachables risk should be assessed", when applied to all single-use/multi-use materials that touch the bioprocess, could lead to a very onerous expectation that is costly and difficult to achieve comprehensively. If scope or focus is limited to materials downstream of final clearance step, this becomes more practically achievable.	Augment wording to keep focus on final container or bioprocessing steps downstream of final clearance step. (add) "…should be assessed for components downstream of the final clearance step"
Bio-Process Systems Alliance	181	182	3.4.1	The contribution from multiple manufacturing components may not be cumulative due to equilibrium effects. No mention of physical chemistry is given here.	Revise to introduce equilibrium effects in this section.
EfPIA	181	182	3.4.1	In cases where manufacturing components are made from different materials but release the same extractables, should the cumulative effect not be considered? Why is the focus placed solely on components made from the same materials?	Reword to "When multiple manufacturing components, the cumulative leachables risk should be assessed."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	181	182	3.4.1	Safety assessments itself are conservative. Additional conservatism from cumulative exposure is not needed.	
EfPIA	181	182	3.4.1	The cumulative leachables risk assessment cannot be made in a manufacturing line based on the "summation" of all extractables determined for each of the manufacturing components (based on 3.4 guidance) without overestimating the global risk, since it is known (as also acknowledged in the ICH document) that extractables that actually leach may be adsorbed or flushed/reduced over manufacturing steps. This means that the cumulative effect can concretely only be assessed through leachables testing...which contradicts the guidance provided earlier	Skip the cumulative assessment - or provide guidance on how to assess it via extractables testing.
EfPIA	181	182	3.4.1 Special Considerations	Cumulative leachable risk is proposed mainly for manufacturing components constructed of similar materials. This is not in line with USP 1665 definition for cumulative effects, which more of consider entire process under cumulative.	Please clarify and align cumulative effect with USP content. Cumulative effect is also required when Table A.1.1 Scenario 3 and 4 are considered.
EfPIA	181	182	3.4.1	When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should be assessed. How in practice? overall assessment? based on extractables data? only after relevant purification?	
EfPIA	181	182	3.4.1	Testing the finished product should mitigate all cumulative leachables risk, as this is what the patient is ultimately exposed to.	Proposed wording: "When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk ~~should~~ may be assessed. Otherwise, leachables testing of the finished product will confidently evaluate all cumulative leachables risk."
EfPIA	181	189	3.4.1	These lines are choppy when read together. Can the statements be organized to read better as a single paragraph?	Example: "When evaluating the effectiveness of the risk control strategy, special cases may arise that merit further consideration. In general, the quality risk assessment and derived control strategies, when appropriate, should encompass potential leachables from containers used to store liquid or semi-solid drug substances. Drug substance may be stored in the frozen state, and, while minimal leaching occurs in the frozen state, the potential for leaching from these storage components/systems should be evaluated before and after thawing. Furthermore, the cumulative leachable risk should be assessed, especially when multiple manufacturing components having the same materials are used. In addition, for biological and biotechnology-derived products risk identification and mitigation may also include: "
EFPIA	181	182	3.4.1	The guideline states, "When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should be assessed." Comment: Testing the finished product should mitigate all cumulative leachables risk, as this is what the patient is ultimately exposed to. Cumulative effects are of interest for extractables for which dedicated studies are performed.	
ELSIE	181	182	3.4.1	In cases where manufacturing components are made from different materials but release the same extractables, should the cumulative effect not be considered? Why is the focus placed solely on components made from the same materials?	Reword to "When multiple manufacturing components, the cumulative leachables risk should be assessed."
ELSIE	181	182	3.4.1	"When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should be assessed" • Testing the finished product should mitigate all cumulative leachables risk, as this is what the patient is ultimately exposed to. • The assessment of cummulative leachables risk should also apply to packaging systems.	• Leachables risk associated with manufacturing components can be adequately addressed through finished product testing, since the product has already been exposed to all elements of the manufacturing process. Accordinglly, we propose completion of sentence: "When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should may be assessed through finished product testing."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	181	182	3.4.1 Special considerations	Cumulative leachable risk is proposed mainly for manufacturing components constructed of similar materials. This is not in line with USP 1665 definition for cumulative effects, which more of consider entire process under cumulative.	Please clarify and align cumulative effect with USP content. Cumulative effect is also required when Table A.1.1 Scenario 3 and 4 are considered.
Ferring Pharmaceuticals	181	182	3.4.1	Some companies are using the platform approach (e.g 1 type of multilayer film for SU bags, standardized connectors..). This should be encouraged to simplify the cumulative evaluation	Add a sentence to encourage the move to standardized materials and platform approach.
AESGP	182	182	3.4.1	Cumulative effects are mentioned	It would be helpful to add what would be needed: rationales for downstream clearances sufficient or intermediate testing?
AESGP	182	182	3.4.1	Here, a test before and one after freezing is mentioned but nor what tests	Is an extractables test needed for this F/T test?
Medicines for Europe	182	189	3.4.1	Language is unclear:	An assessment of risk of cumulative leachables should be performed when multiple manufacturing components (e.g., processing aids or contact materials) of same or similar material are utilized. The assessment should also encompass consider potential leachables from a container closure and packaging materials used to store a liquid or semi-solid drug substance.
EfPIA	183	185	3.4.1	If the Container Closure System for the Drug Substance is in scope, this should be clarified in the scope section (currently only drug products and CGT products are in scope)	
ELSIE	183	185	3.4.1	Unclear what is the goal of this paragraph in the context of a special consideration	Remove entire paragraph
ELSIE	183	185	3.4.1	"Quality risk assessment and derived control strategies, when appropriate, should also encompass potential leachables from a container used to store a liquid or semi-solid drug substance" • Testing the finished product should mitigate all leachables risk from drug product storage. • Rationale: Due to the high product-to-surface area ratio in storage containers, which results in a lower Analytical Evaluation Threshold (AET), the leachables risk is considered minimal and may be sufficiently mitigated by food contact compliance statements.	• Leachables risk from manufacturing components and bulk storage can be effectively addressed through finished product testing, since the product has already been exposed to all relevant materials and conditions during the manufacturing process. • We recommend that the guidline highlight that 'semi-solid drug substances' tend to have lower leachables due to increased viscosity and higher molecular weight.
GUERBET	183	185	3.4.1	Procise that in the case where solid drug substance is stored in a packaging, the quality risk assessment and derived control straztegies do not need to encompass the potential leachables from packaging	Add this sentence for clarification
Merck KGaA, Darmstadt, Germany	183	185	3.4.1	Minor addition to clarify the workflow to evaluate potential leachables of an API storage container as described in Figure 4, Annex 1 (Workflow E&L assessment for manufacturing components/systems).	"Quality risk assessment and derived control strategies, when appropriate, should also encompass potential leachables from a container used to store a liquid or semi-solid drug substance as described in Annex 1, Figure 4."
Ferring Pharmaceuticals	184	185	3.4.1	If DS containers should full fill this guideline, then propose to include a sentence in the 'scope' and/or 'introduction' section. Should 'Risk based' approach be included in the sentence e.g. depending on storage time and temperature?	
EfPIA	186	187	3.4.1	There is negligible possibility of leaching for a frozen solution. This should be deemed to be of negligible risk in the guidance document warranting little attention. The duration of liquid exposure to the container is the only relevant concern..	Suggest rewording: Negligible leaching occurs in the frozen state; therefore, leaching of frozen material presents very low risk and does not warrant further consideration. However, the time spent in a liquid state before freezing and after thawing should be considered appropriately (and is likely to be of short duration with respect to the final DP shelf-life).

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	186	187	3.4.1	Is the text recommending to perform E&L before freezing the container and after thawing? If it is minimal, why perfrom such evaluation? Also, potential mislignement with Table A.1.2	Rewrite it for clarification purposes
EfPIA	186	187	3.4.1	Why evaluating the leaching before freezing ? From a safety point of view what counts is what has leached after thawing. Making a requirement to test also before freezing is likely to be relevant from scientific/academic perspective (and hence more relevant for materials suppliers/manufacturers) however not from safety point of view (and hence not relevant for drug manufacturers. This is unnecessary and trigger testing that cannot bring value to patient.	Proposed wording/change: "The potential for leaching from storage components/systems stored under the frozen state should be evaluated over thawing, i.e. when the drug is in a semi-solid or liquid form".
EfPIA	186	187	3.4.1	Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing	add 'During' and after thawing
ELSIE	186	187	3.4.1	Is the text recommending to perform E&L before freezing the container and after thawing? If it is minimal, why perfrom such evaluation? Also, potential mislignement with Table A.1.2	Rewrite it for clarification purposes
ELSIE	186	187	3.4	"Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing." . Is possible to have the same consideration for Freeze dried product or powder after reconstitution with liquid ?	Have an additional clarification for reconstituted solid products.
ELSIE	186	187	3.4.1	"Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing." • Clarification is needed on whether this refers to performing an extractables study for the storage component/system, or assessing leachables in the formulation before freezing and after thawing. As currently written, it appears to suggest evaluating extractables before and after freezing, but this requires clarification. Additionally, it is important to understand and clarify how much additional risk—or in other words, what differences in the extractables profile—might be expected from the freeze–thaw cycle.	
IPAC-RS	186	187	3.4	"Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing." Is it possible to have the same consideration for freeze dried product or powder after reconstitution with liquid?	Have an additional clarification for reconstituted solid products.
Medicines for Europe	186	187	3.4.1	Does this mean that freeze thawed (or thermo-cycling) samples should be tested for leachables prior and after exposure? Can there be clarification as to if the freeze/thaw sample analysis is for any time the product is thermally treated, including shipping/distribution studies, or is this only referring to if a product is long term stored frozen and is warmed for final use?	
Bio-Process Systems Alliance	188	197	3.4.1	No discussion is given regarding the potential of PERLs to impact the manufacturing process, such as the cell culture, protein aggregation etc.	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device or revise this section to include mention of the potential of leachables to impact the manufacturing process.
Bio-Process Systems Alliance	188	189	3.4.1	Single use manufacturing systems are most widely used in biological processes. Making them not a "special" case but a core target audience for this Guidance. This Guidance does not provide appropriate level of Guidance for biological processes.	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device or revise to be supportive of biological processes.
EfPIA	188	194	3.4.1	Quality attributes of the drug product are regularly monitored throughout the manufacturing process and prior to release. It is hence unnecessary to check the impact of any individual E&L on those quality attributes.	Delete. State "the quality attributes of the drug product are routinely measured throughout the manufacturing process and prior to release."
ELSIE	188	194	3.4.1	Quality attributes of the drug product are regularly monitored throughout the manufacturing process and prior to release. It is hence unnecessary to check the impact of any individual E&L on those quality attributes.	Delete. State "the quality attributes of the drug product are routinely measured throughout the manufacturing process and prior to release." As noted in the general comments above, this area seems to reqest E&L evaluations without considering the quality risk management approaches that should be done, rather than using E&L testing to test quality into products. The guideline should make reference to the ICH quality management guidelines. The comment in the next row below, is similarly related to this issue.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	188	194	3.4.1	"In addition, for biological and biotechnology-derived products risk identification and mitigation may also include: -- Evaluation of the potential interactions between reactive leachables and formulation components that may lead to potentially adverse impact on product quality, safety, and/or efficacy. If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered (such as denaturation, aggregation or degradation). " • Clarification is needed on whether this aspect is already addressed by drug product stability testing. • The examples given in the brackets are not necessarily mechanism of chemical modification: e.g. aggregation could be a physical change. Further, not all product-leachable interactions are chemical modification in nature. Suggest removing "reactive", or replace with something like "incompatible".	• "If impacts to critical quality attributes of the product by known incompatible reactive leachables are identified, potential mechanisms of chemical modification should be considered (such as denaturation, aggregation or degradation). " Clarify if already addressed by drug product stability testing
AESGP	190	194	3.4.1	Potential interactions between leachables and formulation are mentioned. Besides three common protein-based tests, no further information is provided	E.g. investigating protein degradation it will be challenging to verify which extend of change is significant. Can hints be proposed when a interaction is supposed to be critical? Or if not, in case all other protein-related API QC tests are without e.g. OOS, can it be assumed that there are not significant interactions to be expected?
Octapharma	190	194	3.4.1	Quality attributes of the drug product are regularly monitored throughout the manufacturing process and prior to release. It is hence unnecessary to check the impact of any individual E&L on those quality attributes.	Delete. State "the quality attribute of the drug product is routinely measured throughout the manufacturing process and prior to release."
Rentschler Biopharma SE	190	194	3.4.1	Evaluation of potential interactions between reactive leachables and formulation components is stipulated. If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered. Comment: Predicition of potential interactions of leachables with complex biomolecules and mechanisms of chemical modification is considered difficult.	Provision of a list of reactive leachables / substance classes may be helpful.
Medicines for Europe	192	202	3.4.1	Some of the risks are not only inherent in biologically derived products. Suggest to modify language as shown right:	In addition, risk identification and mitigation may also include: •Evaluation of the potential interactions between reactive leachables and formulation components that may lead to potentially adverse impact on product quality, safety, and/or efficacy. If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered. For small molecule components, examples include formation of adducts or degradation products. In particular, for biological and biotechnology derived products, such mechanisms include denaturation, aggregation or degradation. •For manufacturing of drug substance, leachables may be removed during the last purification step. Therefore, the quality risk assessment will typically focus on subsequent manufacturing processes, including packaging and storage.
Maven E&L Ltd	195	197	Section 3.4.1	Is "quality risk assessment" really the best term? I would suggest the term "leachable risk management" is used throughout. This term leachable risk management being added to the glossary (section 7), where it can describe the risk assessment process in more detail	leachable risk management
AstraZeneca	195	197	Section 3.4.1	Is "quality risk assessment" really the best term? I would suggest the term "leachable risk management" is used throughout. This term leachable risk management being added to the glossary (section 7), where it can describe the risk assessment process in more detail	leachable risk management
Axplora - Novasep	195	197	1	Is it possible to further develop the section relating to the medicinal substance? Does the paragraph mean that the study of extractables and leachables does not apply to the manufacturing steps of the medicinal substance but only to the manufacturing steps of the medicinal product?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Bio-Process Systems Alliance	195	197	3.4.1	This statement further discusses leachable removal via downstream steps, and puts the focus on "subsequent manufacturing processes" This is unclear and either limits the scope of this Guidance to steps downstream of the last leachables clearance step. This is ignorant of most bioprocesses having multiple clearance steps with potentially varying degrees of efficacy for PERL removal and the changing equilibrium conditions throughout the process.	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device only or revise Guidance to include explicit guidance on scaling via surface area or equilibrium and guidance on the estimation of leachables removal capacity of downstream steps.
EfPIA	195	196	3.4.1	The sentence is too vague - "may be removed" --> does the manufacturer need to provide evidence or is literature sufficient to argue that removal of leachables is widely applicable and that the risk to not include in the quality risk a assessment the steps prior the last purification? and not really aligned with USP<665> considerations -"will typically focus on subsequent processes" --> does this mean that this practice can be considered as standard ?	Provide clarity or delete sentence
EfPIA	195	198	3.5	This makes clear that small molecule drug substance manufacture is usually out of scope	This should also be made clearer in the earlier scope section
Sartorius-Stedim Biotech GmbH	195	197	3.4.1.	This is too simple. PERLs are removed during the entire downstream process not only in the last steps. As mentioned above (line 20) there are potential sources of PERLs in the last production steps, which require adequate assessment; e.g., bag systems and mixing systems for excipient formulations and filters for the last filtration step.	
AESGP	196	197	3.4.1	DS subsequent manufacturing means DP processing	Can this be rephrased to something like: … quality risk assessment will typically focus on DP and not DS manufacturing processes
BioPhorum	198	227	3.5	guideline is unclear about what needs to be included in regulatory filings, suggest that requirements for extractables and leachables should be distinctly stated.	requirements for extractables and leachables should be distinctly stated
BioPhorum	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Propose to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA
BioPhorum	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of assessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
BioPhorum	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focussed on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements
BioPhorum	198	227	3.5	extractables studies require a description of analytical methods, while leachables studies need full validation, propose that the guideline should clearly differentiate these requirements.	propose that the guideline should clearly differentiate these requirements.
EfPIA	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Prpopse to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA
EfPIA	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of asessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
EfPIA	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focussed on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	198	227	3.5	• There is no discussion regarding the control strategy - specifically, when it is needed and when it is required.	• We recommend reference to ICH M7 regarding genotoxic impurities indicates that routine testing is not required when levels are below 30% of the PDE
ELSIE	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Propose to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA
ELSIE	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of asessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
ELSIE	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focused on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements
IPAC-RS	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Propose to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA
IPAC-RS	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of asessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
IPAC-RS	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focused on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements
Maven E&L Ltd	199	211	Section 3.5	Suggestion that sentence which starts on 207, "The quality risk assessment…" is moved to start of 199 and rewritten to form the starting sentence, replacing 199 to 201, "Leachable risk management can be used in registration applications to form the justification for extractable / leachable studies which have been conducted and provide the structure for any risk control strategy for leachables". Output such as study reports, and safety assessment of substance above a set AET are then incorporated in the overall process of leachable risk management to demonstrate low risk from leachables has been achieved	Leachable risk management can be used in registration applications to form the justification for extractable / leachable studies which have been conducted and provide the structure for any risk control strategy for leachables". Output such as study reports, and safety assessment of substance above a set AET are then incorporated in the overall process of leachable risk management to demonstrate low risk from leachables has been achieved
AESGP	199	201	3.5 Documentation and Compliance	Include a clear statement that shows in some scenarios, studies are not warrented.	Registration applications should include the justification for 'the approach taken for' either the extractable/leachable studies conducted, the associated study reports, the safety assessment of substances above the AET and any requisite risk control strategy 'OR a justification of why studies are not warranted'
AstraZeneca	199	211	Section 3.5	Suggestion that sentence which starts on 207, "The quality risk assessment…" is moved to start of 199 and rewritten to form the starting sentence, replacing 199 to 201, "Leachable risk management can be used in registration applications to form the justification for extractable / leachable studies which have been conducted and provide the structure for any risk control strategy for leachables". Output such as study reports, and safety assessment of substance above a set AET are then incorporated in the overall process of leachable risk management to demonstrate low risk from leachables has been achieved	Leachable risk management can be used in registration applications to form the justification for extractable / leachable studies which have been conducted and provide the structure for any risk control strategy for leachables". Output such as study reports, and safety assessment of substance above a set AET are then incorporated in the overall process of leachable risk management to demonstrate low risk from leachables has been achieved
EfPIA	199	201	3.5	extractable/leachable	E&L

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	199	200	3.5	It is not clear if the expectation is to submit all extractable reports obtained from the vendors or just the studies performed by the sponsor or risk assessment report that will include approach and rationale	Add clarity on type of report that should be submitted for registration
EfPIA	199	227	3.5 Documentation and Compliance	The guidance provides submission requirements for registration applications. While the guidance document under Section 2 Scope specifies this guidance is not applicable for clinical programs.	It would be helpful to specifically (or generally) understand requirements for evaluations for clinical programs as the risks may be similar, even if the amount of data submitted are not the same.
EfPIA	199	201	3.5	ICH step2 mentions "Registration applications should include the justification for the extractable/leachable studies conducted, the associated study reports, the safety assessment of substances above the AET and any requisite risk control strategy" it means that sponsor is requested to include justification of overall control strategy/risk assessment/safety assessment for extractable/leachables. Study report is not directly required. is our undestanding correct?	N/A
ELSIE	199	201	3.5	Is the expectation being set that all asscoaiated study reports are presented for all manufacturing components and CCS materials studied. Some of these may be sourced from suppliers.	Replace "the associated study reports" with "details of the extractable/leachable studies conducted"
ELSIE	199	201	3.5	extractable/leachable	E&L
Ferring Pharmaceuticals	199	201	3.5	Associated study reports' are - for extractable studies - typically 50-100 pg for each component. (Screening) leachable study reports are also typically 50-100 pg for each time point for each storage condition.	Propose to align the wording with the requirements set out in the proposed ICH M4Q(R2) in which summary result instead of the associated study reports is proposed.
IPAC-RS	199	201	3.5	Is the expectation being set that all associated study reports are presented for all manufacturing components and CCS materials studied. Some of these may be sourced from suppliers.	Replace "the associated study reports" with "details of the extractable/leachable studies conducted"
Sartorius-Stedim Biotech GmbH	199	201	3.5	Please consider that justification of extractables conditions are required for CCS tests but not for SUS, where standardized methods are applied (e.g. USP 665). We see no reason and advantage in justifiing procedures which are defined in pharmacopoias.	
AstraZeneca	200	200	Section 3.5	The inclusion of study reports in the registration applications is considered onerous when other ICH guidance documents state that study results can be provided in CTD sections instead of internal reports (Q11, Q8)	Revise to state: Registration applications should include justification for the extractable/leachable studies conducted, the results of these studies, the safety assessment of substances above the AET and any requisite risk control strategy.
EfPIA	200	203	3	Registration applications should include the justification for the extractable/leachable studies conducted, a summary of the associated studies, the safety assessment of substances above the AET and any requisite risk control strategy.	suggest not to submit the associated study reports but keep current practice for regulatory documents and submit a summary of the relevant conducted studies.
EfPIA	200	200	3.5	Don't like use of AET here as this seems more a TDI compared against SCT process. AET is more applicable to the analytical space rathen than the tox space. I think SCT or similar is a better term. But a change in terminology here would also require a more extensive review of AET, SCT, TDI, etc. thorughout the document to ensure uses are aligned.	Suggest using phrasing such as "TDI above the SCT" instead of AET.
Ferring Pharmaceuticals	200	200	3.5	Substances above the AET'	Is 'substances' the right term? Should it be 'compounds' (organic) as used in previous sections?
IPAC-RS	200	200	3.5	This should be the SCT, not the AET. The AET defines compounds to be identified so that they can be accurately quantified and assessed against the SCT. See lines 488-490	the safety assessment of substances above the ~~AET~~ SCT
EfPIA	201	203	3.5	Since the DP manufacturing process may involve numerous single-use (SU) components (e.g., connectors, tubing), it can be challenging to include all extractables data in the filing submission. It is recommended to revise the statement to focus only on components with high risk, prolonged contact time, or storage interactions.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	203	211	3.5 Documentation and Compliance	Currently E and L studies are typically conducted under 'accelerated' conditions e.g. 40C for 8 weeks. Where there are no findings under accelerated conditions it should not be necessary to also conduct E+L as part of routine stability testing	Add, 'In the event that substances are above the AET', adequate leachable data should be provided to address safety and quality concerns throughout the drug product's shelf life.
EfPIA	203	204	3.5	"Adequate leachables": what does it mean ?	
EfPIA	203	203	3.5	Comment: the wording "filing submissions" sounds strange. Rationale: Both words cover the same information.	Recommend to use the same wording as used in ICH M4Q.
EfPIA	203	204	3.5	Although the use of extractables-only assessments are prevalent leading up to this line, it then states, "Adequate leachable data should be provided . . ." This should also include the extractables option.	Modify to: " . . as applicable. Adequate extractable or leachable data should be . . ."
Ferring Pharmaceuticals	203	204	3.5	Leachable data - is it data obtain as described in section 4.4 and in line 317-319 (section 4.3)? Should a leachable study only be performed, if extractables are above AET?	It should be clarified which leachable data is referred to. It could for instance be data from a screening leachable study i.e. a study where the same analytical screening techniques are used as in the extractable studies. In comparison a 'leachable study' is, where a specific method is developed to monitor and quantify a specific extractable (compound above AET).
BioPhorum	205	207	3.5	If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.
EfPIA	205	207	3.5	If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.
EfPIA	205	207	3.5	regarding leachables data, are 3 different product batches required? Is it also required to include three different batch of materials?	
EfPIA	205	207	3.5	Suggest making regulatory consultation "recommended" rather than mandatory when data is incomplete.	Reword to: "It is recommended to seek prior concurrence..." Align with Table A.1.2 footnote. Proposed wording: It is generally acceptable to submit leachable study results aligned with available stability data, with the provision to submit additional data post-authorization. It is recommended to seek ~~subject to~~ prior concurrence with the relevant regional regulatory authority.
ELSIE	205	207	3.5	The current ICH text could be interpreted to mean that whenever complete studies are not available, prior agreement with the regulatory authority is always required. However, in practice, prior consultation does not always take place, and in some cases, companies may take the risk of submitting data up to a certain time point (TP) and agree on the commitment to provide updated result at later stage. Could we propose a rewording to indicate that consultation with authorities is "recommended" rather than mandatory? This approach would also align with the footnote to Table A.1.2 on lines 337–338. RATIONALE: Adjusting the wording to suggest consultation as "recommended" rather than strictly required would provide greater flexibility while still encouraging engagement with regulatory authorities where appropriate. This approach reflects the balance between regulatory compliance and practical decision-making in situations where data may be incomplete. If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	"It is recommended to seek prior concurrence with the relevant regional regulatory authorities, where appropriate." Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.

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Ferring Pharmaceuticals	205	207	3.5	Is it the impact of E/L on the DS/DP e.g. increased pH, aggregation or what is meant?	Should be elaborated.
IPAC-RS	205	207	3.5	COMMENT: The current ICH text could be interpreted to mean that whenever complete studies are not available, prior agreement with the regulatory authority is always required. However, in practice, prior consultation does not always take place, and in some cases, companies may take the risk of submitting data up to a certain time point (TP) and agree on the commitment to provide updated result at later stage. Could we propose a rewording to indicate that consultation with authorities is "recommended" rather than mandatory? This approach would also align with the footnote to Table A.1.2 on lines 337–338. RATIONAL: Adjusting the wording to suggest consultation as "recommended" rather than strictly required would provide greater flexibility while still encouraging engagement with regulatory authorities where appropriate. This approach reflects the balance between regulatory compliance and practical decision-making in situations where data may be incomplete.	"It is recommended to seek prior concurrence with the relevant regional regulatory authorities, where appropriate."
IPAC-RS	205	207	3.5	If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.
Medicines for Europe	205	207	3.5	Does this mean that additional data must be submitted also after approval, or is it possible to only submit data in case of an unexpected result?	
EfPIA	207	210	3.5	The inclusion of multiuse materials in the guidance does not recognise that these are inherently low risk from an E&L perspective wrt single use materials. Single use materials present virginal surfaces to the product/process fluids every single batch. Reusable materials have a finite load of potential leachable load that is likely mitigated by cleaning activities prior to first use and their impact is aceraged out over the number of doses of products made during their use lifetime.	Omit multi-use components from the guidance
EfPIA	207	207	3.5	Quality risk assessment	Remove "quality"
ELSIE	207	207	3.5	Quality risk assessment	Remove "quality"
EfPIA	209	210	3.5	Delivery device components should be removed as should not be in scope	Remove
EFPIA	209	210		it should be clarified that the provisions are only applicable to drug-contacting delivery device components	Rationale: Clarification of scope
ELSIE	209	210	3.5	Delivery device components should be better defined and inclusion should be explained within the context/scope of the guideline	As per previous comments, please better define "drug device components"
AESGP	210	210	3.5 Documentation and Compliance	The text refers to semi-permeable packaging materials but never gives a definition for what constitutes semi-permeable packaging. This clarification would be helpful.	Add context and/or examples of semi-permeable packaging materials
Chiesi Farmaceutici	210	211	3.5	When semi-permeable packaging materials are mentioned, it is not direcly specified that the reference is to primary packaging/materials directly in contact with pharma products. It could be useful to specify the distinction between primary and secondary packaging, since it is not always clear. It could be useful to report such defitions also in the glossary.	It is suggested to modify the sentence as follows: "For semi-permeable materials in direct contact with pharma products, secondary packaging should also be evaluated as applicable". The use of the term "materials in direct contact" should be preferrable to "primary packaging", as in this way also components of delivery device can be included.
EfPIA	210	211	3.5	"Semi-permeable packaging" needs examples.	Add example, e.g., LDPE neubules. Proposed wording: For semi-permeable packaging materials, e.g., LDPE neubules, secondary packaging should also be evaluated as applicable.
ELSIE	210	211	3.5	"For semi-permeable packaging materials, secondary packaging should also be evaluated as applicable" • The guidline mentiones semi-permeable materials but does not provide any examples	Provide example(s) for semi-permeable packaging. • We recommend to include example, e.g., LDPE neubules.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	210	211	3.5	"For semi-permeable packaging materials, secondary packaging should also be evaluated as applicable." Is it possible to have the same consideration for Varnish and Ink that are part of the Primary packaging (when semi-permeable)	Update to add clarification about the varnish, ink or adhesive on semi-permabale primary packaging
IPAC-RS	210	211	3.5	"semi-permeable packaging". What is defined as semi-permeable packaing? Can expamples be provided?	Provide example for semi-permeable packaging.
IPAC-RS	210	211	3.5	"For semi-permeable packaging materials, secondary packaging should also be evaluated as applicable." is it possible to have the same consideration for Varnish and Ink that are part of the Primary packaging (when semi-permeable	Update to add clarification about the varnish, ink or adhesive on semi-permabale primary packaging
Laboratoires Théa	210	211	3.5	It is mentioned that the secondary packaging should be evaluated for semi-permeable packaging materials. -Do we also have to evaluate the tertiary packaging or it is not mandatory? -Does the secondary packaging have to be evaluated for both Europe and US markets (to my knowledge, the evaluation of the secondary packaging for Europe was not currently mandatory)?	
BioPhorum	212	216	3.5	Please clarify if a list of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated?	It is not clear which documentation shall be submitted. Propose to provide a bullet-point list instead of a narrative focussing on general expectations and to reference ICH M4Q for details.
BioPhorum	212	216	3.5	It is unclear how to report prior knowledge on extractables and leachables in the filing submission.	Propose to include guidance on reporting prior knowledge on extractables and leachables in the filing submission. Include recommendation to manage prior knowledge through establishment of curated E&L databases to streamline future analyses and reduce redundancy (current practices involve repetitive analysis without centralized knowledge management)
EfPIA	212	216	3.5	Please clarify if a list of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated?	It is not clear which documentation shall be submitted. Propose to provide a bullet-point list instead of a narrative focussing on general expectations and to reference ICH M4Q for details.
EfPIA	212	212	3.5	extractables and leachables studies	E&L studies
EfPIA	212	216	3.5	For leachables studies, the description of temperature, duration (like mentioned for extractables) should also be included	Add
EfPIA	212	216	3.5	Is this expectation for DP/container closure only for for DS as well? Most of the extractable data will be used from the supplier testing/documentation. Also, can a list be provided to state vendor data was leveraged for all single use components or where applicable?	Provide clarity
EFPIA	212	216	3.5	The guideline currently states, "A list of extractables and leachables studies conducted should be included along with an assessment report which will typically include analytical method and extraction condition selections along with justifications (solvents, temperature, duration, surface/volume ratio, etc.) for extractables studies and a description of the sample preparation and analytical procedures for leachables studies."	We recommend this requirement be reconsidered, as the details that are currently being requested seem to be excessive and to not seem to be aligned with current industry experience.
ELSIE	212	212	3.5	In discussion of method qualification, it would be helpful to have more specifics about precise expectations for method qualfication.	Add more specific expectations and provide reference citations.
ELSIE	212	212	3.5	extractables and leachables studies	E&L studies
ELSIE	212	220	3.5	Details being requested seem excessive and not aligned with current experience	Can this section be less explicit, so that it doesn't become a check list for regulatory reviewers
ELSIE	212	216	3.5	For leachables studies, the description of temperature, duration (like mentioned for extractables) should also be included	Add

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	212	216	3.5	Please clarify if a list of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated?	It is not clear which documentation shall be submitted. Propose to provide a bullet-point list instead of a narrative focussing on general expectations and to reference ICH M4Q for details.
Ferring Pharmaceuticals	212	216	3.5	Different guidance from what is described in line 199-203, where all reports should be submitted.	Propose alignment with the wording for line 199-201. For this section alignment with the wording in ICH M4Q(R2) is proposed.
IPAC-RS	212	220	3.5	Details being requested seem excessive and not aligned with current experience Revisions are suggested to make the text appropriate to all dosage types/formats and enable the applicant to define the appropriate details included within these documents Please clarify if a list of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated? Missing part of sentence - would be beneficial to mention to include the information in a regulatory filing (red text suggested in following column)	Consider revising this section to describe more clearly at a high level what is being recommended regarding documentation. For example, describe generally what is meant by "assessment report." We recommend that full reports are excessive and not needed. Summaries, with for example, tables should suffice. Additionally, consider referring to ICH M4Q for any details. Please also ensure that the examples provided in the parentheses do not become a check list for regulatory reviewers -- these can be shortened or put into context of what is meant by "assessment report." This approach will also help make the text more applicable to all dosage types/formats and provide more flexibility, e.g., the following may also be revised to read, "assessment report which will may typically include analytical method and extraction condition selections along with justifications (solvents, temperature, duration, surface/volume ratio, etc.) for extractables studies and a description of the sample preparation and analytical procedures for leachables studies Also, consider revising: "A list of extractables and leachables studies conducted should be included in a regulatory filing along with...."
AstraZeneca	213	213	Section 3.5	Same comment as Line 200 on the inclusion of study reports and consistency with other ICH guidance.	Revise to state: A list of extractables and leachable studies conducted andthe results of these studies should be included along with analytical method
EfPIA	214	214	3.5	surface/volume ratio,	surface area/volume ratio,
ELSIE	214	214	3.5	surface/volume ratio,	surface area/volume ratio,
Sartorius-Stedim Biotech GmbH	214	214	3.5	dito.	
Ferring Pharmaceuticals	215	216	3.5	Description of 'sample preparation and analytical procedures for leachable studies'. Assume that 'Sample preparation and analytical procedures' also should be included for extractable studies. Is this coorect? Analytical procedures = analytical techniques?	Please specify
EfPIA	216	218	3.5	Unclear if the parameters listed are required for extractables studies, leachables studies or both type of studies?	Clarification needed
EfPIA	216	218	3.5	See comments related to 361 and 367. ICH Q3E leverages a risk based strategy, thus the analytical methods should be suitable for their intended purpose, consistent with ICH Q3D.	
ELSIE	216	217	3.5	Semi-quantification needs to be included as well	Add
ELSIE	216	218	3.5	Unclear if the parameters listed are required for extractables studies, leachables studies or both type of studies?	Clarification needed

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	216	218	3.5	"In addition, the quantification procedure(s) should be described including the suitability of the procedures used for quantification (e.g., limit of detection (LOD), limit of quantification (LOQ), specificity, linearity, accuracy, and repeatability). " • It may not be necessary to provide linearity when assessing the method, considering that its only requirement is to detect at the AET for an extractables method	• We recommend following text change: "In addition, the qualification quantification procedure(s) should be described including the suitability of the procedures used for quantification (e.g., demonstration of mathod capability to detect levels at the AET within the approirate matrix, be it solovent or drug product matrix)."
Ferring Pharmaceuticals	216	217	3.5	Analytical screening techniques are used for extractable studies and for screening leachable studies. As the analytical techniques are screening techniques, it is not possible to evaluate and specify: specificity, linearity, accuracy and repeatability).	Does these lines describe both E&L studies? Extraction studies are performed using semi-quantitative calculations and screening techniques. Requirements listed here is for a specific and quantitative method and can only be obtained for a method specifically developed to detect a leachable and not for analytical methods used for semi-quantitative extractables and screening-leachable study. Would it be possible to rephrase and include this info?
IPAC-RS	216	218	3.5	Documentation and Compliance: This paragraph is speaking about quantification and not limit test. See suggested revision.	As the paragraph is speaking about quantification and not limit test, our recommendation will be to remove the reference to the LOD (Limit Of Detection). ICH-Q2(R2) requires quantitation limit for quantitative test and detection limit for limit test.
A3P	217	218	3.5	Some methods used are limit tests (and not quantitative methods)	Limit tests shoud be considered.
EfPIA	218	221	3.5	It is unclear how to report prior knowledge on extractables and leachables in the filing submission.	Propose to include guidance on reporting prior knowledge on extractables and leachables in the filing submission.
EfPIA	218	218	3.5	Precision should be used instead of repeatability to align with ICH Q2 since repeatability is one the parameters required to evalute precision (along with intermediate precision and reproducibility?	linearity, accuracy, and precision
EfPIA	218	220	3.5	Why would all peaks above the AET require reporting.	Suggest reported peaks only be for those above a TTC value.
EfPIA	218	221	3.5 Documentation and compliance	Requirement of listing all > AET E&L compounds in the filing submissions is not reasonable.	All > AET safety relevant extractables and/or leachables. When ICH Q3E is for protecting patient safety and product quality, only safety relevant data should be requested for compliance. More detailed data need to be available and shared then upon health authority request.
EfPIA	218	221	3.5	Full identification of extractables >AET may not be necessary if not observed as leachables.	Revise to focus on safety-relevant extractables/leachables. Suggest conditional reporting. Proposed wording: All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level if they are considered safety-relevant.
ELSIE	218	218	3.5	Precision should be used instead of repeatability to align with ICH Q2 since repeatability is one the parameters required to evalute precision (along with intermediate precision and reproducibility?	linearity, accuracy, and precision

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	218	221	3.5	"All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level. " Structure elucidation may not be necessary for all extractables above the AET if they are not observed in the leachable study. This could be a significant burden to the safety assessment team with minimal value added. • Providing full identification for extractables may not be necessary when the data is not representative of patient exposure and the compounds may never become leachables Requirement of listing all > AET E&L compounds in the filing submissions is not reasonable.	Revise to include "All leachables peaks…." • We recommend folowing text based on our rationale: "All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level. Where extractables data is used, as a justification to omit leachables data, chemical name, structure, CAS Registry Number (if available) and observed level, should be provided" All > AET safety relevant extractables and/or leachables. When ICH Q3E is for protecting patient safety and product quality, only safety relevant data should be requested for compliance. More detailed data would then be available and shared upon health authority request.
IPAC-RS	218	221	3.5	"All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level. " I do not feel that structure elucidation may be necessary for all extractables above the AET if they are not observed in the leachable study. This could be a significant burden to the safety assessment team with minimal value added.	Revise to include "All leachables peaks…."
Luye Pharma	218	221	3.5	"All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level." - Full identification of all extractables might be omitted, especially if those are not considered as leachables. - IUPAC name might be sufficient. Structure elucidation might be performed for leachables only.	All ~~extractables and~~ leachables peaks above the AET (see Section 5) should be included in the filing submission with IUPAC chemical name, ~~structure,~~ CAS Registry Number (if available) and observed level.
EfPIA	219	219	3.5	extractables and leachables	E&L
EfPIA	219	222	3.5	This section states that Extractables above AET do not need to be assessed for safety, or at least that their safety assessment is not a requirement for filings. This is not consistent with USP<665> which relies on Extractables testing and on the safety assessment of extractables.	Consider the inconsistency with USP<665> - which implies that safety assessment of extractabes is a must do.
EFPIA	219	221	3.5	The guideline currently states, "All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level."	We recommend this requirement be reconsidered, as the details that are currently being requested seem to be excessive and to not seem to be aligned with current industry experience.
ELSIE	219	219	3.5	extractables and leachables	E&L
ELSIE	219	221	3.5	What is the value of including all of the extractables above the AET in the filing? Many extractables, even if above the AET, are not very likely to show up as leachables, especially since some of the solvents used may not be relevant to a given drug product. Also, a single manufacturing process could utilize hundreds of polymeric components, resulting in an overwhelming amount of data for the reviewer to read through.	Recommend limiting to clinically relevant solvents and extractables data for container closure systems. For manufacturing components, include a risk scoring step and limit the data to those components ranking as medium or high risk.
Hikma	219	221	3.5	Extractables above the AET should be included in the filling submission with structure. For low AET high risk product, there could be 100 extractables. I think as long as the name is IUPAC name, do not need to include structures. Software like chemdraw or chemsketch can draw the structure based on name.	All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with IUPAC chemical name, CAS Registry Number (if available) and observed level.
IPAC-RS	219	219	3.5	This should be the SCT, not the AET. The AET defines compounds to be identified so that they can be accurately quantified and assessed against the SCT. See lines 488-490	extractables and leachables peaks above the ~~AET~~ SCT (see Section 5)
EfPIA	220	221	3.5	Should compounds be listed even if they are below AET?	Include "observed level if above AET"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	220	220	3.5	The draft guideline proposes the inclusion of chemical structures for all extractables and leachables with the intent to enhance traceability. The requirement as currently stated lacks practical clarity and may introduce unnecessary complexity. For instance: - Full identification of all extractables is not be necessary, especially if those are not considered as leachables. - Structure shall not be necessary for all substances, consequently the IUPAC name shall be sufficient. There are multiple approaches to specifying the structure of a compound, ranging from sum formulas to detailed molecular geometries including stereochemistry and spatial arrangements. This requirement may lead to inconsistent submissions and interpretation challenges. Structure shall not be necessary for all substances, thus the IUPAC name shall be sufficient. In practice, the use of a universally accepted CAS number provides a reliable and unique identifier for chemical substances. CAS numbers are widely recognized across regulatory agencies and scientific databases, and their use ensures unambiguous identification of extractables and leachables. Further structural clarification should only be necessary if a CAS number is not available.	Change text from "chemical name, structure, CAS Registry Number (if available) and observed level" to " IUPAC chemical name, CAS Registry Number (if available), structure (if no CAS available) and observed level"
ELSIE	221	222	3.5	"For leachables (or extractables when such testing is used for qualification), safety risk assessment as described in Section 6 should be included. " • Clarification is needed regarding the use and definition of "extractables testing for qualification"	• We recommend addition of "extractables testing for qualification" definition to glossary
EfPIA	223	223	3.5	quality risk assessment	risk assessment
EfPIA	223	224	3.5	It is not clear on what kind of correlation is expected. is the intent to have a table with potential leachables from extractable study and actual leachables detected?	Provide clarity
EfPIA	223	224	3.5	not clear what to do if correlation is not verified between leachables and extractables data	Require correlation matrix listing explained discrepancies and corrective plan for deviations.
EfPIA	223	225	3.5	Clarify when leachables-to-extractables correlation is needed, especially if leachables < PDE.	Recommend correlation only if leachables exceed AET and pose safety concern. Proposed wording: In addition to the quality risk assessment, a leachables to extractables correlation should be included in the registration application, as appropriate (refer to Section 4.6), particularly when leachables exceed AET and pose safety concern
ELSIE	223	223	3.5	quality risk assessment	risk assessment
ELSIE	223	225	3.5	"In addition to the quality risk assessment, a leachables to extractables correlation should be included in the registration application, as appropriate (refer to Section 4.6). Finally, the adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation" • In aqueous product, there are often no leachables to perform a correlation. • Clarification is needed on why performing pre-washing before and after implementation is considerd as mitigation measure. Question: To which extent is this correlation necessary if the leachable is < PDE but > AET?	• We recommend following text change: "In addition to the quality risk assessment, where leachables are demonstrated to exceed the AET and present a safety concern, a leachables to extractables correlation should be included in the registration application, as appropriate (refer to Section 4.6)." Could consider: Only for substances close to PDE - within a MoS of 1.5.
Medicines for Europe	223	224	3.5	Is it required to include the extractables and leachables (E&L) risk assessment and E&L correlation as part of the product registration dossier even when all observed leachables are below the Safety Concern Threshold (SCT) or compound-specific safety limits like PDE or ICH Q3C?	

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EFPIA Drug-MD ICH STG	224	227	3.5	The guideline currently states, "Finally, the adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation." Comment: The current text of the guideline is unclear as the whether this type of testing is only required as part of mitigation or if it is required for all extractable studies.	We recommend the guideline be updated to clarify whether this type of testing is only required as part of mitigation or if it is required for all extractable studies.
ELSIE	224	224	3.5	Is a SMILES code a suitable substitute for a structure, for a more concise document?	Please add the possibility of using SMILES codes.
Medicines for Europe	224	227	3.5	Pre-flushing: We usually use extractable data from supplier and perform pre-flushing as per filter supplier`s recommendation based on adsorption study. However, efficacy of volume is not tested. Will this be required in future? Does this mean that - for filter for example - extraction studies should be made with AND without preflushing to show the risk mitigation?	Clarify if efficacy of pre-flushing volume is to be tested, propose example in training materials
ELSIE	225	227	3.5	Does this mean we need extractable data of all before and after steps? (before and after washes, depyro vs. non dypro etc.) Is this type of testing only required as part of mitigation or for all extractable studies?	Recommend specifying that adequacy be demonstrated only for steps that claim mitigation of leachables
IPAC-RS	225	227	3.5	the text here is not applicable to all formats, so may be beneficial to indicate this rather then the reader be under the impression that this may be the case	adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation, where this is appropriate for the container closure system and dosage format.
Sartorius-Stedim Biotech GmbH	226	226	3.5	Mitigations can be demonstrated by generic studies or can be justified by prior knowledge, it is neither suitable nor neccessary to request for each and every mitigation a dedicated experimental study. For example in a case where the mitigation principle is dilution it makes even no sense to "qualify" it by a laboratory study (please note, dilution is a base principle commonly applied in validation studies, nobody would try to qualify a dilution with a measurement ... commonly the opposite is accedpted practice, dilution series are used to validate the measurements).	
Maven E&L Ltd	228	260	Section 3.5	What is missing is the concept of Planned vs Unplanned Change. I suggest that is added. There is also no mention of alignment to concepts given in ICH Q12 which breaks change into the two broad categories of Prior Approval (High risk change) and Notification (Moderate to low risk). It would be helpful to include that into this section.	
AESGP	228	241	3.6 Risk Review/LCM	Drug formulation changes for products already assessed as low to no risk, that involve minor changes in composition or introduction of a compendial excipient and/or replacement of one compendial packaging material by another, should not necessitate the conduct of further E+L studies.	241 ADD, 'Drug formulation changes for products already assessed as low to no risk, that involve minor changes in composition , should not necessitate the conduct of further E+L studies.'
AstraZeneca	228	260	Section 3.5	What is missing is the concept of Planned vs Unplanned Change. I suggest that is added. There is also no mention of alignment to concepts given in ICH Q12 which breaks change into the two broad categories of Prior Approval (High risk change) and Notification (Moderate to low risk). It would be helpful to include that into this section.	
BioPhorum	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5
EfPIA	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	228	231	3.5	We propose that data collected before implementation of mitigation measures not be required for submission in the registration application as the extractable/leachable profile of the proposed manufacturing process is more relevant.	We recommend that this sentence be deleted as the concept of implementing a mitigation measure is captured in lines 123 - 128.
ELSIE	228	228	3.6	Risk Review / Lifecyle Management	Risk Review / Lifecycle Management
ELSIE	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5
Ferring Pharmaceuticals	228	259	3.6	To make the list holistic, may be interesting to quote the ICHQ12 as reference	Add a sentence to refer to ICHQ12. To be added in Section 8.
IPAC-RS	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5
Laboratoires Théa	228	260	3.6	Is it acceptable to perform only a risk assessment and demonstrate that the change has no impact on the E&Ls study and/or safety of the final drug product and, therefore, an additional E&Ls study is not required?	
Medicines for Europe	228	260	3	In discussing lifecycle management (Section 3.6), the guideline outlines various changes that may necessitate re-evaluation of leachable profiles	Specific metrics or parameters that should trigger a re-evaluation after a change or a modification of manufacturing processes would be necessary to be deataile din the guideline
EfPIA	229	233	3.6	In terms of implementation, there was no timeline for when the concepts should be applied, and whether or not this is retroactive for all products out on the market. Retroactive applications are very challenging as all leachable studies and submissions were based on application of existing guidances.	Include statement with timeline for implementation, and this does not apply to products that are already on the market unless there is new information, or changes as mentiond in section 3.6.
EfPIA	230	230	3.6	Drug	drug product
ELSIE	230	230	3.6	Drug	drug product
Medicines for Europe	232	233	3.6	Will extractable studies be sufficient as "new studies" when all potential leachables are well below AET or PDE? Or are new leachable studies required?	A link to Figure 4 or Table A.1.1 would be helpful here.
EfPIA	234	236	3.6	What is an example of new information? The change of raw material or components for packaing material is relevant?	N/A
AstraZeneca	235	236	Section 3.6	the phrase cause for concern is again included in the draft guideline yet again as earlier in the docment there is no clarification as to what it means and what it encompasses. This is especially unclear given it also states new patient safety information may trigger a concern. Is this truly referring to patient safety information, triggered by adverse event reporting that is then linked to a leachable or the far more likely scenario that there is new pre-clinical safety data?	Consider revising this text
EfPIA	235	235	3.6	Reference is made to cause for concern, This is problematic term previously used in ICH M7 and resulted in considerable ambiquity surrounding it's definition	Provide clarity on what this actually means including examples
EfPIA	239	239	3.6	And/or delivery device components	remove "and/or delivery device components"
ELSIE	239	239	3.6	and/or delivery device components	Better define "delivery device components"
AESGP	242	248	3.6 Risk Review/LCM	See above	248 ADD, 'Changes to container closure, that involve minor changes involving changing one compendial packaging material by another, should not necessitate the conduct of further E+L studies.'

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	242	242	3.6	Delivery device	remove "delivery device"
EfPIA	242	246	3.6		Include examples of supplier driven changes? Mention quality agreements with suppliers? Consider in context of Training Material examples, and cross reference exisiting ICH guidance where appropriate
ELSIE	242	242	3.6	delivery device	Better define "delivery device components"
ELSIE	242	243	3.6	"Changes to container closure system, delivery device, or manufacturing components/systems that contact drug substance and/or drug product" • Clarification is needed on what the term "delivery device" refers to, and whether it is considered part of the packaging of the drug product.	• We recommend highlighting and clearly stating in this part of the guideline that clinical in-use delivery devices (such as syringes used for withdrawing the drug product from a vial) are excluded and are not considered part of the drug product packaging system.
Medicines for Europe	242	248	3.6	In this section the impact of changes of the materials on leachable and extractable including change of suppliers is evaluated	It is necessary to be specific in terms of supplier change, especially for formulations with low risk for L&E. It is suggested to have assessment only in case of material production process change but not necessary supplier change.
EfPIA	243	243	3.6	The term "Known" is not relevant in this context. While unknown changes cannot be directly assessed, they may still influence the leachables profile	Remove "known"
EFPIA Drug-MD ICH STG	243	244	3.6	The guideline currently states, "When there are known changes such as the 244 composition, supplier, manufacturing process, geometry or pretreatment of materials..." Comment: The geometry of a component is unlikely to have a significant impact on the extraction profile since, if that is the only change, the material of construction is the same.	We recommend the following revision in the text of the guideline, "When there are known changes such as the 244 composition, supplier, manufacturing process, ~~geometry~~ or pretreatment of materials..."
ELSIE	244	244	3.6	The geometry of a component is unlikely to have a significant impact on the extraction profile since, if that is the only change, the material of construction is the same.	Recommend replacing geometry in the list of changes to the container closure system with contact surface area.
ELSIE	246	248	3.6	"In addition, for some products there may be a potential for non-direct packaging components to contribute potential leachables to the drug product." • The risk to "some products" actually refers to semi-permeable products.	• We recommend change based on the rationale: "In addition, for semi-permeable products ~~some products~~ there may be a potential for non-direct packaging components to contribute potential leachables to the drug product."
AESGP	249	253	3.6 Risk Review/LCM	Changes in manufacture process should not apply to no to low risk processes that have undergone minor changes. Major changes should be evaluated on a case by case basis.	253 Changes in manufacture process should not apply to no to low risk processes that have undergone minor changes. Major changes should be evaluated on a case by case basis.
BioPhorum	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, outside previously tested worst-case conditions, may cause different leachables or different amounts of leachables from the existing formulation contact material."
EfPIA	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, outside previously tested worst-case conditions, may cause different leachables or different amounts of leachables from the existing formulation contact material."
EfPIA	249	251	3.4 Figure 4	The workflow for manufacturing components does not seem to allow for an initial risk assessment process that allows for a limited amount of extractables testing on a low risk component. The workflow appears to go from material/component selection directly to whether or not the extractables data meets the requirements listed in lines 199 - 205, which involve comprehensive analyitcal testing. This is particularly cumbersome for small surface area components that pose little risk to the drug product.	Include risk assessment box as second box from the top of the figure which can lead to no testing is isk is low

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	249	278	3.4 Figure 4, 3.5 and 3.6	It is related to the qualification of production components/systems. The ICH Q3E draft guideline for constituent review describes that the leachables risk for short contact time production components/systems is lower than the risk compared for long contact time CCS. For CCS it seems reasonably that both extractables and leachables documentations is needed. In the lower part of Figure 4, related to production components/systems, it is mentioned that if extractables are observed above the initial acceptance criteria (defined as the Analytical Evaluation Threshold (AET)) one needs to do a leachables study to document the actual concentrations of the compounds as leachables for safety evaluation.	If the extractables study data for a production component/system reflects a worst case situation compared the use scenario/leachables situation and if the extractable above the AET have been positively identified and quantified, we recommend to use a PDE evaluation of the extractable for safety evaluation, instead of going to a leachables study. This would reflect the lower leachables risk related to production components/systems compared to CCS.”
ELSIE	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, outside previously tested worst-case conditions, may cause different leachables or different amounts of leachables from the existing formulation contact material."
IPAC-RS	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, outside previously tested worst-case conditions, may cause different leachables or different amounts of leachables from the existing formulation contact material."
Medicines for Europe	249	253	3.6	"Changes to a manufacturing process": Section revised for clarity	Proposed changes text: Changes to process conditions may result in different leachables or different amounts of leachables to manifest in the otherwise unchanged formulation. For example, change in solvent system, duration, temperature, pressure, pH, cleaning/sterilization process, surface area/volume ratio, pre-operation preparation (e.g., flushing or filtration), amongst others can affect both the composition and amount of leachables.
Sartorius-Stedim Biotech GmbH	249	253	3.6.	Please refer to the comparator principle of USP 665 . It gives a suitable scheme, when a re-quilification of SUS extractbales is NOT neccessary.	
Ferring Pharmaceuticals	252	252	3.6	Would it make sense to mention 'post-sterilization'?	N/A
EfPIA	255	255	3.6	Is a reassessment of the risk required when the patient population changes? As SCTs/TTCs are generally protective of all populations and this will not change the exposure (unless the dose changes with the new population).	Proposed wording change: "....administration and patient population (i.e. geriatric/pediatric) (where population specific thresholds were originally applied)
AESGP	259	260	3.6 Risk Review/LCM	Is the example of a change in indication meant to suggest that more risk can be accepted with a condition that is lifethreatening in the shorter term, such as cancer versus arthritis? If so, this point is not explained but left for interpretation.	Explain in a little more detail this point.
EfPIA	259	260	3.6	This section is unclear. What constitutes a change in therapeutic indication? The example provided does not appear relevant. When such changes occur, additional factors—such as MDD—must be considered.	Remove or clarfy
EfPIA	259	260	3.6	this is the first reference to what is typically defined as an ICH S9 population	The scope in terms of ICH S9 should be far clearer, here and in the earlier scope
EfPIA	259	260	5	An example is provided to illustrate the "changes in indication that might affect patient benefit:risk" that might necessitate re-evaluation of the leachable profile during the lifecycle of the drug. This example may be too specific. Suggest to use a more general language and to mention the ICH S9 and M3 guidelines.	Changes in indication that might affect patient benefit:risk: e.g. when the preclinical evaluation conducted according to ICH S9 needs to be revisited and would fall under ICH M3.
ELSIE	259	260	3.6	"Changes in indication that might affect patient benefit:risk: e.g., oncology to rheumatological disorders" This section is unclear. What constitutes a change in therapeutic indication? The example provided does not appear relevant. When such changes occur, additional factors—such as MDD—must be considered.	Clarify

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	259	260	3.6	"Changes in indication": Section revised for clarity	Proposed changes text: Changes in indication that might affect patient benefit:risk calculus (e.g., repurposing an approved oncology medication for treatment of rheumatological disorders).
AESGP	261	261	4	Chapter Title should be aligned with Fig. 1, Risk Assessment 1.	Add "Chemical Characterisation"
EFPIA Drug-MD ICH STG	261	444	4 Chemical testing	Add a subsection within Section 3 (Risk Assessment) or Section 4 (Chemical Testing) discussing how the specific function of the device component (e.g., mechanical stress during injection, heat generation, specific flow paths) might influence the E&L profile differently than passive container closure systems.	Rationale: Device functions can create unique physical or chemical stresses not typical for standard packaging, potentially altering leachable profiles.
Bio-Process Systems Alliance	262	277	4.1	Risk Assessment Framework-The flowchart decision nodes (“Is adequate data available?”) are subjective.	Exemplify what constitutes “adequate data”—e.g., minimum number/type of extraction studies, acceptable analog data, or read-across justification—so that sponsors and assessors apply consistent criteria.
EFPIA Drug-MD ICH STG	262	290	4.1 Prior Knowledge, 4.2. Component Selection	Integrate explicit references, where appropriate, to relevant ISO standards, particularly ISO 10993-18 (Chemical Characterization) and ISO 14971 (Risk Management), within the text (e.g., in Sections 4.1 Prior Knowledge, 4.2 Component Selection, or 3.3 Risk Assessment). A brief mention that principles from ISO 10993-17 may inform the safety assessment of device constituents contributing to the final leachable profile could be useful.	Rationale: Integration provides clearer linkage for manufacturers familiar with device standards and acknowledges established practices for device material assessment.
Hikma	262	277	4.1	Is the list presented on this section expected to be fully covered as part of supplier qualification, so that an "abbreviated data package" can be used for submission of changes to packaging systems?	If this is the case, clarify the information to be filed to support changes can be abbreviated data packages, adjusted to the type of change based on prior knowledge. The list presented on the section is indicative and can be adjusted based on the application/change being proposed.
Maven E&L Ltd	263	277	Section 4.1	Given the title of this section is Chemical Testing and assessment it is not clear why some items in the bulleted list are here and not it the risk assessment section as prior knowledge which assists the leachable risk management assessment. For example, a biological reactivity test gives no insight into chemical test other than a failure in a biological test might prompt a chemical test. Therefore consider moving some or all of this section and this list into Section 3, It would then make it possible to clear differentiate role of chemical testing	
AESGP	263	265	4.1 Prior Knowledge	Prior knowledge may include gathering sufficient information to support the safety of the manufacturing process or the container closure system without additional extractables or leachables testing. This should be mentioned.	Prior knowledge may comprise information useful to obtain before performing chemical testing, including information available from a supplier and any relevant information with regard to other drug products and processes. 'Prior knowledge information may also provide sufficient reassurance to support the safety of the manufacturing process or the container closure system without additional extractables or leachables testing.'
AstraZeneca	263	277	Section 4.1	Given the title of this section is Chemical Testing and assessment it is not clear why some items in the bulleted list are here and not it the risk assessment section as prior knowledge which assists the leachable risk management assessment. For example, a biological reactivity test gives no insight into chemical test other than a failure in a biological test might prompt a chemical test. Therefore consider moving some or all of this section and this list into Section 3, It would then make it possible to clear differentiate role of chemical testing	
EFPIA Drug-MD ICH STG	263	265	4.1 Prior Knowledge	Section currently excludes Delivery devices. Suggest to add text to cover a material based approach (e.g. for delivery devices components or administration materials) or any other "prior knowledge" based approaches .	Align the content of this section with Figure 2 i.e. clarify whether other approaches than extractables and leachables testing are considered applicable depending on the level of risk.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
POLPHARMA	263	264	4	Chemical testing may not always be required e.g. for pharmacopeial materials used for solid oral dosage forms, therefore modification of the first sentence is proposed.	Prior knowledge may comprise information useful to obtain before performing chemical testing (if applicable, see section 3.2), including information….
ELSIE	265	424	4	Section 4 describes all types of studies i.e. - semi-quantitative, quantitative, leachables, simulated. When are these different study types required and when are they not?	Please clarify the expectations on when each type of test is required.
AESGP	266	270	4.1 Prior knowledge	Should add a reference to compendial grade pack mats	268 ADD food contact compliance 'and/or compendial grade'
EfPIA	266	267	4	Retrieving information related to plasticizers, processing aids, catalysts, antioxidants may be very complicated, as some may be covered by IP, especially for catalysts and processing aids.	A declaration from the Supplier of the plastic resin / the device constituent part / the standalone devices extended to the suitability of all the components could be sufficient.
EfPIA	266	267	4	Composition of polymer is typically IP and not shared with customers	remove expectation
EfPIA	266	267	4.1	The Bisphenol A is an important topic and the confirmation of its absence is a standard that should be indicated in the example provided.	"• composition (e.g., base polymer and copolymer, any known additives such as plasticizers, processing aids, catalysts, antioxidants, absence of specific chemical substances or chemical classess such as Bisphenol-A)"
EfPIA	272	272	4.1	The phrase "any available extractables studies" is redundant. As with other types of information listed, availability is a prerequisite and does not need to be explicitly stated.	extractables studies
POLPHARMA	272	273	4	We propose additional bullet point, where literature data maybe a valuable source of information.	available literature data for typical materials
EfPIA	276	277	4.1	Does this statement infers that ICH Q3E allows grandfathering regarding "prior use history"? A material/component that has a safe history of use is very relevant even if according to state of the art E&L techiques a favorable TRA cannot be generated with such material. This information is relevant but it should not be consiered in the prior knowledge list	Remove
BioPhorum	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	include recommendations on responsibilities
Bio-Process Systems Alliance	278	290	4.2	Analytical Evaluation Threshold (AET)-The inclusion and selection of an “analytical uncertainty factor” (UF) lack quantitative guidance.	Provide default UF ranges (e.g., 1.5–2.0) for common analytical situations or matrix types and specify when empirical validation of UF is expected. This would reduce arbitrary conservatism or under-correction.
Bio-Process Systems Alliance	278	290	4.2	Unknown Compounds Above AET-The draft implies all unknowns above AET must be identified and evaluated, which is often infeasible for complex polymeric systems.	Consider tiered identification expectations: e.g., semi-quantitative classification (high/medium/low concern) based on mass spectral features, abundance, and chemical plausibility, with targeted identification limited to higher-concern features.
EfPIA	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	
ELSIE	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	
IPAC-RS	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	
Medicines for Europe	278	278	4.2	Does the title "Component Selection" refer to "Packaging Components"?	An example would be illustrative and a clearer title advised.
Maven E&L Ltd	279	290	Section 4.2	Again, this section might be better as part of Section 3 as it discussing risk assessment . That would leave Section 4 to focus on technical aspects of E&L studies, which seems more appropriate.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	279	290	Section 4.2	Again, this section might be better as part of Section 3 as it discussing risk assessment . That would leave Section 4 to focus on technical aspects of E&L studies, which seems more appropriate.	
EfPIA	279	281	4.2	In the opening sentence, you state that a "pharmaceutical product manufacturer is responsible for establishing requirements in alignment with regulatory expectations for…". The extended list of responsibilities indicated, ranging from DP manufacturing to delivery of the DP, includes multiple actors, not just the "manufacturer". It is unclear whether the intent here is to imply that the final "marketing authorisation holder" is accountable ultimately for the E&L assessment or whether each actor in the supply chain is responsible for their own assessment of E&L.	Clarify who is intended by the mention of "pharmaceutical product manufacturer". Suggest replacing "pharmaceutical product manufacturer" with "drug product marketing authorization holder"; alternatively, do list in detail which sites should be held responsible, calling out their specific responsibility: "manufacturers", "packer", "labeler", "batch release qaulity unit", "distributor", and so on.
Luye Pharma	279	281	4.2	"A pharmaceutical product manufacturer is responsible…" - To our understanding it is the MAH which is responsible to only commercialise medicinal products that meet the criteria for quality, efficacy and safety.	"A pharmaceutical product manufacturer" shall be replaced by "The marketing authorisation holder", or, alternatively, the MAH shall be mentioned along with the manufacturer which shall support the MAH, as applicable.
Medicines for Europe	279	281	4.2	"A pharmaceutical product manufacturer is responsible…" - Ultimate responsibility for quality, efficacy and safety is with the marketing authorisation holder.	"A pharmaceutical product manufacturer" shall be replaced by "The marketing authorisation holder", or at least a joint responsibility shall be introduced mentioning the MAH with the support of the manufacturer.
Medicines for Europe	279	280		Is it the responsibility of the MAH which AET calculation method should be applied?	
EfPIA	280	281	4.2	The concept of "regulatory expectation" should not be included in an ICH guideline. The responsibility lies with the manufacturer, but without a defined legal framework or official documentation, it is unreasonable to expect manufacturers to anticipate what those expectations might be. Plus, the word "unique" is unnecessary.	Reword to "A pharmaceutical product manufacturer is responsible for establishing requirements for the manufacturing, packaging, storage, and delivery of a drug product safely and effectively to an intended patient population."
ELSIE	280	281	4.2	The concept of "regulatory expectation" should not be included in an ICH guideline. The responsibility lies with the manufacturer, but without a defined legal framework or official documentation, it is unreasonable to expect manufacturers to anticipate what those expectations might be. Plus, the word "unique" is unnecessary.	Reword to "A pharmaceutical product manufacturer is responsible for establishing requirements for the manufacturing, packaging, storage, and delivery of a drug product safely and effectively to an intended patient population."
AESGP	281	286	4.2	Contents overlap with Fig 2	Add cross-refererence to Fig. 2
BioPhorum	285	286	4.2	Non-lyophilized solids are described as an example for dosage forms which exhibit a minimal propensity for leaching. Also lyophilized solids show a low risk for interaction. Drug product is reconstituted and administered within a short time-period and the duration between filling and lyophilization is also short.	It is proposed to give further examples like lyophilized or frozen DPs.
EfPIA	285	286	4.2	Non-lyophilized solids are described as an example for dosage forms which exhibit a minimal propensity for leaching. Also lyophilized solids show a low risk for interaction. Drug product is reconstituted and administered within a short time-period and the duration between filling and lyophilization is also short.	It is proposed to give further examples like lyophized or frozen DPs.
ELSIE	285	286	4.2	Non-lyophilized solids are described as an example for dosage forms which exhibit a minimal propensity for leaching. Also lyophilized solids show a low risk for interaction. Drug product is reconstituted and administered within a short time-period and the duration between filling and lyophilization is also short.	It is proposed to give further examples like lyophized or frozen DPs.
EfPIA	286	287	4.2	In general, extractables reports provided by suppliers have limited value for manufacturers—unless the component is used as a stand-alone, off-the-shelf item. Ultimately, it is the manufacturer's responsibility to assess how the material is processed and to evaluate its impact in the final finished form.	remove "extractable report"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Qualimetrix SA	286	287	4.2	The data available from suppliers may correspond to extractables from raw materials (i.e. pellets of the polymer masterbatch) but not actual parts. This means that the manufacturer for the parts does not provide extractables data that reflects how the processes affect the materials, i.e. additivation at that level, process agents, cross-contamination due to the production line handling multiple parts, etc. Can those data be considered? Line 272 refers to "any extractable studies", as per raw materials or components?	
Chiesi Farmaceutici	288	290	4.2	To further clarify and strenghten this point it is suggested to specify that possible additional testings, beyond information provided by the supplier, should be performed with reference to the specific application under evaluation for the component object of the selection. In fact in this sense additional testings should integrate information package coming from supplier.	It is suggested to integrate the sentence as follows: "The information obtained from the supplier (e.g. extractables report, compliance with compendial requirements) may be supplemented with additional testing appropriate for conducting a risk assessment and developing extractables/leachables procedures to demonstrate acceptable component selection for the specific application under evaluation"
AESGP	291	297	4.3 Extractable Study	Worst case should refer to use of extraction solvents such as methanol or ethanol or other aggressive media conducted at elevated temperatures	An adequate extractables study incorporates solvents and extraction conditions ~~relevant to the 294 anticipated leaching propensity of the drug product formulation under the~~ 'to create a 'worst-case scenario of manufacturing or storage conditions and employs multiple complementary analytical techniques to establish a comprehensive extractables profile. ADD, 'In the event that no substances are above the AET, no further assessment is warranted'
Bio-Process Systems Alliance	291	319	4.3	Correlation Between Extractables and Leachables-The text encourages using extractables data to justify reduced leachables testing but lacks specific guidance on demonstrating correlation.	Provide examples or acceptance criteria of a comparative assessment (e.g., slope / R^2 thresholds, comparative ratios within ± X %) to support regulatory acceptance of predictive models.
Medicines for Europe	291	297	4.3	The guideline does not specify what level of deviation between supplier test conditions and actual product conditions is acceptable when leveraging supplier extractables data. For example, if supplier testing was performed at pH 2 and pH 8, while the drug product is pH 6, it is unclear whether this difference requires additional testing or if bridging justification is sufficient. This ambiguity can lead to inconsistent regulatory interpretations and uncertainty in risk assessment strategies.	Add clarification in Section 3.5 (Documentation and Compliance) and Section 4.3 (Extractable study) to include: Criteria for acceptable deviation between supplier test conditions and actual product conditions (e.g., pH, temperature, contact time). Guidance on when bridging justification is sufficient versus when confirmatory testing is required. Examples of acceptable scenarios (e.g., intermediate pH values within tested range) and documentation expectations.
Sartorius-Stedim Biotech GmbH	291	319	4.3	It is neccessay to differentiate between CCS and SUS in this paragraph, as explained above, for SUS extraction solvents, S/V ratio extr.-temp. etc. etc. are defined in standardized protocols, e.g. USP 665. We see no advantage in re-justifiing something which is already given e.g. in a pharmacopoia chapter.	
EfPIA	292	293	4.3	The definition of extractable study is circular because it contains the word "extracted". Generally not a good practice for the definition to contain the word.	Change to: "An extractable study is a process by which chemical entities are forced from the component into a medium."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	292	296	4.3	"...anticipated leaching propensity of the drug product formulation under the worst-case scenario of manufacturing or storage conditions ..." • Rationale: An extraction study performed using aggressive extraction mechanism such as reflux has the potential to generate an unrealistic profile of potential leachables, and this should be highlighted within the guidance.	• Based on rationale, extractables studies should be designed to represent the worst-case scenario to identify potential leachables. However, we recommend referncing in this guidline that applicants should be mindful that the use of aggressive extraction method, such as reflux, may generate unrealistic and unrepresentative profile of extractables. We are proposing following text: "Applicants should be mindful that the use of aggressive extraction method, such as reflux, may generate unrealistic and unrepresentative extractables profile, which is not represetnative of patient risk. "
Medicines for Europe	292	294	4	It is essential to clarify the concept of a "worst-case scenario" for extractable studies.	Providing a more detailed definition or examples of what constitutes such scenarios (e.g., specific conditions under which leaching is most likely to occur) would help manufacturers design more effective extractable studies. Additionally, guidelines on how to document and support the rationale for selected worst-case conditions would strengthen the process.
Laboratoires Théa	293	306	4.3	Is it possible to add an annex containing more details regarding the selection of appropriate extraction conditions (example for ophthalmic drug products…).	
Chiesi Farmaceutici	294	294	4.3	It is not completely clear what "anticipated" leaching propensity means.	It is suggested to better specify this point, even in the glossary.
ELSIE	294	294	4.3	It is unclear what constitutes an anticipated scenario for worst-case leaching. A clear and consistent definition is needed. Table A.2.1 briefly mentions that conditions should exaggerate both the number and quantity of leachables, but this is not sufficiently elaborated. Furthermore, lines 304–306 state that solvents must be "relevant" and "representative," which appears to contradict the concept of a worst-case scenario from a migration or diffusion standpoint.	Clarification needed
Sanjay Desai (Cipla Ltd.)	295	295	4.3	The usage conditions are equally important in the determination of in-use leachable profile, as the leachables contribution from device components are majorly takes place during usage.	The sentence must be modified as "of manufacturing, storage or usage conditions"
BioPhorum	296		4.3	(SUT) For component extractables data (referenced in 4.2) there may only be a reporting limit at the time the data are generated, and application of the AET by the sponsor would come at the time the sponsor is trying to use the component/system. Please change #296 starting with "Key characteristics ..." to proposed language.	"Key considerations characteristics of an adequate extraction study for generation and application of extractables studies include:"
EfPIA	296	299		This section states, "Key characteristics of an adequate extraction study include: Establishment and application of a drug product-specific AET to indicate extractable chemical entities to be identified and treated as potential leachables." However, in practice extractable studies are often conducted to support multiple products (current, future, or unknown), and the AET applicable to each product is typically not known when the study is conducted.	Revise text to clarify that the AET applicable to a product should be considered when interpreting extractable study results quantitatively but that the product-specific AET is not a key component of the extractable study itself.
Qualimetrix SA	296	297	4.3	Should there be any requirement regarding the components analyzed during an extractable study, as there is during leachable testing? i.e. sterilization status, number of articles, different Lot./Batches	
EfPIA	297	297	4.3	Editorial comment.	Consistency in terminology ("extractables study," "extraction study")—recommend standardizing to "extractables study."

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Maven E&L Ltd	298	303	Section 4.3	I would suggest drug specific AET is not the primary driver as suggested by this being the 1st sentence of the 1st bullet point. Rather that "...extractable studies should be adequately sensitive to enable a comparison to drug leachables AET, and thus enable a extractable - leachable correlation. This change of wording and emphasis would then enable one extractable study to service a range of extractable - leachable correlations. Further the 2nd sentence might be written, " Testing would allow an estimate of levels in final components, either through direct testing of said components (including any processing and pre-treatment) or through extrapolation from inputs into the final componentry where is it possible to do so "	...extractable studies should be adequately sensitive to enable a comparison to drug leachables AET, and thus enable a extractable - leachable correlation " Testing would allow an estimate of levels in final components, either through direct testing of said components (including any processing and pre-treatment) or through extrapolation from inputs into the final componentry where is it possible to do so "
AstraZeneca	298	303	Section 4.3	I would suggest drug specific AET is not the primary driver as suggested by this being the 1st sentence of the 1st bullet point. Rather that "...extractable studies should be adequately sensitive to enable a comparison to drug leachables AET, and thus enable a extractable - leachable correlation. This change of wording and emphasis would then enable one extractable study to service a range of extractable - leachable correlations. Further the 2nd sentence might be written, " Testing would allow an estimate of levels in final components, either through direct testing of said components (including any processing and pre-treatment) or through extrapolation from inputs into the final componentry where is it possible to do so "	...extractable studies should be adequately sensitive to enable a comparison to drug leachables AET, and thus enable a extractable - leachable correlation " Testing would allow an estimate of levels in final components, either through direct testing of said components (including any processing and pre-treatment) or through extrapolation from inputs into the final componentry where is it possible to do so "
EfPIA	298	298	4.3	Rewording required "Establishment and application of a drug product-specific AET to indicate extractable chemical entities to be identified and treated as potential leachables"	"Establishment and application of a drug product-specific AET to select extractables to be identified and considered as potential leachables"
EfPIA	298	299	4.3		Remove sentence, "Estabishment and application of a drug product-specific AET to indicate extractable chemical entitites to be identified and treaed as potential leachables." Add a bullet at the end stating something like, "Compare extractables method sensitivity to the drug product-specific AET to ensure proper sensitivity for assessment."
ELSIE	298	298	4.3	rewording required "Establishment and application of a drug product-specific AET to indicate extractable chemical entities to be identified and treated as potential leachables"	"Establishment and application of a drug product-specific AET to select extractables to be identified and considered as potential leachables"
EfPIA	300	300	4.3	Is an "assembled system" the same as final finished product/system?	Harmonize nomenclature as "assembled system" does not show anywhere else in the document
ELSIE	300	300	4.3	Is an "assembled system" the same as final finished product/system?	Harmonize nomenclature as "assembled system" does not show anywhere else in the document
Maven E&L Ltd	304	306	Section 4.3	Add into this bullet a mention of extraction medium to deal with non-liquid systems. For example adding this to the current bullet, "..This would include dry drug product formulations which are not appropriately modelled by solvent extraction, and thus would require alternative approaches such as thermal desorption to produce extractables"	..This would include dry drug product formulations which are not appropriately modelled by solvent extraction, and thus would require alternative approaches such as thermal desorption to produce extractables
AstraZeneca	304	306	Section 4.3	Add into this bullet a mention of extraction medium to deal with non-liquid systems. For example adding this to the current bullet, "..This would include dry drug product formulations which are not appropriately modelled by solvent extraction, and thus would require alternative approaches such as thermal desorption to produce extractables"	..This would include dry drug product formulations which are not appropriately modelled by solvent extraction, and thus would require alternative approaches such as thermal desorption to produce extractables
BioPhorum	304	306	4.3	What does it mean "Proper extraction media selection.."?	proposal to elaborate more on this or add reference where it is described. Elaborate on when to make the justification.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chiesi Farmaceutici	304	306	4.3	An extraction study, in addition to evaluate a proper range of extraction media, should also evaluate the use of different extraction technique.	It is suggested to integrate the sentence as follow: "Proper extraction media selection, including appropriate solvents of varying pH and polarity relevant to and representative of the drug product formulation (e.g. excipients, surfactants), and evaluate multiple techniques. Example of extraction techniques include, but are not limited to, Soxhlet, reflux, and sonication."
EfPIA	304	304	4.3	"Proper extraction media selection" is imprecise.	"Proper extraction solvent selection, including appropriate"….
EUCOPE	304	309	4.3	General information are reported on extractable study testing: no suggestion on how to define time/temperature of the extraction, no indication on how to choose appropriate solvent, etc.	Report some indications on how to perform the extractable study (e.g.: +10°C from accelerated as per ICH Q1, duration according to Arrhenius equation, pH at least 2 units from the target, alcohols appropriate to emulate cosolvents, etc.)
Chiesi Farmaceutici	307	309	4.3	In the third point of key characteristics, delivery device components are not mentioned. They should be mentioned together with packaging components as they could be in direct contact with the formulation as well.	It is suggested to modify the sentence as follows: "Represents the drug product specific worst-case scenario for leachables occurring during manufacturing or arising from packaging or delivery device components/systems in direct contact with pharma product during shelf life (e.g. contact area, temperature, duration)
Ferring Pharmaceuticals	307	309	4.3	The age of the materiel is not considered as an important dimension.	Consider the age of the material in the risk assessment/studies design
BioPhorum	308		4.3	(SUT) For single-use, extractables as a function of "shelf-life" is not generally considered a significant risk or expectation for additional data representing end of shelf life. This language can create an undue expectation for data.	Remove single-use from scope, or change wording to focus on DP, 'Represents the drug product specific worst-case scenario for leachables occurring during manufacturing or arising from packaging components/systems during shelf life of the drug product (e.g., contact area, temperature, duration)"
AESGP	310	310	4.3	Term "adequately qualified" not clearly defined	Add definition of appropriate method qualification
BioPhorum	310	310	4.3	Clarify the meaning of "adequately qualified" analytical procedures	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
EfPIA	310	311	4.3	The phrase “The analytical procedures used are adequately qualified at a level commensurate with the purpose of the extraction study” seems to imply that all method qualification parameters—such as accuracy, precision, etc.—must be evaluated at the AET. However, the guidance is unclear and too high-level.	Clarification needed
EfPIA	310	311	4.3	"Adequately qualified" is vague. Define what parameters are expected.	Add glossary definition for "adequately qualified analytical procedure" with expected parameters.
ELSIE	310	311	4.3	The phrase “The analytical procedures used are adequately qualified at a level commensurate with the purpose of the extraction study” seems to imply that all method qualification parameters—such as accuracy, precision, etc., must be evaluated at the AET. However, the guidance is unclear and too high-level. •Clarification is needed on what is considered "adequately qualified" in this context	Clarification needed regarding "adequately qualified" Consider adding a definition of term "adequately qualified analytical procedure" to the glossary.
EUCOPE	310	319	4.3 Extractable Study	Clarity is need about whether GMP qualified instrument required for performing these analytical procedures.	
Laboratoires Théa	310	311	4.3	Can you please give more details regarding the term “adequately qualified”. Which parameters need to be verified? How many surrogate standards need to be included in the qualification of the screening analytical method?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Qualimetrix SA	310	311	4.3	This requirement becomes more "demanding" considering the table at line 513. The lower (compared to UV) linear range of MS-based methods makes it improbable that the same preparation procedure covers the TTC and the QT levels (with a difference of up to a 32-fold or more). Are the methods to be validated across the entire range of application(s) in both extractables and leachables? Is the validation at the TTC level to be "limit test" like?	
IPAC-RS	312	312	4.3	Extractable Study: Analytical procedures are mandatory, we should make a distinction between different route of administration, for example for inhalation non volatile are not relevant	Current wording : Key characteristics of an adequate extraction study include : appropriate analytical procedures for volatile, semi-volatile, and non-volatile organic extractables and elemental extractables. Comment: please be more precise rather than using the word "appropriate," or add wording saying that "appropriate" has to be defined according to the product. For example, with regards to a delivery system using a powder formulation, testing non-volatile compounds is not relevant for components without any contact to the patient mucosa, whereas it makes sense to analyse volatile compounds. The 4 categories should be assessed, and the assessment can be that no testing is required for a specific category and this should be justified
Octapharma	312	313	4.3	Appropriate analytical procedures for elemental extractables are listed, while in the beginning of the document, it is stated that elemental impurities are out of scope. Please clarify.	Align whether elemental impurities are in or out of scope and adjust text accordingly.
BioPhorum	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
EfPIA	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
EfPIA	313	313	4.3	The bullet point ends with "elemental extractables"; however, in line 25 it is clearly stated that "elemental leachables (…) are out of scope", in that convered by ICH Q3D. It seems contradictory to that statement to bring in elemental extractables.	Recommend deleting "and elemental extractables".
ELSIE	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
IPAC-RS	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
Medicines for Europe	314	314	4.3	Bullet point "The extractables report describes details on analytical procedures" revised for clarity	The extractables report describes details of analytical procedures, methodology and demonstration of their suitability
Octapharma	314	314	4.3	Details on analytical procedures are not always reported by CROs and sometimes, pharmaceutical companies need to use CROs.	Amend potential exceptions with CRO since detailed analytical procedures may be intellectual property of the CRO and will not be disclosed.
Maven E&L Ltd	315	319	Section 4.3	It is unclear in this paragraph what "risk analysis should be performed as appropriate" is intended to mean. Does it mean a leachable risk management process, whereby the hazard identification surfaces the possibility of a Class 1 element to be presence, and furthermore the probability is not low? The choice of words is important here use of risk analysis is ambiguous.	
AstraZeneca	315	319	Section 4.3	It is unclear in this paragraph what "risk analysis should be performed as appropriate" is intended to mean. Does it mean a leachable risk management process, whereby the hazard identification surfaces the possibility of a Class 1 element to be presence, and furthermore the probability is not low? The choice of words is important here use of risk analysis is ambiguous.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	315	319	4.3	What is the difference between 'targeted tests' (line 315-317) and 'analysis' (line 315-317)? Line 315-317 - would it be possible to differentiate between a screening leachable study (same as a stability study but performed with use of the screening techniques) and leachable study (a specific analytical method developed to a specific organic compound). 'Quantitative extractable studies' (line 318) - how can this be performed, when screening methods are used and semi-quantitative determinations. The purpose with an extractable study is to screen for extractables and this is performed with a some uncertainty due to the inherent characteristic of the analytical techniques.	Would it be possible to specify and maybe rephrase? Should be elaborated in further details
AESGP	317	319	4.3	Sentence not clear: does the Class 1 testing need to follow the E&L-testing principles or does this sentence focus on the timing?	Rephrasing needed
EfPIA	317	317	4.3	Unclear what "quality" means here. Product quality?	Clarification needed
EfPIA	317	317	4.3	The term "risk analysis" should be replaced with "risk assessment," as the evaluation of Class 1 leachables requires consideration of Steps 1 and 3 of the risk assessment process. Using the correct terminology ensures alignment with established risk management frameworks.	Correction suggested
ELSIE	317	317	4.3	Unclear what "quality" means here. Product quality?	Clarification needed
ELSIE	317	317	4.3	The term "risk analysis" should be replaced with "risk assessment," as the evaluation of Class 1 leachables requires consideration of Steps 1 and 3 of the risk assessment process. Using the correct terminology ensures alignment with established risk management frameworks.	Correction suggested
Sartorius-Stedim Biotech GmbH	317	317	4.3	From our experience in extractables analyis we can state, that Class 1 impurities are not present in SUS extractables profiles. Please define reasonably, why and when this measurement is necessary or remove this requirement. ICH guideline shall not provide black/white lists for extractables. In this context we would like to add, that since many years we are conducting elemental analysis in the frame of extractables studies. During all the years we NEVER saw a Class 1 chemical or critical elements in our extracts of SUS. That means since years we make redundant analysis - and I ask myselfe how long shall we proceed with this useless analyticasl work?	It is recommendable to define a strategy how we can come out of the never ending analysis of things we never saw in our extracts.
A3P	320	332	4.3.1	Section 4.3.1 introduces the concept of grouping extractables into chemical families, yet the guideline does not provide any practical guidance on how such families can be reliably assigned when using LC-MS or ICP-MS techniques, which often lack comprehensive or validated spectral libraries. In LC-MS, most extractables are Non-Intentionally Added Substances and do not match database entries; the guideline does not clarify how to classify them using mass defect, Kendrick analysis, fragmentation patterns, homologous series, neutral losses, or other cheminformatics approaches. In ICP-MS, only elemental information is obtained, which cannot directly define a “chemical family”, and this limitation is not discussed. This may result in inconsistent or non-reproducible classification of families between laboratories and stakeholders. Furthermore, the ELSIE database (https://elsiedata.org/elsie-database/) describes already a long list of compounds for which "families" are multiple, and several compounds can be related to several families. And overall, different products from a same family can have very different response factors, leading to potential misinterpretation of results This concept of families, from an analytical perspective, may generate confusion rather than rationalisation. Except if one refers to "non volatil", "semi volatil" "volatil" and elemental impurities.	Include specific recommendations or examples on how to assign chemical families when databases are unavailable or insufficient, e.g.: - using fragmentation motifs, mass defect patterns, homologous series, or predicted structures for LC-MS, - clarifying the limited role of ICP-MS for defining families, - encouraging the use of prior knowledge of materials, additive packages, and expected degradation products : this knowledge should be provided by the supplier.
Bio-Process Systems Alliance	320	332	4.3.1	This passage ignores USP <665>	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device only or revise to specifically state that USP <665> meets the criteria, and that any study that also meets the criteria meets the Guidance.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	320	348	4.3.1 and 4.3.2	These paragraphs are difficult to follow and create confusion. The definition of semi-quantification presented here differs from that in ISO 10993-18, which further the argument that "delivery systems" should be excluded from the scope of ICH Q3E. It is unclear how the quantification process differs between semi-quantitative and quantitative studies in practice and in which cases each study should be applied. In semi-quantitative studies, extractables are quantified against relevant standard compounds, while in quantitative studies, extractables above the AET are quantified using standards with identical or similar analytical responses. Since both E&L studies rely heavily on estimating quantities and selecting appropriate surrogate standards, the terminology and approach should be harmonized. See recommendation.	Propose to replace in both sections "Quantification of observed extractables should be performed using surrogate standard compounds that possess similar physicochemical properties to the compound(s) being estimated".
EfPIA	320	348	4.3.1 and 4.3.2	Are the recommendations for method qualification different between semi-quantitative and quantitative approaches? In the case of semi-quantitative methods, it is stated that “Analytical procedures are qualified using several relevant standard compounds typically observed as extractables or leachables.” In contrast, for quantitative methods, the guidance specifies that “The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the specific standard compound.” This raises questions about the consistency of qualification requirements between the two approaches.	Clarification needed
EfPIA	320	348	4.3.1 and 4.3.2	Defining separately semi-quantitative and quantitative extractable study is not required. Defining quantitative extractable study uses terms which are solely referring to analytical method validation parameters. After detecting eg +50 extractables it is not feasible to generate a quantitative metod for all those. That does not improve safety. It would be more realistic to state requirements for instrument performance, which could be confirmed appropriate with suitable surrogate standards.	Setting confirmed identifications for extractable studies a requirement is not feasible. One should have correct reference standard, perhaps structure confirmation eg with NMR if standard not available, quantification refer solely to qualified analytical method developed for a specific compounds, then in the same sentence is mentioned ' or similar analytical response' which refers clearly use of surrogate. Attempt to define semi-quantitative and quantitative extractable study is not logical and is not align with ICH definitions for analytical method validation. None of the vendor studies would not comply with the quantitative extractable study definion. How to apply then that data?
ELSIE	320	348	4.3.1 and 4.3.2	These paragraphs are difficult to follow and create confusion. The definition of semi-quantification presented here differs from that in ISO 10993-18, which further the argument that "delivery systems" should be excluded from the scope of ICH Q3E. It is unclear how the quantification process differs between semi-quantitative and quantitative studies in practice and in which cases each study should be applied. In semi-quantitative studies, extractables are quantified against relevant standard compounds, while in quantitative studies, extractables above the AET are quantified using standards with identical or similar analytical responses. Since both E&L studies rely heavily on estimating quantities and selecting appropriate surrogate standards, the terminology and approach should be harmonized. See recommendation.	Propose to replace in both sections "Quantification of observed extractables should be performed using surrogate standard compounds that possess similar physicochemical properties to the compound(s) being estimated".
ELSIE	320	348	4.3.1 and 4.3.2	Are the recommendations for method qualification different between semi-quantitative and quantitative approaches? In the case of semi-quantitative methods, it is stated that “Analytical procedures are qualified using several relevant standard compounds typically observed as extractables or leachables.” In contrast, for quantitative methods, the guidance specifies that “The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the specific standard compound.” This raises questions about the consistency of qualification requirements between the two approaches.	Clarification needed

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	320	348	4.3.1 and 4.3.2	Defining separately semi-quantitative and quantitative extractable study is not required. Defining quantitative extractable study uses terms which are solely referring to analytical method validation parameters. After detecting eg +50 extractables it is not feasible to generate a quantitative method for all those. That does not improve safety. It would be more realistic to state requirements for instrument performance, which could be confirmed appropriate with suitable surrogate standards.	Setting confirmed identifications for extractable studies as a requirement is not feasible. One should have correct reference standard, perhaps structure confirmation eg with NMR if standard not available, quantification refer solely to qualified analytical method developed for a specific compounds, then in the same sentence is mentioned ' or similar analytical response' which refers clearly use of surrogate. Attempt to define semi-quantitative and quantitative extractable study is not logical and is not align with ICH definitions for analytical method validation. None of the vendor studies would not comply with the quantitative extractable study definion. How to apply then that data?
Medicines for Europe	320	343	4.3.1	In the Semi-Quantitative Extractable Study, screening methods are used for the determination of extractables. Therefore, a UF should be applied to calculate the product specific AET. What about extractables that are exceeding the calculated AET (with included UF) but where MDE would still be below the applied SCT? Will these extractables be evaluated in the Quantitative Extractable Study even if the MDE would be below the SCT?	Line 819, table A.1.1., scenario 3: Clarify if extractables resulting from a semi-quantitative study below SCT are also considered qualified and no quantitative extractable study is required.
Maven E&L Ltd	321	323	Section 4.3.1	Since a leachable study will not measure substance in a material but rather in the drug product formulation it is unclear from the wording how a leachable study will "..establish the suitability of materials for intended use..". Thus perhaps this sentence should be deleted or reworded. "A semi-quantitative extractable study might be used to predict leachables"	A semi-quantitative extractable study might be used to predict leachables
AESGP	321	322	4.3.1 Semi-Quantitative Extractables Study	The way this is written suggests that a semi-quantitative extractable study is not sufficient to complete the risk assessment, however, a semi-quantitative extractable study with the correct uncertainty factors applied (to account for the semi-quantitative nature), may be sufficient to complete the assessment and a leachables staudy may not be required.	Add clarification to the text that a semi-quantitative extractable study may be sufficient without further testing requirements.
AstraZeneca	321	323	Section 4.3.1	Since a leachable study will not measure substance in a material but rather in the drug product formulation it is unclear from the wording how a leachable study will "..establish the suitability of materials for intended use..". Thus perhaps this sentence should be deleted or reworded. "A semi-quantitative extractable study might be used to predict leachables"	A semi-quantitative extractable study might be used to predict leachables
BioPhorum	321		4.3.1	"a semi-quant … where a leachables study will subsequently be conducted" … (SUT) For single-use applications, the statement "a semi-quant … where a *** leachables study will subsequently be conducted" creates an undue expectation that the USP <665> or BioPhorum aligned extractables data (employ semiquant) are not adequate to address the risk, or must be supported by additional leachables studies.	Add “primary packaging” in place of *** “A semi-quantitative extractables study may be appropriate in scenarios where a primary packaging leachables study……”
EfPIA	321	322	4.3.1	A representative limit test at the AET can provide enough evidence of no concern when worst-case extractables do not exceed the AET.	Modify to: "A semi-quantitative (e.g., limit test) extractables study may be appropriate to determine if there are any potential leachables that exceed the AET or in scenarios where a ..."
ELSIE	321	343	4.3.2	The difference of a semi-quantitative and quantitative extraction study are not as distinct as the document describes them to be. This is because the only difference between the two is that the quantitative study requires use of an authentic standard for confirmation and quantification of the extractable. We note that this is a standard practice of any extraction study via the supplemental collection of data from such standards. As such, an initial semi-quantitative study can be made quantitative via analysis of a reference standard, as described in Section 4.3.2, without the need to perform a separate study. The only difference is the specification that the compound also be qualified using an authentic standard, which could be done as part of the initial semi-quantitative study as well.	If warranted, update section 4.3 so that semi-quantitative and quantitative extraction studies don't appear to be two completely separate studies.
ELSIE	321	323	4.3.1	Leachables studies are requested even if semi-quantitative extractable studies were conducted. However, if the extractables (exaggerated data) show no risk, what is the point of conducting yet a leachable study?	Allow for risk assessment of extractables, which represent a worst-case of potential leachables and ask for leachable studies only where extractables indicate a risk.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	321	321	4.3.1	Leachable study -> Screening leachable study? Performed as a stability study, but with analytical screening methods (section 4.4).	Introduction of the term 'screening leachable study'? Screening leachable study differentiate from a 'leachable study'. Three or four categories: - Semi-quantitative ex. study - Quantitative ex. study, when (1) shows extractables above AET - leachable study
Octapharma	321	323	4.3.1	Leachables studies are requested even if semi-quantitative extractable studies were conducted. However, if the extractables (exaggerated data) show no risk, what is the point of conducting yet a leachable study?	Allow for risk assessment of extractables, which represent a worst-case of potential leachables and ask for leachable studies only where extractables indicate a risk.
Maven E&L Ltd	326	330	Section 4.3.1	Suggested revision, " To establish the study as semi-quantitative, not qualitative : (1) procedure should be qualified using multiple standard compounds to provide response factors or relative response factors (2) Include a consideration of how analytical uncertainty in detection, identification and quantitation will be controlled (3) Where possible, use of relevant reference standards to ensure higher accuracy	To establish the study as semi-quantitative, not qualitative : (1) procedure should be qualified using multiple standard compounds to provide response factors or relative response factors (2) Include a consideration of how analytical uncertainty in detection, identification and quantitation will be controlled (3) Where possible, use of relevant reference standards to ensure higher accuracy
AESGP	326	330	4.3.1 Semi-Quantitative Extractables Study	Include the option to use semi-universal detectors to provide a robust, broad-coverage option for quantification and screening of extractables and leachables	Add as bullet
AstraZeneca	326	330	Section 4.3.1	Suggested revision, " To establish the study as semi-quantitative, not qualitative : (1) procedure should be qualified using multiple standard compounds to provide response factors or relative response factors (2) Include a consideration of how analytical uncertainty in detection, identification and quantitation will be controlled (3) Where possible, use of relevant reference standards to ensure higher accuracy	To establish the study as semi-quantitative, not qualitative : (1) procedure should be qualified using multiple standard compounds to provide response factors or relative response factors (2) Include a consideration of how analytical uncertainty in detection, identification and quantitation will be controlled (3) Where possible, use of relevant reference standards to ensure higher accuracy
BioPhorum	326	326	4.3.1	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
EfPIA	326	326	4.3.1	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
EFPIA Drug-MD ICH STG	326	327	4.3.1	The guideline currently states, "Analytical procedures that are qualified using several relevant standard compounds typically observed as extractables or leachables." Same in lines 342-343 Comment: The term "qualified" analytical procedures is not defined in the guideline and should be clarified. Typically, extractables procedures should be suitable and fit for purpose, e.g., adequate detection and quantification limit covering the AET.	We recommend clarifying the meaning of "qualified" analytical procedures as used in the guideline and to state e.g. Methods for extractables studies need not to be validated but should be suitable for their intended use.
ELSIE	326	326	4.3.1	Clarify the meaning of "qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
EUCOPE	326	332	4.3.1 Semi-Quantitative Extractables Study	If there are recommended standards for use of different technique (e.g. GC, LC. Are GMP qualified instrument required for performing the testing) the should be outlined in the document.	
IPAC-RS	326	326	4.3.1	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.

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Sartorius-Stedim Biotech GmbH	328	329	4.3.1.	As explained above, in extr.-studies for SUS commonly AETs are not applied and cannot be applied, because at time the extractables study is conducted no dedicated application is in focus. Extr.-Studies for SUS are standardized studies (e.g. defining a surface to volume ratio rather than an AET).	
ELSIE	330	330	4.3.1	"•Quantification of observed extractables against relevant standard compounds." • The quantification suggests validation but section considers semi-quantitative extractable study/method	• Based on the rationale, we recommend change in text: ""•Semi-quantification of observed extractables against relevant standard compounds."
Ferring Pharmaceuticals	330	330	4.3.1	Quantification' but as it is a semi-quantiative ex. study, then it is a 'semi-quantification' due to the uncertainty factor and target compounds as 'reference standards'.	Suggest rephrasing
Maven E&L Ltd	331	332	Section 4.3.1	Suggested revision: The output from a semi-quantitative study should be used to define targets in subequent studies such as a quantitative extractable study or a leachable study. Those substances observed at highest concentration or known to represent a plausible safety concern being prioritized as future targets	The output from a semi-quantitative study should be used to define targets in subequent studies such as a quantitative extractable study or a leachable study. Those substances observed at highest concentration or known to represent a plausible safety concern being prioritized as future targets
AstraZeneca	331	332	Section 4.3.1	Suggested revision: The output from a semi-quantitative study should be used to define targets in subequent studies such as a quantitative extractable study or a leachable study. Those substances observed at highest concentration or known to represent a plausible safety concern being prioritized as future targets	The output from a semi-quantitative study should be used to define targets in subequent studies such as a quantitative extractable study or a leachable study. Those substances observed at highest concentration or known to represent a plausible safety concern being prioritized as future targets
EfPIA	331	332	4.3.1	Include the simulated leachables study option	Modify to: ". . .for a quantitative extractables study, simulated leachables study, or a leachables study."
EfPIA	331	332	4.3.1	Extractable data from suppliers for manufacturing components is often semi-quantitative. Assessment approaches can involve subsequent quantitative extractable studies or utilizing the extractable information to ascertain which extractables may manifest as leachables in the drug product, consistent with sections 323 to 324. Accordingly, we recommend incorporating a new statement.	Semi-quantitative extractables observed above the AET can subsequently be used as targets for a leachables study. Semi-quantitative extractables study can also provide an understanding of potential leachables in the drug product, thus the quantification provided by the leachables study can make a separate quantitative extractables study optional.
ELSIE	331	332	4.3.1	It is not the extractables themselves that are semi-quantitative, but rather the estimation of their levels at or above the AET. The phrase "Semi-quantitative extractables observed above the AET can subsequently be used as targets for a quantitative extractables study or a leachables study" is misleading. Additionally, the added value of conducting a quantitative extractables study instead of proceeding directly to a leachables study is unclear. It seems that quantitative studies are only applicable to manufacturing components and low-risk systems but is unclear why.	Clarification needed
ELSIE	331	332	4.3.1	"Semi-quantitative extractables observed above the AET can subsequently be used as targets for a quantitative extractables study or a leachables study" • Clarification is needed as to why it is necessary to assess in a subsequent quantitative extractables or leachables study when the extractables levels are significantly below the PDE	• We recommend following text change: "Semi-quantitative extractables observed above the AET can subsequently be used as targets for ~~a quantitative extractables study or a~~ subsequent leachables study (or quantitative extractables)."
ELSIE	331	332	4.3.1	Extractable data from suppliers for manufacturing components is often semi-quantitative. Assessment approaches can involve subsequent quantitative extractable studies or utilizing the extractable information to ascertain which extractables may manifest as leachables in the drug product, consistent with sections 323 to 324. Accordingly, we recommend incorporating a new statement.	Semi-quantitative extractables observed above the AET can subsequently be used as targets for a leachables study. Semi-quantitative extractables study can also provide an understanding of potential leachables in the drug product, thus the quantification provided by the leachables study can make a separate quantitative extractables study optional.
EUCOPE	331	331	4.3.1	It's reported that "Semi-quantitative extractables observed above the AET can subsequently be used as targets for a quantitative extractables study or a leachables study" and it's specified for manufacturing equipments that if no extractables are above the semiquantitative AET the leachables study could be skipped.	Since the sentence reports "can be used", is it reasonable to think that the reported approach is applicable even to container closure systems? If so, please add

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Maven E&L Ltd	333	343	Section 4.3.2	The nature of the use of a quantitative extractable study as presented here seems to be quite specific. To act as a replacement for a leachable study. I would suggest the title of the section reflects that e.g. Quantitative Extractable Studies as replacement for leachable studies	Quantitative Extractable Studies as replacement for leachable studies
A3P	333	348	4.3.2	Section 4.3.2 discusses extractables quantitation, but the relationship between (1) semi-quantitative extractables screening (Section 4.3.1), (2) extractables quantitation, and (3) quantitative or semi-quantitative leachables testing (Section 4.4) remains unclear. It is not specified when an extractable should move from semi-quantification to full quantification. This may lead to duplicated efforts (quantification during extractables and again during leachables) or to inconsistent decision-making regarding which extractables require full quantification.	Provide clearer criteria or decision trees for when extractables should be quantitatively measured during the extractables stage, versus when they should be deferred to tracer-based leachables studies or final quantitative confirmation. Examples of scenarios benefiting from early quantitation (e.g., structurally known additives, potential genotoxic compounds, high-abundance extractables) would help ensure harmonized application.
AstraZeneca	333	343	Section 4.3.2	The nature of the use of a quantitative extractable study as presented here seems to be quite specific. To act as a replacement for a leachable study. I would suggest the title of the section reflects that e.g. Quantitative Extractable Studies as replacement for leachable studies	Quantitative Extractable Studies as replacement for leachable studies
Medicines for Europe	333	343	4.3.2	Please confirm: A semi-quantitative extractables study and a quantitative extractables study typically involve the same experimental design. The distinction lies in data evaluation. In a semi-quantitative study, extractables detected above the AET, including an applied UF, are reported with estimated concentrations based on relative response factors or surrogate standards. In contrast, a quantitative study provides accurate concentrations for these extractables using validated calibration curves and authentic standards, enabling a toxicological qualification?	Clarify if toxicological evaluation is only required for quantitative extractable studies and leachable studies, but not for semi-quantitative extractable studies.
AESGP	334	338	4.3.2 Quantitative Extractables Study	As written, the text suggets that all low risk scenarios require extraction studies, which is not the case. There are low risk scenarios for manufacturing and component closure systems that should require no E&L studies, as discussed in other comments. Also, for thescenarios where extractables is required, a semiquantitative study with the correct uncertainty factors applied (to account for the semi-quantitative nature), may be sufficient to complete the assessment and a leachables staudy may not be required.	To support qualification of manufacturing components/systems and ~~certain low-risk packaging~~ components/systems scenarios (Refer to Appendix 1 Table A.1.1 and A.1.2, respectively) for which extractables 'studies are required and' were observed at a level above the AET during the semi-quantitative extractables study, a quantitative extractables study to quantify these specific extractables would be warranted. . Add text to clarify the semi-quantitative extractables study with the correct UFs may be sufficient
Chiesi Farmaceutici	334	338	4.3.2	Among scenarios described, delivery device components are not mentioned. They should be mentioned together with packaging components as they could be in direct contact with the formulation as well.	It is suggested to integrate the sentence as follows: "To support qualification of manufacturing components/systems and certain low-risk packaging/delivery device components scenarios (Refer to Appendix 1 Table A.1.1 and A.1.2, respectively) for which extractables were observed at a level above the AET during the semi-quantitative extractables study, a quantitative extractables study to quantify these specific extractables would be warranted."
EfPIA	334	348	4.3.2	The quantitative extractables study appears as warranted, i.e. somehow "recommended" and may be regarded as somehow mandatory...? Where is the value if the leachables study is performed by default when the semi-quantitative extractables study shows levels of extractables above the qualification limit ? This section is unclear as it does not state that the quantitative extractables study can be skipped if leachables study is performed on one hand, and also does not state that if the quantitative study concludes that all extractables are below the qualification limit the the leachables study is not necessary...which would be anyway inconsistent since an Extractables/Leachables correlation is mentioned in the guideline as a requirement.	Clarify when a quantitative Extractables study is mandatory or recommended/warranted (it should logically not be mandatory if a leachables study is performed based on the outcome of the semi-quantitative extractables study.)
EfPIA	334	335	4.3.2	Why only manufacturing components and low-risk packaging components are considered in this context ? Does it mean that for moderate and high risk manufacturing / packaging components a quantitative extractables study is considered not required ?	Clarify the scope of materials and why.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	334	338	4.3.2	A description using a quantitative extractables study for when extractables were reported above the AET in the semi-quantitative study is presented.	It would be helpful to clarify that the quantitative extractables study would be conducted to address potential safety concerns or other specific concern prior to leachables testing.
ELSIE	334	348	4.3.2	"4.3.2 Quantitative Extractables Study" Section • Prioritisation of resources should be placed on leachables studies rather than on quantitative extractables studies	
Sanjay Desai (Cipla Ltd.)	334	335	4.3.2	For the overall risk assessment and control of leachables, it is important to consider the risk of leachables contributed from delivery device in addition to manufacturing equipments and packaging components to ensure pharmaceutical quality and safety.	To support qualification of manufacturing components/systems and certain low-risk packaging as well as delivery device components/systems
ELSIE	336	338	4.3.2	"...which extractables were observed at a level above the AET during the semi-quantitative extractables study, a quantitative extractables study to quantify these specific extractables would be warranted." • The safety assessment should be considered prior to performing quantitative extractables studies. Clarification is needed on why these guidelines statments are necessary for extractables below PDE	
EfPIA	339	339	4.3.2	What is the defiition of "confirmed identify"?	Align with USP <1663> definition
EFPIA Drug-MD ICH STG	339	339	4.3.2	The guideline currently states, "Confirmed identification of extractables above the AET." Comment: Not all extractables that exceed the AET can be confidently identified, due to limitations in analytical methods or reference standards availability. The text should be modified to address this limitation.	We recommend the following revision in the text of the guideline, "Confirmed identification of extractables above the AET, where possible."
ELSIE	339	340	4.3.2	A key characteristic is "confirmed identification of extractables above the AET."	It is recommended to clarify that compound ID should be performed prior to the quantitative study and not as a part of the quantitative study. Performing accurate quantitation depends on having an appropriate standard and the ID must be performed to know which standard to select.
ELSIE	339	339	4.3.2	What is the defiition of "confirmed identity"?	Align with USP <1663> definition
ELSIE	339	339	4.3.1	It is simply impossible and unrealistic to obtain confirmed identification of extractables above AET, if the latter is very low. There is no state-of-the art solution to this. "...Confirmed identification of extractables above the AET" • Not all extractables that exceed the AET can be confidently identified, due to limitations in analytical methods or reference standards availability — with propylene oligomers given as an example of such a substance.	Rewrite to "seek identification of extractables above AET". Allow for reality, which is, some peaks cannot be confirmed.
Medicines for Europe	339	348	4.3.2	In this section it is mentioned multiple times "confirming" the identification of an extractable compound, however, in some cases, there are not reference standards available for all compounds, therefore, being able to "confirm" the identification is not possible. In addition, what if there are many compounds above the AET (example: greater than 20), does that mean you have to validate a method for all 20 compounds to be able to adequately quantify the compound with the known/similar reference standard? That seems to be an extrordinary amount of work, why not be able to use a similar/surrogate reference standard to quantify many/all of the compounds.	Update the wording to clarify the level of identification to include both scenarios when authentic reference standards are and are not available, or is it possible to use a word other than "confirmed", or remove the word all together? Example: line 339, "Identification of extractable above AET"; line 342-342, "The analytical prodcedure used for quantifying the identified extractables above the AET should be qualified for the applicable standards used for quantitation"; line 348: "the AET when those extractables cannot be identified."
Octapharma	339	339	4.3.1	It is simply impossible and unrealistic to obtain confirmed identification of extractables above AET, if the latter is very low. There is no state-of-the art solution to this.	Rewrite to "seek identification of extractables above AET". Allow for reality, which is, some peaks cannot be confirmed.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sartorius-Stedim Biotech GmbH	339	343	4.3.2.	In that list a plausability control is missing. It is neccessary to correlate materials of construction and extractables profiles; without that or in case it is not achievable, the respective extractables study is useless. As discussed above today we know very well the substance clusters, which can be found in extractables studies - and we can correlate it with the material of construction and manufacturing (including the influence of sterilizatiuon methods).	Add a bullet point asking for a correlation of the extractables profile with the material of constuction (as a kind of plausability control)
EfPIA	340	341	4.3.2	Even in the case where no commercially available standards exist, it is impossible to know if the response factor of the extractable in the test article is similar to the surrogate standard used	Propose to replace "Quantification of observed extractables should be performed using surrogate standard compounds that possess similar physicochemical properties to the compound(s) being estimated".
EfPIA	340	341	4.3.2	Using standards with similar identical response may not be scientifically sound if the chemistry of the identified extractable(s) and the "standard with identical or similar analytical response" have different chemistries.	Proposed wording/change: "Quantification of the identified extractables above the AET using authentic standards or appropriate surrogate standards (e.g. with similar chemistry and/or analytical response)
EFPIA Drug-MD ICH STG	340	341	4.3.2	The guideline currently states, "Quantification of the identified extractables above the AET using standards with identical or similar analytical response." Comment: Even in the case where no commercially available standards exist, it may not be possible to know if the response factor of the extractable in the test article is similar to the surrogate standard used. The text should be revised to reflect this limitation.	We recommend the following revision in the text of the guideline, "Where possible, quantification of the identified extractables above the AET using standards with identical or similar analytical response."
ELSIE	340	341	4.3.2	Even in the case where no commercially available standards exist, it is impossible to know if the response factor of the extractable in the test article is similar to the surrogate standard used	Propose to restate as, e.g., "Quantification of observed extractables should be performed using surrogate standard compounds that possess similar physicochemical properties to the compound(s) being estimated".
ELSIE	340	341	4.3.2	"Quantification of the identified extractables above the AET using standards with identical or similar analytical response" • Clarification is needed on how the use of standards with a similar analytical response can be confirmed when the actual standard is not available • In addition to quantifiation of identified extractables above the AET using standards with the same or similar analytical resonse, it is also reasonable to use reference standards with a response which is not similar to the analytical response of the extractable quantified if the difference in analytical response is established, demonstrated to be precise, used to adjust the amount of the extractable determined and the resultant analytical procedure is qualified, particularly for accuracy.	We recommend following text change: "•Quantification of the identified extractables above the AET using suitably qualified analytical procedures standards with identical or similar analytical response" We would also like some advice to be added for the selection of suitable surrogates.
ELSIE	340	341	4.3.1	In a screening extractable study, we do not know what types of extractables we will get. Hence, we cannot always use standards with identical or similar analytical response. If the margin of safety is large (>2), the exact concentration of the extractable plays no role. It does not change anything.	Ask for precise or overquantification in accordance with a worst-case approach only for extractables which indicate a risk (MOS < 2).
Octapharma	340	341	4.3.1	In a screening extractable study, we do not know what types of extractables we will get. Hence, we cannot always use standards with identical or similar analytical response. If the margin of safety is large (>2), the exact concentration of the extractable plays no role. It does not change anything.	Ask for precise or overquantification in accordance with a worst-case approach only for extractables which indicate a risk (MOS < 2).
Maven E&L Ltd	342	343	Section 4.3.2	Is the use of the term qualification correct here? I would suggest since you are now considering target with a standard this would be validation.	
AstraZeneca	342	343	Section 4.3.2	Is the use of the term qualification correct here? I would suggest since you are now considering target with a standard this would be validation.	
BioPhorum	342	343	4.3.2	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
EfPIA	342	343	4.3.2	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	342	343	4.3.2	This sentence is unclear. Is this about the way the method has to be qualified, i.e. with which standards ? The qualification of the method with the specific standard compound cannot be practically performed for all existing extractable compounds - for the reasons that such standards are not commercially available or cannot be produced (think about rubber oligomers - not the main ones which may be considered as commercially available but all the hundreds others - or all hydrocarbons from polyolefins, or degradation products from complex additives, etc...). On a side note: Qualifying the methods as described for ALL identified extractables using the specific standard compound is practically impossible if one considers the potential x-thousands of extractables triggered by the multitudes of polymers. Such qualification shall occur only at the leachables study stage.	Proposed wording/change: "The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the identified extractables or for compounds with similar chemistry and analytical response (surrogates) as appropriate" or "The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the identified extractables or for compounds with similar chemistry and analytical response, unless a leachables study is performed withe appropriate qualification (see section xxx)"
ELSIE	342	343	4.3.2	Clarify the meaning of "qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
IPAC-RS	342	343	4.3.2	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
Medicines for Europe	342	343	4.3.2	The guideline states: "The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the specific standard compound" (Line 342). However, the term "qualified analytical procedure" is not defined.	Add clarification in Section 4.3.2 (Quantitative Extractables Study) to define what constitutes a "qualified analytical procedure," including the minimum requirements (e.g., specificity, accuracy, precision, LOQ).
BioPhorum	344	346	4.3.2	If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted.	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
EfPIA	344	346	4.3.2	If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted.	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
EfPIA	344	344	4.3.2	There is a lack of clarity around what constitutes an "adequately identified and quantified extractable." What criteria are used to assess adequacy in this context?	Clarification needed
EfPIA	344	348	4.3	The term "qualification limit" is used here but is inconsistent with the rest of the document. The term "qualification threshold" is used later, but was intended prior to developing a PDE. The term "acceptable level" seems more applicable to Figure 1 of the document.	Replace "qualified limit" with "acceptable level".
EfPIA	344	346	4.3.2	Clarify that leachables study may be omitted if extractables < qualification limit.	Add sentence allowing omission of leachables study in low-risk cases in Appendix 1.
ELSIE	344	344	4.3.2	There is a lack of clarity around what constitutes an "adequately identified and quantified extractable." What criteria are used to assess adequacy in this context?	Clarification needed

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	344	346	4.3.2	"If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit." The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. • Clarification is requested regarding the need for a leachable study when the extractables are below their qualification limit, considering that extractables studies are typically more aggressive and tend to result in higher levels. Reference: lines 418 to 420	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
ELSIE	344	346	4.3.2	The patient exposure in this situation is calculated assuming the specific extractable is leached 100% in to the drug product. This is an over estimate and a leachables study is required in order to show that the compound is below the PDE level in the drug product. Is the testing required for the drug product at multiple time points during its intended shelf life period.	A claification is needed since this section is concerning manufacturing components. Should the study be conducted on the drug product (i.e. a stability study) or under the component use conditions?
IPAC-RS	344	346	4.3.2	If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted.	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
Laboratoires Théa	344	348	4.3.2	Can you confirm that targeted leachables analysis (for FDA included) is not required if no extractables above its qualification limit are observed? Only a non-targeted leachables analysis is required in this case?	
Luye Pharma	344	346	4.3.2	"qualification limit" (only mentioned in 4.3.2) and "qualification threshold" are used in the document	unified wording is preferred "qualification threshold" is already listed in glossary
Medicines for Europe	344	346	4.3.2	There seems to be no difference in the meaning of "qualification limit" (only mentioned in 4.3.2) and "qualification threshold"	harmonize throughout the guideline - "qualification threshold" is preferred as listed in glossary
EfPIA	345	346	4.3.2	Suggest clarifying leachables studies should only be expected for DP primary containers.	Clarification needed.
AstraZeneca	347	348	Section 3.4.2	this sentance does not make sense or at the very least requires reading several times to determine what it actually means	Consider revising this text
EfPIA	347	347	4.3.2	"quality risk" is unnecessary	"risk"
EfPIA	347	348	4.3.2	this sentence is difficult to understand and interpret	Clarify this entire sentence
EfPIA	347	348	4.3	How can a leachable study "be used to assess the quality risk for extractables above the AET when those extractables cannot be identified with confirmed identities"? Not clear what kind of quality risk assessment could be conducted if no information on the extractables identities is available.	Please clarify what would be the expectations in case an extractable that is present above the AET cannot be analytically identified.
EfPIA	347	348	4.3.2	Include the simulated leachables study option	Modify to: " . . . In addition, a simulated leachable study or a leachables study . . ."
ELSIE	347	347	4.3.2	"quality risk" is unnecessary	"risk"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	347	348	4.3.2	" In addition, a leachables study can also be used to assess the quality risk for extractables above the AET when those extractables cannot be identified with confirmed identities" • There is a potential inconsistency within the guideline — the quoted sentence suggests that leachables studies may be used even when extractables lack confirmed identification, while line 339 appears to require confirmed identification for extractables above the AET. Clarification is needed. •- Additional detail needs to be added to the same point to also reiterate that "a semi-quantitative extractables study may be appropriate in scenarios where a leachables study will subsequently be conducted", as per line 321-323. A leachables study would mitigate against complete confirmation of identities and full quantification of all extractables. Point needs to be clarified throughout to ensure that there would not be an expectation with regulatory authorities for all of a semi-quantative extractables study, a quantitative extractables study and a leachables study.	
AESGP	349	367	4.4 Leachables Study	Should not be necessary for no to low risk products	352 ADD, 'Leachables studies are only required in the event that substances are above the AET in prior extractables studies.'
ELSIE	349	414	4.4 and 4.5	No mention of any bracketing approach while this is a possibility in the ICH Q1A and could be justified as well in Leachable studies of several products in the same packaging system or for the simulated leachable study. We would add this possibility in the document.	Add bracketing approach for at least the simulation leachable study and give some potential rules or guidelines on how to proceed with this kind of approach.
Laboratoires Théa	349	371	4.4	What is the minimum number of batches to be included in leachables studies for the manufacturing components? What is the minimum number of batches to be included in leachables studies for the container closure system (3 batches as stated in USP <1664>)?	
EfPIA	350	353	4.4	The expectations regarding the 'in-use period' are unclear. Furthermore, the phrasing suggests that the 'multiple time points' may also apply to the 'in-use' testing, while it applies to the CCS. Does this mean that testing has to be performed systematically or are there other approaches possible relying on risk assessment (e.g. leveraging prior knowledge, materials based approach)?	Clarify the expectations regarding in use.
EfPIA	350	367	4.4	This section implies a link to stability studies, but doesn't explicitly call out ICH Q1. It would be good to make this link rather than leave this in some ways "free form" in terms of study design and number of batches.	Link this section to ICH Q1 in a meaningful way in terms of the overall design of study.
EfPIA	350	367	4.4	The term lot and batch seems to be used interchangeably, however they have two different meanings. So it should be clear if you are intending to mean multiple batches or lots. Also mulitple, is not specific. It would be good to know the minimum amount of batches needed.	Use batch only (not lot) and include a minimum of 3 batches.
IPAC-RS	350	353	4.4	Inhalation products such as DPI, pMDI and inhalation solution/suspensions for nebulization, where in-use stability involves the removal of secondary packaging (as described in Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry, draft Apr 2018), should not require a leachable study during in-use testing since the primary container is not affected during the in-use period.	Propose to add further clarification as to when in-use stability is required to be assessed as part of leachable studies.
Sanjay Desai (Cipla Ltd.)	350	352	4.4	Inclusion of in-use leachable studies, targeting the leachables contributed by delivery device / delivery system should be considered.	Leachables studies intended to support drug product registration are designed to represent the actual manufacturing conditions, usage conditions and intended storage conditions throughout the proposed shelf-life and in-use period. Appropriate and harmonised modifications in strategy and methodology are recommended.
AESGP	352	352	4.4	multiple time points also mentioned for in-use studies. However, this might often not be feasible	Extend sentence like: During shelf life and in-use period, time points as being representative for the duration should be evaluated…
EfPIA	352	352	4.4	"in-use period" requires definition	Include defintion in glossary
EfPIA	352	353	4.4	More to the point of linking to the newly revised ICH Q1, why should "mulitple time points be evaluated to characterize trending…" during in-use period? Wouldn't two time points (T0 and end of in-use period) be more than sufficient?	Suggest separating assessement over shelf-life (for which an ICH Q1 protocol framework is usually applicable) from in-use (for which a product-specific plan is more suitable).

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	352	353	4.4	In-use leachable assessment should not be a blanket requirement for all parenteral drug products. Instead, it should be based on a risk assessment that considers the drug product formulation and any auxiliary delivery components (e.g., disposable syringes, IV bags) supplied by the manufacturer (i.e., combination products). Drug delivery devices that are not provided as part of the drug product should be out of scope, as leachables are highly product- and process-specific. For example, if the manufacturer only supplies the drug product (e.g., in a bag) and point-of-care uses its own syringes or transfer devices, those devices should not be included in the leachable assessment—unless the drug product formulation is highly unique and has a high leaching propensity (e.g., lipid nanoparticles, organic vehicles rather than aqueous solutions).	Provide clarification that drug delivery devices means combination products, and in-use leachable is only limited to high risk formulations. Also consider adding "the fluid path in contact with drug product in the" in front of the "Drug-device combination products".
ELSIE	352	352	4.4	"...and intended storage conditions throughout the proposed shelf-life and in-use period. During the shelf life and in-use period, multiple time points should be evaluated to characterize trending of leachables to estimate maximal occurrence." • Clarification is needed on term "in-use period" in this guideline context. • Rationale: Flexibility in the number of time points, aligned with product-specific risk rather than a fixed expectation (multiple time points)	• We recommend definition of term "in-use period" in the context of leachebles studies, in the Glossary • We recommend highlighting time points aligned with product - specific risk instead of referencing multiple time points.
EUCOPE	352	352	4.4	The term "in-use period" is used several times in the document without a clear explanation of what is in scope of this term. Off the shelf administration items (such as IV bags, IV sets, syringes) that are not supplied by the sponsor, are understood as typically out of scope for leachables testing as there is no control over the item used for administration.	Propose to add to section 2: "Off the shelf" products are not in scope (when not supplied by the sponsor).
Ferring Pharmaceuticals	352	353	4.4	Relevant to trend on leachables detected in screening-leachable study? The results are connected with a certain uncertainty.	Propose only to trend on real leachables detected in a leachable study where a method is developed and validated for that specific leachable.
Medicines for Europe	352	352	4.4	It is assumed that the definition of "in-use period" is compliant to ICH Q1 guideline ("intended use of the drug product after the primary container is first breached").	to be confirmed with reference to ICH guideline or defined in glossary
Medicines for Europe	352	355	4.4	Note: trending implies a statistical analysis. Rather we need to consider that the maximum amount of leachable across the shelf life and provide tox risk assessment of this range.	Proposed text: The leachable profile of a product may change during its storage period. Accordingly, multiple time points across the shelf life and in-use period should be evaluated to characterize leachables and permit quantitation of their maximal occurrence.
Maven E&L Ltd	353	355	Section 4.4	The sentence"..actual drug product.." seems to proclude the use of placebo? I would suggest it should be ammended to allow for that. Revised suggested text: "…is performed on drug product or a valid alternative such as a placebo if it is reasonable to conclude the API will not influence leachables"	…is performed on drug product or a valid alternative such as a placebo if it is reasonable to conclude the API will not influence leachables
AstraZeneca	353	355	Section 4.4	The sentence"..actual drug product.." seems to proclude the use of placebo? I would suggest it should be ammended to allow for that. Revised suggested text: "…is performed on drug product or a valid alternative such as a placebo if it is reasonable to conclude the API will not influence leachables"	…is performed on drug product or a valid alternative such as a placebo if it is reasonable to conclude the API will not influence leachables
EfPIA	353	353	4.4	The inclusion of multiple time points in leachables studies primarily serves to capture the maximum potential exposure. However, depending on the compound's migration behavior, the true maximum may be missed. Therefore, it is important to clarify that these studies serve a dual purpose: both to monitor trends over time and to identify the potential maximum exposure levels.	"be evaluated to characterize trending of leachables and to estimate potential maximal occurrence"
EfPIA	353	353	4	"In-use" is described several places in different context e.g. "in-use period" "in-use limitations" and in-use (clinical) preparations".	Glossary section: Add "in-use"
ELSIE	353	353	4.4	The inclusion of multiple time points in leachables studies primarily serves to capture the maximum potential exposure. However, depending on the compound's migration behavior, the true maximum may be missed. Therefore, it is important to clarify that these studies serve a dual purpose: both to monitor trends over time and to identify the potential maximum exposure levels.	"be evaluated to characterize trending of leachables and to estimate potential maximal occurrence"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	353	358	4.4	It is recommended that multiple batches be tested for leachables. Question: What is the intention of using multiple batches with the batches of same packaging/manufacturing materials, especially for generic products? In the development of generic products, typically validation/exhibit batches are produced within one production slot. In many cases, only one batch of the respective production equipment (e.g. filter) or CCS (e.g. stopper) is available from the respective suppliers. Testing 3 batches of the drug product manufactured with the same batches of CCS and manufacturing equipment does not provide added value. For this reason, there should be flexibility to avoid unnecessary delays and costs in the development of generics.	It is more important to consider the diversithy of components evaluated rather than batches of product. It would be helpful to suggest what specifically should vary in the different batches. For example, typically the expectation is that the different batches should be different drug product batches (i.e. - different API). Since this document focuses on E&L, it would be good to understand the expectation with regards to different materials. Provide flexibility in number of "batches" that includes situations where exhibit/validation batches are manufactured with the same lots of CCS and (large surface) production equipment. "at least two batches"
AstraZeneca	355	356	Section 4.4	Testing multiple batches of the drug product makes little sense. Testing multiple batches of materials incorporated into the CCS would provide a more comprehensive idea of possible variance	Consider revising this text to refect the point made
BioPhorum	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.
EfPIA	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.
EfPIA	355	359	4.4	Multiple batches mean 3 batches? If justified, 2 batches are acceptable?	N/A
EfPIA	355	355	4.4	Although leachables studies may be a form of a stability study, stability studies imply GMP activities. Leachables studies are NOT GMP activities.	Modify to: ". . . during registered storage conditions and may include . . ."
EfPIA	355	359	4.4	The substantial supply generated by drug product manufacturing, depending on its intended application, could meet needs for several years. In this context, the requirement for multiple batches and the prescriptive use of 'should' may present significant hurdles. While alternative approaches with justification are proposed, it is important to note that for certain products, meeting this requirement may be technically or logistically impracticable.	Recommend use of "may involve multiple"
EfPIA	355	358	4.4	Is there a reason that multiple batches is the standard? The DP is typically not variable enough to impact, and many container-closures are also not.	Recommend "may involve multiple" and examples of when multiple batches should be evaluated.
EFPIA Drug-MD ICH STG	355	358	4.4 Leachables Study	For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product. Unclear whether the expection of multiple batches is only for primary packaging (in case of non-permeable primary packaging) or also for secondary packaging as well as the delivery device (which can be separate and only be combined with the drug at the point of use)	clarify for which parts of a CCS testing of multiple batches is expected
ELSIE	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	355	359	0.16944444	We believe that testing a single representative drug product batch may be sufficient to demonstrate the absence of leachables. Involving multiple batches might not add significant value from a scientific perspective, but we are happy to discuss this further to ensure alignment. The purpose of leachables studies differs from ICH stability studies: leachables studies evaluate the interaction between the drug product and its primary packaging over time, whereas stability studies assess the intrinsic stability of the drug product itself. Packaging materials and drug formulation are standardized and tightly controlled, minimizing batch-to-batch variability and making additional batches unnecessary. Furthermore, leachables studies include multiple timepoints throughout the entire shelf-life, which is critical for assessing migration trends over time. The trend of leachables is reliably evaluated through a combination of extractables data, quality risk assessment, and one batch leachables study involving multiple timepoints. The leachables methods applied are accurate and designed for their purpose. Additional batches would not provide meaningful scientific benefit but would significantly increase resource use, as leachables studies are as complex as ICH stability programs. This approach aligns with regulatory flexibility under ICH Q3E, reflects established industry practice, and supports sustainability by avoiding unnecessary duplication.	For a container closure system, the study should involve multiple at minimum one primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product. If multiple batches are not available, alternative approaches may be proposed with justification.
IPAC-RS	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.
POLPHARMA	355	359	4	The use of single representative batch is proposed provided that adequate justification is presented.	Currently: For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product. If multiple batches are not available, alternative approaches may be proposed with justification. Proposed: For a container closure system, the study should preferably include multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for commercial use. If multiple batches are not available, the study may be performed on a single representative batch, provided that a scientific justification is documented and, where appropriate, additional risk-mitigation measures such as worst-case selection, bracketing, or supporting extractables data are applied.
ALK (HJODK)	356	361	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product. If multiple batches are not available, alternative approaches may be proposed with justification." In line 359 it is suggested to use the same lots of components. What is the purpose of performing the leachables study using multiple drug product batches? The batches are manufactured according to specifications, hence within a narrow window of process variation and product matrix variation that could impact the leachables.	Delete the requirement for multiple batches.
EfPIA	356	356	4.4	a minimum number of batches should be defined and not "multiple"	"at least two batches"
EfPIA	356	357	4.4	Specify minimal required number of "multiple" primary drug product stability and/or development batches; also it wuld be helpful to clarify if multiple lots of packaging/delivery components should be matrixed with multiple batches of DP.	Specify the minimum number for "multiple", and clarify expectations for the number of batches for packaging/delivery components
EfPIA	356	358	Section 4.4	In line 356, it mentioned "multiple primary drug product stability and/or development batches" required for L study, in Line 358, "if multiple batches are not available, alternative approaches may be proposed with justification", is there any definition of "multiple batches", for example, more than 2 batches can be considered as "multiple batches"?	propose to give an example in the training material or Q&A after implementation
ELSIE	356	358	4.4	Why is it required to test multiple drug product batches? It is more valuable to use multiple lots of container closure system components rather than multiple batches of drug product. This would give a better picture of lot to lot variation in the components.	Recommend suggesting multiple lots of CCS components versus multiple DS/DP batches.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	356	361	4.4 Leachables Study	A clarity is needed on the expectation of number of batches related to the use of the same lots of components used in extractables assessments to enable more meaningful correlation between extractables and leachables.	
EfPIA	357	357	4.4	"Delivery system"	remove
ELSIE	357	357	4.4	"Delivery system"	We highly recommend better defining "delivery system"
AESGP	358	359	4.4 Leachables Study	For the sentence, 'If multiple batches are not available, alternative approaches may be proposed with justification.' what alternative approaches could be used?	Suggest alternative approaches or delete the sentence.
EfPIA	358	359	4.4 Leachables study	If multiple batches are not available, alternative approaches may be proposed with justification. It is not clear what alternative approaches could be justified.	Please provide an example or considerations for an alternative approach.
Medicines for Europe	358	359	4.4	How are multiple batches defined (2, 3 or more batches)? Currently, only one E&L batch per CCS submitted for EU.	
BioPhorum	359	361	4.4	It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. It needs some time to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability have to be demonstrated before starting a leachables study. In addition, extractables studies can be performed product independently. So they can be performed long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	Proposal: The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be used.
EfPIA	359	361	4.4	It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. It needs some time to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability have to be demonstrated before starting a leachables sudy. In addition, extractables studies can be performed product independently. So they can be performed long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	Proposal: The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be be used.
EfPIA	359	361	4.4	It is extremely unlikely the same lots of components used in the extractables studies will be available for any subsequent leachables assessment.	Please address comment (suggest removing the indicated sentence).
EfPIA	359	359	Section 4.4	Is it mandatory to "use of same lot components used in extractables assessments" or just a recommendation?	propose to give an example in the training material or Q&A after implementation

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	359	361	4.4	Using same lots for extractables/leachables is ideal but often impractical.	Revise to suggest representative lots; use same lots only if feasible. Proposed wording: Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables. If using the same lots is not feasible use of representative lots should be considered. "Using the same lot may not be achievable. Propose to revise to read, ""The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be be used."""
EfPIA	359	362	4.4	Extractables data is often assessed during initial material selection, where testing and data review take place. This early testing includes a number of aspects beyond extractables and leachables, such as filling operations, manufacturing testing, sterility testing, mechanical testing, and product quality. Because a specific leachables study may occur several years after the extractables assessment, the practical use of the same component lot is often nearly impossible. Instead, the material selection and quality procedures, including supplier quality agreements, support the fundamental assumption that new lots of the material remain representative of the material originally tested. Moreover, these supplier agreements typically guarantee lot-to-lot production within specifications for the life cycle of the drug product and require communication of vendor-initiated changes.	Where possible, use of the same lots of components used in extractables assessments potentially enables a more meaningful Linkage or Establishing Sources of Leachables between extractables and leachables.
EFPIA Drug-MD ICH STG	359	361	4.4	The guideline currently states, "Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables." Comment: It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, this may not be feasible, because extractables studies have to be performed at least several months before any leachables study. Time is needed to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability has to be demonstrated before starting a leachables study. In addition, extractables studies can be performed product independently, so they can be performed a long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	We recommend the following revision in the text of the guideline, "Where feasible, use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables."
ELSIE	359	361	4.4	Use of the same lots of components used in extractables Assessments potentially enable a more meaningful correlation between extractables and leachables. It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. Time is needed to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability has to be demonstrated before starting a leachables sudy. In addition, extractables studies can be performed product independently. So they can be performed a long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	Using the same lot may not be achievable. Propose to revise to read, "The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be be used."
ELSIE	359	361	4.4	While it may be ideal, it is impractical to use the same lot of components for the extraction study and leachables study. Extraction studies are executed months, more likely years, before the batches for leachables studies are manufactured and the same lots of components are probably no longer available. Rare opportunity to have the same component lots for both extractables and leachables	Recommend removing the suggestion to use the same lots of compoents for both E and L studies.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ferring Pharmaceuticals	359	361	4.4	Extractable study and leachable study will most often be prepared with some years in between. Not necessarily possible to get the same lot of the items. Will it then make sence to correlate E and L data? In addition, the extractable study is a screening study, where a real leachable study is with validated method(s), so anticipate the comparison should be qualitatively as it can't be quantatively.	Please consider
IPAC-RS	359	359	4.4	Leachables Study: It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. It needs some time to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability have to be demonstrated before starting a leachables sudy. In addition, extractables studies can be performed product independently. So they can be performed long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies. Can raise some customer difficulties to perform on some lot. Components ageing will be different due to the timing between extractables and leachables studies.	Current wording : Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables. Proposal: The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be used.
EfPIA	360	361	4.4	extractables and leachables	E&L
ELSIE	360	361	4.4	extractables and leachables	E&L
Medicines for Europe	360	361	4.4	The draft guideline proposes the use of the same lots of packaging or manufacturing components for both extractables and leachables evaluations to facilitate direct correlation. This approach presents significant practical limitations. Sourcing sufficient quantities of identical lots from external vendors is often not feasible due to supply chain constraints, batch variability, and limited availability of freshly manufactured components. Moreover, this approach would necessitate repeating extractables studies for each drug product that utilizes the same component, even when the component's extractables profile is already well-characterized. This redundancy increases resource burden without proportionate scientific benefit.	Change text to allow for use of different lots of packaging or manufacturing components. Can this be re-worded so that one doesnt read this and assume it's a requirement, or clarified that it is not a requirement? The wording is broad, but some people may infer that if something is listed in the guidance, even if it is a suggestion, that it is a requirement.
EfPIA	361	367	4.4	The AET appears relevant only for non-targeted screening methods according to the curent wording. Why ? The AET should also be considered for target leachables methods.	State that the AET is applicable to any type of leachables methods (target/non-target)
EfPIA	361	367	4.4	Clear guidance is given for the validation of target leachables methods. It is unclear what is expected for non-target leachables methods	Clarify what is expected regarding qualification of non-target methods
EfPIA	361	365	4.4 Leachable study	Leachable study targets require validation only when there is a need to have quantitative results. Based on safety this is occurring only when leachable compound may affect patient safety, and true amount is needed to evaluate whether eg batch release testing in regard of impurity is required.	Clarify that analytical method qualification or may be even validation is required only for leachables which posess safety risk for patients in the evaluated product.
EfPIA	361	367	4.4	Clarify expectations for non-targeted analysis of unexpected and low-risk leachables.	Recommend lighter validation for low-risk leachables in line 367. Proposed wording: It is recommended to apply abbreviated validation protocols for leachables identified as presenting low-risk.
EfPIA	361	367	4.3	The guideline has inconsistencies regarding validation requirements and suitability. We recommend aligning with a risk assessment methodology, ensuring analytical procedures are suitable for their intended purpose and proportionate to the risk level. Please see ICH Q3D which provides a statement that the procedures should be suitable for their intended purpose.	To be updated: Use words such as fit for its intended purpose, or suitable for intended purpose. Methods descriptions can be provided.

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ELSIE	361	367	4.4	Section 4.4 specifies the monitoring of specific target leachables, is sensible when such an approach is justified. It also advocates for the non-targeted analysis of "unexpected leachables" which is a more complicated task then this section appropriately captures. For example, does this section advocate developing and validating a method for leachable targets and then analyzing the sample with the suite of non-targeted methods used in the extractables characterization study? Or, is the intent to identify any unexpected peaks with the targeted leachable method? Cannot unexpected leachables be captured in the extractables/screening assessment via the analysis of actual aged or representative product samples? "Analytical procedures for specific, targeted leachables should be appropriately validated to establish that they are sensitive, selective, accurate, and precise" • A full validation with sensitivity, selectivity, accuracy and precision is a heavy task in terms of ressources, especially for large volume parenterals where the number of actual leachables can be elevated. If we agree that critical leachables should be analyzed with such validated methods, then for leachables with less risk, a lighter process should be allowed. Therefore the notion of critical leachables (Safety margin ~1) should be noted here. • Term "validated" suggests the quantitative analysis is expected for targeted leachables, not merely qualitative or semi-quantitative detection Leachable study targets require validation only when there is a need to have quantitative results. Based on safety this is occurring only when leachable compound may affect patient safety, and true amount is needed to evaluate whether, e.g., batch release testing in regard of impurity is required.	More information is warranted as to how the non-targeted analysis of unexpected leachables fits in with the overall E/L program as well as the specifics of how it should be executed. For leachables with less risk, a lighter process should be allowed. Therefore the concept of critical leachables (Safety margin ~1) should be noted here. • Based on rationale we recommend following text change: "Analytical procedures for specific, targeted leachables should be appropriately validated qualified to establish that they are sensitive, selective, accurate, and precise" Clarify that analytical method qualification or may be even validation is required only for leachables which posess safety risk for patients in the evaluated product.
Laboratoires Théa	361	362	4.4	Is it acceptable to use a limit test to prove that the leachable concentration is lower than the tox limit?	
EfPIA	362	365	4.4	What are the method qualification requirements for non-targeted screening procedures?	Clarification needed
EfPIA	362	365	4.4	What would the mentioned "non-targeted screening procedures" be in the context of trying to detect and measure "unanticipated degradtion of leachables, …"? Are you implying that the analytical method should be developed to capture hypotethical or potential secondary leachables? How relevant would these be to define risk of hazard to the patient? This sentence seems speculative.	Recommend deleting the entire sentence: hunting after "secondary" degradation products, whether they are from forced degradation studies or from leachable studies, doesn't seem to be a useful exercise that can provide relevant information to the risk assessment. Only chemical entities that are directly detected during the extractable study/ies should be in scope.
EfPIA	362	367	4.4	This statement sounds like screening is mandatory, but Why? When we have relavent extractable data and know to be risk is low such as tox assessment of extractable profile, route of adminstartion, treatment duration....Such cases no need of screening	Clarify wording to avoid misinterpretation.
ELSIE	362	362	4.4	Method parameter validation should follow ICH Q2	Include reference
ELSIE	362	365	4.4	What are the method qualification requirements for non-targeted screening procedures?	Clarification needed
Laboratoires Théa	362	367	4.4	As the goal of the non-targeted screening study is to look for unknows compounds and it is therefore not possible to qualify/validate adequately an analytical method, is it acceptable to use the screening analytical method from extractables study to perform this analysis? Which extraction conditions need to be applied?	
EfPIA	363	366	4	For non-targeted screening procedures in leachable studies it is stated that these "should also be used", consider to open up for a more scientically sound risk based approach.	Modify l. 364: "Non-targeted screening procedures should also be used if scientifically justified".
EUCOPE	363	367	4.4 Leachables Study	Clarity is need about whether method qualifications are required for non-targeted screening procedures (i.e., are GMP qualified instrument required)	

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Ferring Pharmaceuticals	363	363	4.4	Screening leachable study introduced here in addition to a real leachable study. Not clear which requirements there are for each type of study and when to initiate them. Not clear whether this is both for primary packaging, devices and process contact items (PCI's). Anticipate this is primarily for primary packaging.	Propose to make the definition for these studies clear and when to use them. E.g. If no extractables above AET is detected, then a screening leachable study is initiated to investigate potential leachables originating from e.g. secondary packaging. A real leachable study is performed to monitor extractables detected above the AET and to explore whether the extractable becomes a leachable. Also worth to specify that a screening leachable study use screening techniques, where a real leachable study use specific and validated analytical methods developed with the purpose to detect the specific and identified leachable. Define which kind of items these study should be performed on e.g. primary packaging and devices. It should be clarified if this is not for process contact items (PCI's).
EfPIA	364	365	4	Performance of leachables study from secondary packaging may not be relevant, as the primary packaging should be suitable for protecting the medicinal product.	Proposal to remove the leachables study performance from secondary packaging.
EfPIA	365	367	4.4		It is proposed to adapt "The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, quantified, and reported for toxicological assessment." to "The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified and quantified, and reported for toxicological assessment at level above the SCT."
IPAC-RS	365	367	4.4	Leachables need to be reported when they exceed SCT, not AET, unless they cannot be definitively identified and quantified.	"The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, quantified, and potentially be reported for toxicological review." We note that the term AET can be used here but please add some text to ensure that the AET is not the trigger for a toxicological assessment. The SCT is used to determine if any tox assessment is done. It may be helpful to provide a brief explanation of the conversion of an SCT to AET and the use of AET. Note that this comment is also applicable to Lines 393, 421 and 538 (Section 6.3). Note the comments in the next row
ELSIE	367	367	4.4	"The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, quantified, and reported for toxicological assessment" • The guideline's expectation to "quantify" leachables in a non-targeted study implies that the method used must be sufficiently validated, even though non-targeted methods are typically used for identification and detection, not precise quantification	•We recommend following text change: "The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, semi-quantified, and reported for toxicological assessment"
EfPIA	368	368	4.4	Using reference standards enhances the accuracy of extractables quantification by ensuring the measured values closely reflect the true concentrations. Precision, on the other hand, refers to the method’s ability to consistently produce repeatable results under the same conditions.	"more accurate quantitation"
EfPIA	368	368		Here correlation is described as "correlation between extractables and leachables" is is not in aligment with section 4.6 which describes "leachables to extractables correlation"	Change wording to "leachables to extratables correlation"
EfPIA	368	368	4.4	Refernce standards or appropriately justified and characterized standards (even if they have to be surrogate standards) must be used for leachables studies	Modify to: ". . . Reference standards or appropriately justified and characterized standards must be use to facilitate the most accurate and . . ."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	368	368	4.4	Using reference standards enhances the accuracy of extractables quantification by ensuring the measured values closely reflect the true concentrations. Precision, on the other hand, refers to the method’s ability to consistently produce repeatable results under the same conditions.	"more accurate quantitation"
ELSIE	368	368	4.4	"Reference standards, if available, are preferred as they facilitate more accurate and precise quantitation of target leachables that may be present as actual drug product leachables when ...." • The term"reference standards" could be missleading or too broad. suggesting that the standards used for E&L studies are qualified for use as detailed in ICH Q7	• We recommend replacing "refernce standards" term with more specific terminology aligned with pharmacopeial definitions such as "traceable standards" or "authentic verification compounds", as defined in USP
ELSIE	371	371	4.4	• Editorial correction : "...analytical accuracy and precision is high."	• "...analytical accuracy and precision are high."
AESGP	372	372	4.5 Simulated Leachable Study	A Simulated Leachable Study is also commonly called "Simulated-Use Extractable Study". Consider adding this for clarity.	Add this information in 373.
BioPhorum	372		4.5	As technologies evolve, there is an expectation that well-constructed simulation or extractables studies should be able to satisfy risk assessment requirement, especially for components further and further upstream of the final container. The language in this section continues to emphasize that leachables are required for all components (including single-use and perhaps many upstream low-risk materials), and that simulation/extraction studies may be considered in addition to this onerous expectation. Statements such as #425 elude to advantages, but the messaging feels disjointed)	Recommend ICH advocating for when simulation studies or extractables studies may be able to replace leachables studies, especially is this offers advantages to drug development cost and timelines.
EfPIA	372	372	4.5	"Simulated leachable study" is misleading—actual drug product not used.	Rename to "Simulated extractables study" or "Simulation Study" with a description to avoid confusion.
ELSIE	372	414	4.5	In the simulated leachable study, can you propose some solvent to be used?	Please consider: (1) common solvent to be used for simulated leachable study as Isopropanol:water such as in USP <1663>; (2) time point and duration of Simulation should be tested, same as ICH Stability studies requirements? (3) if product is terminal sterilized, but solvent can not be sterilized should one use USP <661.2> such as 50°C for 72hrs or 70°C 24 hrs before storage?
Ferring Pharmaceuticals	372	372	4.5	Introduction of an additional leachable study (simulated). How does these different leachable studies hormonize with USP 1664 and WHO guideline?	Propose to make it clear e.g. by an overview - the different kind of E&L studies and for which kind of items (primary packaging, device or PCI's they are supposed for). Would be helpful with alignment with USP chapters for E&L as well as WHO guideline.
EfPIA	373	391	4.5	If an extractables-only assessment is acceptable, then simulated leachables studies ARE also acceptable. Simulated leachables studies are a more realistic, yet still worst-case assement than leachables. In effect, simulated leachables studies are another scientifically justified step available in a thoughtful, scientifically rigorous e/l program.	Begin paragraph something like, Another option in the e/l process is a simulated leachables study. Less rigorous than an extractables study, yet more rigorous than a leachables study. Simulation leachables studies typically involve higher temperature, greater product contact surface area, worst-case extracting solvent and/or formulation or placebo. Simulated leachables studies can be semi-quantitative (e.g., limit test) or quantitative. In addition to being another option in an e/l program, it can help address shortcomings in leachables studies. [then go into the examples]
ELSIE	373	376	4.5	Circumstances that would preclude a drug product leachables study are presented.	It would be helpful to clarify if the reference to leachables studies in this context refers to both targeted and non-targeted (screening) leachables studies.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	373	386	4.5	Section "Simluated leachable study" revised for clarity	Proposed text: Circumstances may exist when performing a drug product leachables study is not technically feasible. Such circumstances may include challenging detection or quantification thresholds associated with large volume parenterals (LVPs), significant analytical matrix interference inherent with complex drug product formulations, or a combination of such factors. Prior to performing simulated leachables studies, due diligence should be performed to evaluate a product leachables study, which may include systematic investigation of multiple diverse sample preparation techniques coupled with highly sensitive and selective analytical methods, techniques and instrumentation. Where impractical or not feasible, the use of a simulation study to support actual drug product leachables evaluation may be justifiable.
Ferring Pharmaceuticals	380	381	4.5	Meening of the sentence is not fully clear. Seems like a 'simulated leachale study' is a supplement to a real leachable study, but in line 373 a 'simulated leachable study' should substitute a real leachable study.	It should be rewritten to become aligned with line 373 and the purpose with a simulated leachable study.
EfPIA	382	384	4.5	A clarification would be needed to explain how "a simulation study would be performed to fill in the gap between the LOQ and the AET". The entire section sounds ambiguous and speculative, without adding more specifics on what is expected on a simulation study taht compensate for concrete analytical barriers. Shouldn't this be left to the Applicant to determine an appropriate analytical plan?	The entire Section 4.5 is rather confusing without adding more specifics on what should be considered for "simulation conditions", given the risk of generating spurious data that are not relevant to the manufacturing process and storage conditions. If anything, a simulation study would pertain to the extractable phase of the assessment, not to the leachables.
AESGP	383	385	4.5	Simulation study to fill the gap between AET and LOQ: unclear how this can be used. An example would be helpful.	Is a qualitative evaluation or an evaluation down to LoD needed or what other kind of gap filling is feasible
Ferring Pharmaceuticals	384	386	4.5	Is it the same meaning as in line 373? Line 386: is the word 'established' the right word in this sentence?	Propose to move and / or merge the sentence with line 373. Line 386: "it is established that..." --> "it is concluded that..."
AESGP	389	391	4.5	It is stated that no potential interaction between leachables and DP formulation can be assessed. But this is only the case if artificial solvents are used. If a simulation study is performed with formulation but just using e.g. different thresholds or conditions, these interactions might be detectable	Rephrasing needed: in case of simulation studies with artificial solvents instead of formulation the interactions might not be visible
ELSIE	391	391	4.5	• Editorial correction : "...components of the drug product formulation components" (a duplicated word)	• "...components of the drug product formulation ~~components~~."
Ferring Pharmaceuticals	392	393	4.5	"...that reveals likely true leachables that..."	Propose to rephrase eg. "...that most likely reveals true leachables..."
EfPIA	393	395	4.5	It is considered important to clearly distinguish the purposes of the chemical assessment and the toxicological assessment within the overall evaluation framework. The conversion of SCT to AET enables an analytical chemist to address the question of whether a specific E/L needs to be quantified and identified. The AET represents the threshold above which a compound should be quantified and identified as a prerequisite for its potential toxicological assessment.	It is proposed to adapt "Thus, the simulated leachables detected above the simulation study's drug product specific AET should be identified, quantified, and assessed for safety." to "Thus, the simulated leachables detected above the simulation study's drug product specific AET should be identified and quantified, and reported for toxicological assessment at level above the SCT."
ELSIE	393	395	4.5	"Thus, the simulated leachables detected above the simulation study's drug product specific AET should be identified, quantified, and assessed for safety." •The guideline's expectation to "quantify" simulated leachables above the AET suggests that the analytical method used must be validated, even though the study is simulated and may not involve the actual drug product	• We recommend following text change: "Thus, the simulated leachables detected above the simulation study's drug product specific AET should be identified, semi-quantified or quantified, and assessed for safety."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	393	395	4.5	Simulated leachables need to be assessed for safety if they exceed SCT (not AET)	Thus, the simulated leachables detected above the simulation study's drug product specific ~~AET~~SCT should be identified, quantified, and assessed for safety.
AESGP	395	400	4.5 Simulated Leachable Study	The intent of the simulation study may be to replace a leachables study, but the current text sounds like it should be followed by a leachables study. As the leachables study may no longer be required after the similated study, the text should be clarified.	As the goal of a simulation study is to obtain a simulated leachables profile that closely mimics the actual leachables profile generated by the drug product over its shelf-life~~, the simulation conditions and process used in the simulation study should closely match the drug product manufacturing/storage conditions used in a leachables study~~, with the intent of simulating the conditions experienced by the drug product during its manufacturing, shelf-life storage, and in-use (clinical) preparation.
EfPIA	399	400	4.5	According to this sentence, the simulation study should cover the in-use (clinical) preparation. Does this apply to all cases or only to drugs that are developed/co-packed.	Clarify the scope of in-use materials (i.e. whether the scope goes beyond drugs supplied co-packed)
ELSIE	400	401	4.5	"Furthermore, the simulation solvent should be chosen so that is has a similar propensity to leach as the drug product, and the simulated manufacturing process should be performed using worst-case conditions" • Clarification of the sentence should be provided, along with examples of acceptable justification for the choice of simulation solvent	• We recommend to provide exmples of acceptable approaches to justify the choice of simulations solvent, in this part of guidline • Editorial correction: "Furthermore, the simulation solvent should be chosen so that is it has a similar propensity to leach as the drug product, and the simulated manufacturing process should be performed using worst-case conditions"
Ferring Pharmaceuticals	401	402	4.5	... Simulation solvent...' introduced. Should it be introduced earlier that a solvent is used to mimic the drug product?	Consider to reevaluate the content / study design.
ELSIE	402	402	4.5	"the simulated manufacturing process should be performed using worst-case conditions" "As the goal of the simulation study is …....closely match the drug product manufacturing/storage conditions…" See lines 395-400. "Worst-case" and "closely match" don't align. Can this be clarified? (See suggested revision)	Remove "and the simulated manufacturing process should be performed using worst-case conditions" line 402
IPAC-RS	402	402	4.5	"the simulated manufacturing process should be performed using worst-case conditions" "As the goal pf the simulation study is …....closely match the drug product manufacturing/storage conditions… line 395-400. "worst-case" and "closely match" doesn't align. Can this be clarified?	remove "and the simulated manufacturing process should be perfrmed using worst-case conditions" line 402
ELSIE	403	405	4.5	Moreover, a simulation study can be accelerated versus drug product shelf storage conditions to mimic the outcome of a leachable study over the entire drug product shelf life with shorter duration.	Please provide example of what is duration required " Shorter Duration" such as 40°C- 6 months only?
BioPhorum	406	408	4.5	Clarify the meaning of „qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
EfPIA	406	408	4.5	Clarify the meaning of „qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
EfPIA	406	414	4.5	This paragraph is verbose and can be simplified as the concepts have already been mentioned in the guideline; make cross-references as appropriate	"Simulation leachable studies may be used to augment or replace leachables studies when the latter are impractical. They must meet the same quality standards, including method qualification. Their use must be scientifically justified, supported by appropriate testing, and aligned with regulatory expectations. Prior consultation with the relevant regional Regulatory Agency prior to implementation may be warranted".

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	406	414	4.5	This paragraph is verbose and can be simplified as the concepts have already been mentioned in the guideline; make cross-references as appropriate	"Simulation leachable studies may be used to augment or replace leachables studies when the latter are impractical. They must meet the same quality standards, including method qualification. Their use must be scientifically justified, supported by appropriate testing, and aligned with regulatory expectations. Prior consultation with the relevant regional Regulatory Agency prior to implementation may be warranted".
ELSIE	406	408	4.5	Clarify the meaning of "qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
Ferring Pharmaceuticals	406	408	4.5	Is it screening methods or specific methods that are used? If "all the quality requirements for a leachables study" - it could be read as specific developed and validated methods. If "test procedure qualification" - it could be read as screening methods.	Please clarify / specify what is expected here.
IPAC-RS	406	408	4.5	Clarify the meaning of "qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
ELSIE	412	414	4.5	"When considering the use of a simulation study, consultation with the relevant regional Regulatory Agency prior to implementation may be warranted." This is very US oriented and not all country has the opportunity to discuss in advance. In addition, the study could be submitted to several authorities.	
AESGP	415	444	4.6	In many cases, semi-quantitative extractable studies are the basis for target leachable studies. Target and semi-quantitative data obtained with different methods are not directly comparable. Espacially a quantitative correlation might lead to contradictory results	It should be stated in this paragraph that the L & E correlation should only be made with quantitative target data or response factor variations, UFs... need to be considered and in the usual case of using different analytical methods, differences in quantitative values are to be expected
EfPIA	415	444	4.6 Extractable and leachable correlation	ICH Q3E should provide examples about E&L correlation. When that is presented as requirement for documentation and compliance, it should be solely proven phenomenon where examples are available easy.	Extractable study sample extraction conditions are so harsh that compounds might be decomposed, or then solvent extractions obligatory for materials are not representative for interactions between drug products and contact materials.
EfPIA	415	444	4.6	Suggest that correlation will be only needed if leachables > AET and pose safety concern.	Proposed Wording: If leachables exceed AET ~~Once the E&L profiles above AET are available~~, it is recommended that a qualitative and quantitative correlation ~~between the two~~ be evaluated between the extractables and leachables studies. Provide examples.
EfPIA	415	444	4.6	Change "Correlation" to "Linkage" or "Establishing Sources of Leachables." Clarify that while a qualitative and quantitative link between leachables and extractables is recommended for evaluation, a consistent mathematical correlation is often not achievable. Please see knowledge in relevant publications to support this request.	
EFPIA Drug-MD ICH STG	415	444	4.6 E&L Correlation	Add text to Section 4.6 (E&L Correlation) to specifically highlight the drug-device interface as a critical area where unique interactions (e.g., adsorption, degradation, new adduct formation) might occur and affect the leachable profile.	Rationale: The interface is often a unique chemical and physical environment in DDCPs compared to standard drug product containers.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	415	444	4.6	"4.6 Extractable and Leachable Correlation." Line 421: " Once the E&L profiles above AET are available, it is recommended..." •Correlation is only meaningful if leachables are detected above the AET. This should be highlighted in the guidance. •No need for correlation if leachables are below PDE and pose no safety concern and the rationale for performing a correlation study becomes questionable. This also should be highlighted int he guideline. ICH Q3E should provide examples about E&L correlation. When that is presented as requirement for documentation and compliance, it should be solely proven phenomenon where examples are easily available.	• We recommend replace begining of the sentence in line 421: " If leachables are detected over the AET Once the E&L profiles above AET are available, it is recommended..." Extractable study sample extraction conditions are so harsh that compounds might be decomposed, or solvent extractions obligatory for materials are not representative for interactions between drug products and contact materials.
ELSIE	415	444	4.6	It is suggested that the terminology be updated from 'Correlation' to either 'Linkage' or 'Establishing Sources of Leachables.' Furthermore, it should be clarified that while assessing a qualitative and quantitative connection between leachables and extractables is advisable, achieving a consistent mathematical correlation is frequently not feasible, if not impossible.	Update from 'Correlation' to either 'Linkage' or 'Establishing Sources of Leachables.'
Laboratoires Théa	415	444	4.6	Is it possible to add in annex an example of extractables/leachables correlation?	
Medicines for Europe	416	434	4	The discussion on the correlation between extractables and leachables provides a solid foundation, but the guideline could benefit from clearer protocols on how to conduct such correlations effectively.	For instance, specifying the methodologies for qualitative and quantitative correlation assessments, including best practices for data analysis and interpretation, would aid manufacturers in implementing these concepts.
Ferring Pharmaceuticals	417	417	4.6	Extractable studies are performed by using analytical screening techniques. The purpose of an extractable study is not to development of methods for target leachables, but the screening methods can be used as a starting point for development of a specific method for a specific leachable. Screening methods are not validated, which a specific leachable method should be.	Propose to delete '...develop methods for tartgeted leachables...' or rephrase.
AESGP	418	419	4.6	Besides leachables being prone to degradation or reactive leachables, these usually are a subset of extractables	Extend the sentence with the exceptions of degradable and reactive leachables
Qualimetrix SA	419	420	4.6	This is the theoretical, and especially if the extractable is performed, as suggested by the guideline, under exaggerated conditions, this will be far from truth.	
EfPIA	420	420	4.6	"well conducted" is subjective . See recommendation	"an appropriate" or "adequate"
ELSIE	420	420	4.6	"..well conducted" is subjective. What constitutes a well conducted study might vary from manufacturer to manufacturer and among health authorities. The current language slightly implies a judgment regarding the quality of such studies	Suggest using "fit for purpose" instead
Maven E&L Ltd	421	422	Section 4.6	I would suggest that "…E&L Profile.." is defined. Suggested reword, "Once the E&L Profile (profile meaning the identified collect of substances as both extractable and leachable and their concentrations above the leachable AET)…"	Once the E&L Profile (profile meaning the identified collect of substances as both extractable and leachable and their concentrations above the leachable AET)…
AstraZeneca	421	422	Section 4.6	I would suggest that "…E&L Profile.." is defined. Suggested reword, "Once the E&L Profile (profile meaning the identified collect of substances as both extractable and leachable and their concentrations above the leachable AET)…"	Once the E&L Profile (profile meaning the identified collect of substances as both extractable and leachable and their concentrations above the leachable AET)…
EfPIA	421	422	4.6	It should be clearly stated that leachable studies are not always required.	Please address comment.
GUERBET	421	422	4.6	Is the correlation between Extractables and leachables recommended or mandatory ?	Change the word "recommended" if needed
IPAC-RS	421	421	4.5	This is the SCT not AET, as in multiple other locations in the document. See comment in row 61.	Revise to, "Once the E&L profiles above ~~AET~~SCT are available,…."
Ferring Pharmaceuticals	422	425	4.6	"... quantitative correlation..." Extractable studies are performed by using analytical screening techniques and some uncertainty factors = semi-quantitative results. Real leachable studies are performed by using validated leachable specific analytical method developed to be able to quantify a specific leachable. Extractable studies are normally performed on individual components / items. Is extractables studies supposed to be performed on systems as well and in which cases? (line 425)	Therefore, will it be relevant to correlate two different kind of results (comparison of semi-quantitative data with quantative data)?

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	424	454	4.6 title	The title of the section is "Extractable and leachable correlation" but the text refers to correlating leachables to extractables (line 227 "a leachables to extractables correlation ....", line 431 "A correlation between leachables and extractables…", line 433 "Correlating leachables with extractables….", 454 "meaningful leachables to extractables correlation...".	Change title of section 4.6 to "Correlation of leachables to extractables" to reflect the text describing the correlation
EfPIA	425	428	4.6	The term 'routine' is confusing in the scope of E&L about routine testing as it implies a systematic testing such as a Quality control approach. The concept of "high risk drug product" is not common and will be undertood in different ways (e.g. drug for specific vulnerable population, narrow therapic margin), therefore extending this requierment to different types of "at risk" situations.	In certain cases, Correlating leachables with extractables may support a justification for the use of ~~routine~~ extractables testing of components as an alternative to ~~routine~~ leachables testing ~~during stability studies when appropriate for high-risk drug products, change control, and ongoing quality control.~~
ELSIE	425	428	4.6	A proposal for using routine extractables testing as an alternative to routine leachables testing is presented for high-risk products once an extractables and leachables correlation is established.	Will this be widely accepted by regulatory authorities? Additional rationale, and perhaps a dedicated section, would be very helpful to understand this strategy further, especially for QC applications.
ELSIE	425	428	4.6	"Correlating leachables with extractables may support a justification for the use of routine extractables testing of components as an alternative to routine leachables testing during stability studies when appropriate for high-risk drug products, change control, and ongoing quality control. " •Routine testing should be driven by toxicological relevance, not applied universally. Routine testing may not be necessary if leachables are below AET or pose no safety concern — the guideline should clarify that routine testing is not warranted when leachables are consistently below the AET or the PDE, in line with ICH M7, which allows for reduced testing if exposure is <30% of PDE	• Correlation is meaningful only when safety concerns exist — for high-risk drug products, where leachables are detected above AET and pose potential safety risks, correlation between extractables and leachables can be used to justify routine extractables testing as a surrogate for leachables testing. We recommend addition of the following text: "Routine testing is not necessary if leachables are less than AET or are detected at less than <30% of PDE (in alignment with the ICH M7)."
Ferring Pharmaceuticals	425	428	4.6	How can a routine extractable study substitute a routine leachable study, when screening techniques are used in extractable studies and specific methods in a real leachable study? Will it make sence to do so, if a method is developed and validated for a specific leachable?	Propose to reevaluate the sections and add a definition of routine extractable and leachable testing.
GUERBET	425	428	4.6	Is it possible to use the correlation between Extractables and leachables to perform leachables on 1 batch only, the absence of variability between 3 batches of packaging beeing verified through extractables ?	Add this example in the chapter if possible
BioPhorum	426		4.6	unclear reference to 'routine leachables testing'	clarify "routine leachables"
EfPIA	430	430	4.6	This is not an exhaustive list	"include, among others, inadequate"
EfPIA	430	430	4.6	inadequate desing and/or execution of extractables study' Delete that from ICH Q3E.	Inadequate study design and/or execution must be observed from many other factors as well. Lack of correlation between extractable and leachable study data is not appropriate parameter to evaluate correctness of extractable/leachable studies.
ELSIE	430	430	4.6	This is not an exhaustive list	"include, among others, ..."
ELSIE	430	430	4.6	inadequate design and/or execution of extractables study'. Delete that from ICH Q3E. Inadequate study design and/or execution must be observed from many other factors as well. Lack of correlation between extractable and leachable study data is not appropriate parameter to evaluate correctness of extractable/leachable studies.	Delete phrase
AESGP	431	320	4.3.1 Semi-Quantitative Extractables Study	A semi quantitative extractables study may also provide sufficient reassurance without progressing to a leachables study if the appropriate uncertainty factors are applied to derive the AET, such that the AETs are not underestimated due to analytical concentration estimates.	Add 'A semi quantitative extractables study may also provide sufficient reassurance without progressing to a leachables study if the appropriate uncertainty factors are applied to derive the AET'

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IPAC-RS	432	432	4.6	Extractable and Leachable Correlation: The external environment such as secondary packaging could also be considered as a potential source of non-identified leachables	Suggest to mention awareness of secondary packaging as a potential source of non-identified extractables, during the ICH training sessions (no need to include in the written guideline).
ELSIE	433	433	4.6	" ...due to aging (e.g., exposure to UV light, heat, oxygen) during shelf-life storage." • The term "during shelf-life storage" is not clear.	• We recommend to revise text: " ...due to aging (e.g., exposure to UV light, heat, oxygen) during ~~shelf-life~~ storage."
EfPIA	434	434	4.6	"quality risk" is unnecessary	"risk"
ELSIE	434	434	4.6	"quality risk" is unnecessary	"risk"
BioPhorum	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient. Consider the use of equivalency vs correlation (aligned with USP665) and provide proposals on how to demonstrate equivalency; clarify and provide guidance on where prior knowledge can be applied/leveraged. Verification is still required against routine process conditions (assessed by end user)
EfPIA	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient.
ELSIE	435	436	4.6	"Though the E&L correlation is valuable and informative for the quality risk assessment and may be leveraged for component selection and life-cycle management decisions, it is the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." • The sentence is clear and should be included in section 1. Introduction, of the guidline.	• We recommend adding this sentence to section 1. Introduction, after line 6.

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ELSIE	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient.
IPAC-RS	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient.
Medicines for Europe	437	444	5	According to the guideline: If a specific leachable is observed in the drug product during stability studies at a level significantly greater than anticipated from the calculated potential maximum level of the leachable as established with the extraction study conducted on the same component/system lots as were used for the drug product stability batches, it can indicate that the extraction study was incomplete and it may not be possible to establish a meaningful leachables to extractables correlation for that particular leachable. Clarification is required to ensure alignment.	Clarify if it is mandatory to include and test the specific leachable during stability studies of the drug product? In which cases the specific leachable should be included in the drug product specification?
Medicines for Europe	437	444	4.6	The guideline recommends establishing both qualitative and quantitative correlation between extractables and leachables profiles and re-evaluating these correlations if significant changes occur during the product lifecycle. Certain leachables may originate not only from extractables but also from interactions between leachables and the API and/or excipients, migration of chemicals from packaging, or new leachables formed due to material aging or degradation. In such scenarios, quantitative correlation may not always be achievable or meaningful. Also it is requested that the guideline clarify the recommended approach or way forward when a meaningful correlation between extractables and leachables cannot be established.	Delete "quantitative" correlation and use qualitative correlation of extractables and leachables only. Provide example in training materials how to format such correlation and where to place it in CTD.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	437	444	4.6	The draft guideline proposes both qualitative and quantitative correlation between extractables and leachables profiles. While such correlation may offer scientific value in principle, its practical implementation presents significant challenges. Plastic components used in manufacturing and packaging undergo ageing during their shelf life, similar to finished drug products. This ageing process can lead to fluctuations in extractables profiles over time. To ensure a reliable quantitative correlation, extraction studies would need to be conducted at multiple timepoints for each component. This requirement is logistically burdensome and often infeasible, particularly because it is nearly impossible to consistently source components immediately after manufacturing from vendors. Volatile organic compounds are typically more abundant in freshly produced components and may evaporate before testing, leading to insufficient extractables data. This undermines the reliability of quantitative correlation and may introduce variability that is not representative of actual leachables exposure during product use. Furthermore, identical compounds may originate from non-E&L sources such as residual solvents from API purification, unspecified immediate packaging components from API/excipients or residual cleaning agents from tools used in any of the steps in the manufacturing chain. Such sources are not apparent as typical qualification levels of impurities of API/excipients and cleaning validations exceed the thresholds applied in E&L studies by far. Therefore, a qualitative correlation of leachables to extractables should be sufficient.	Delete "quantitative" correlation and use qualitative correlation of extractables and leachables only.
EfPIA	438	438	4.6	extractable/leachable	E&L
ELSIE	438	438	4.6	extractable/leachable	E&L
Ferring Pharmaceuticals	439	444	4.6	It could also indicate that aging of an item in combination with DP and not neccarily an incomplete extracdtion study. Again - which kind of items are supposed to undergo this assessment? PCI's doesn't have both extractable and leachable studies performed.	Propose to rephrase.
ELSIE	440	442	4.6	"....studies at a level significantly greater than anticipated from the calculated potential maximum level of the leachable as established with the extraction study conducted on the same component/system lots as were used for the drug product stability batches..." Although analysing the same batch for correlation table is an ideal scenario, it is almost impossible to apply it in practice.	
AESGP	445	471	5	The guideline states that the Analytical Evaluation Threshold (AET) should be derived from an appropriate Safety Concern Threshold (SCT), but it is not entirely clear whether, for semi-quantitative extractables assessments, the SCT should be based on the Threshold of Toxicological Concern (TTC) or on a Qualification Threshold (QT). In practice, laboratories often apply the TTC (systemic toxicity basis) during early extractables screening to ensure conservative coverage, while QTs are typically applied during leachables risk assessment when the route-specific local toxicity endpoint is better understood. Clarifying whether ICH Q3E intends for the QT or TTC to be used in the initial extractables AET calculation — or allowing a stepwise approach (TTC for initial screening, QT for confirmation) — would promote consistency and harmonization across industry and regulatory submissions.	
Bio-Process Systems Alliance	445	484	5	Analytical Methodology and Validation-The draft refers generally to “fit-for-purpose validation” but does not detail expectations for non-targeted analyses (e.g., GC-MS, LC-HRMS screening).	Include a table or annex specifying minimal validation characteristics (e.g., mass accuracy, repeatability, semi-quantitative linearity) for non-targeted workflows distinct from conventional ICH Q2(R2) methods.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	445	471	5	The draft guideline proposes the use of compound-specific safety limits exclusively for Class 1 leachables. However, it does not provide a scientific rationale for restricting this approach solely to Class 1 substances. This limitation appears arbitrary and may impede the broader application of scientifically justified safety assessments. The Analytical Evaluation Threshold ensures that no unidentified peak is excluded from toxicological evaluation. It therefore functions as a performance criterion for analytical methods, where failure to achieve a limit of quantification below the AET for a given leachable may render the method inadequate. Mitigation using additional methods or simulated leachable studies can be impractical depending on the number of affected leachables. Once a peak is identified in extractable studies, it becomes feasible to establish compound-specific safety limits based on toxicological data. Therefore, any leachable with a known toxicological profile, regardless of its classification, should be eligible for evaluation using compound-specific safety limits. The guideline should clarify that these limits can be considered in determining the acceptability of analytical methods to reduce the complexity of leachable studies without compromising patient safety.	Clarify that for targeted leachable analysis a compound-specific safety limit (PDE) can be used to determine the acceptability of the analytical method.
EfPIA	446	448	5	AET is not a control threshold. Control threshold is not defined. Also definitions should generally not include exceptions but describe the meaning of the word.	Delete "not a control theshold".
EfPIA	446	448	5	It is considered important to clearly distinguish the purposes of the chemical assessment and the toxicological assessment within the overall evaluation framework. The conversion of SCT to AET enables an analytical chemist to address the question of whether a specific E/L needs to be quantified and identified. The AET represents the threshold above which a compound should be quantified and identified as a prerequisite for its potential toxicological assessment.	It is proposed to adapt "The AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified, quantitated, and reported for safety assessment, forming the foundation of the overall E&L risk assessment and control strategy." to "The AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified and quantitated, forming the foundation of the overall E&L risk assessment and control strategy."
IPAC-RS	446	448	5	We disagree with this definition of AET. Safety assessments should be triggered by SCT, not AET. The definition of AET should align with the definition from PQRI: 'The AET is defined as the threshold at or above which an analytical chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.' The SCT will drive whether the toxicological assessment is undertaken.	The AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified, quantitated, and reported for potential safety assessment, forming the foundation of the overall E&L risk assessment and control strategy.
EfPIA	447	447	5	Its not only above the AET, also at the AET level	"at or above the AET"
ELSIE	447	447	5	Its not only above the AET, also at the AET level	"at or above the AET"
AESGP	448	449	5. AET	A control strategy is not required for certain low risk scenarios, e.g. oral drug, nasal preparations, topical cream for dermal use using GMP manufacturing systems and compendial grade containure closure systems.	Add this statement.
EfPIA	448	448	5	"overall" E&L risk assessment	Remove "overall"
EfPIA	448	448	5	The term "overall E&L risk assessment" is certainly understood by E&L experts, however alignment with the term defined earlier in the guideline (Risk Assessment/Fig 1 and related section) is wished to be consistent throughout the document	Proposed wording/change: "[...] forming the foundation of the E&L risk assessment and control strategy"
ELSIE	448	448	5	"overall" E&L risk assessment	Remove "overall"

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BioPhorum	455		5	(SUT) The statement "extraction study should include the establishment and application of an AET" does not consider that standardized extractions studies may be generated with a reporting limit, and not in conjunction with an AET.	Suggest, 'Assessment of extractables study results should be based on a clearly established AET…" An extraction study should include the establishment and application of an AET (or reporting limits) to indicate extractable chemical entities to be detected, identified and reported as potential leachables for the drug product.
EfPIA	455	455	5	The term "Extraction study" is used, while in other section of the document the term "Extractables study" is used. While we all understand that "Extraction study", "Extractables study" or "Controlled Extraction Study" can equally be used, it would be wished to have in such guideline aiming at harmonizing practices also harmonized vocabulary.	Proposed wording/change: "An extractables study should include the establishment [...]"
EfPIA	456	456	5	simplify "extractable chemical entities"	"extractables"
ELSIE	456	456	5	simplify "extractable chemical entities"	"extractables"
ELSIE	456	460	5	The proposed TTCs/QTs that ultimately lead to the AET would not account for the class I leachables (for example benzapyrene).	Class I leachables should be included as standards in every study; that way, they would be captured if present.
Ferring Pharmaceuticals	456	456	5	Extractables are normally also tox. Evaluated, if the semi-quantitative calculated concentration is above the study specific AET.	Propose to add that --> to be detected, identified, reported as... and finally tox evaluated.
Octapharma	456	460	5	The proposed TTCs/QTs that ultimately lead to the AET would not account for the class I leachables (for example benzapyrene).	Class I leachables should be included as standards in every study; that way, they would be captured if present.
EfPIA	457	457	5	Its not only above the AET, also at the AET level	"at or above"
ELSIE	457	460	NA	"For a leachable study, the AET is established at a concentration above which compounds should be identified and quantitated to enable appropriate safety assessment. For Class 1 leachables (See Appendix 4, Table A.4.1), the compound-specific safety limit, instead of a product-specific SCT, should be used for quantification." Please clarify how would it be feasible to define AET before knowing from analytical data that Class 1 leachables could be present (for instance, BPA)? Does supplier need to inform in advance about materials potentially leaching Class 1 compounds?	Provide clearer explanation
ELSIE	457	457	5	Its not only above the AET, also at the AET level	"at or above"
IPAC-RS	457	460	5	"For a leachable study, the AET is established at a concentration above which compounds should be identified and quantitated to enable appropriate safety assessment. For Class 1 leachables (See Appendix 4, Table A.4.1), the compound-specific safety limit, instead of a product-specific SCT, should be used for quantification." Please clarify how would it be feasible to define AET before knowing from analythical data that Class 1 leachables could be present (for instance, BPA)? Does supplier need to inform in advance about materials potentially leaching Class 1 compounds?	Provide clearer explanation
ELSIE	458	460	5	This sentence says that class 1 leachables should be quantified with their compounds specific safety limit and not the SCT. This doesn't make sense since these values are not used for quantifying the amount of an extractable. Do you mean these are the reporting threshold the compound should be assessed against?	Clarify as necessary.
Rentschler Biopharma SE	458	460	5.	see comment above for lines 151 to 153	see recommendation above for lines 151 to 153
EfPIA	459	514	5, 6	For CAR-T products, the infusion volumes are high (up to 250 mL) that result in extremely low AET, below the analytical LoQ	Suggest adding a paragraph for special cases (e.g., CAR-T products), indicating when the SCT-based AET is technically not feasible to achieve, the analytical LoQ can be considered with justification.
AstraZeneca	461	462	Section 5	study-specific AETS should also consider route of adminstration as a factor	Add route of adminstration as an e.g.

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ELSIE	461	462	NA	"Derivation of the study-specific AET depends on dosing considerations (e.g., maximum dose level, frequency of dosing, and duration of treatment)."Does this mean that Less Than Lifetime (LTL) considerations should be taken into account? Would this be applicable also for vaccines?	Provide clearer explanation
IPAC-RS	461	462	5	"Derivation of the study-specific AET depends on dosing considerations (e.g., maximum dose level, frequency of dosing, and duration of treatment)."Does this mean that Less Than Lifetime (LTL) considerations should be taken into account? Would this be applicable also for vaccines?	Provide clearer explanation
Ferring Pharmaceuticals	464	466	5	Extractable studies for PCI's operates with amount extracted/ surface area (µg/cm2). Does this section only covers primary packaging and devices or also PCI's. Extractable studies are typically given as µg/component. For real leachable study or a screening leachable study, which is normally performed on the container closure system, the result is typically given in the unit: µg/mL or ppm. Is it relevant for leachable studies of PCI. For extractable studies of PCI the unit is typically: amount extracted/ surface area (µg/cm2) - anticiapte it is the same for leachable studies of PCI's.	Should extractables studies of PCI's and the unit be included or should the sentence be rewritten in a more generic way?
Qualimetrix SA	470	470	5	Does this abolish the calculation of 1664.1 that is based on declared number of actuations instead of actual product volume/mass as per all other pharmaceuticals?	
A3P	472	484	5,1	Section 5.1 indicates that uncertainty factors should be applied when establishing the AET, but the guideline does not provide sufficient clarification on how to define, calculate, or justify these analytical "uncertainty" factors. In MS-based techniques, especially GC-MS using EI or LC-MS using ESI, response factors can vary by more than one order of magnitude across different chemical classes. Without guidance, laboratories may apply significantly different uncertainty multipliers, resulting in inconsistent AET values and non-harmonized regulatory decisions. Here, confusion between "safety" factors (toxicological side of the topic) and "response" factors (analytical side of the topic as described above) can lead to misinterpretation	The term "uncertainty" should not be used in this section (and other related sections), as uncertainty has another definition in analytical science. A term such as "safety factor" (as suggested as an alternative in ICHQ3D, Appendix 1) would be more suitable. And reference to Appendix 1 of ICHQ3D may help the readers to avoid confusion. If the "uncertainty" factors include alo the analytical part, please provide guidance or at least examples on how to account for analytical variability when deriving "uncertainty" factors, such as: - using historical datasets of response factor distributions, - applying default conservative "uncertainty" multipliers based on technique (GC-MS vs LC-MS), - describing acceptable scientific rationales for selecting an "uncertainty" factor, - clarifying how semi-quantitative "uncertainty" should be propagated into the AET decision process.
ELSIE	472	484	5.1	Reference for statistical approach for UF determination would be helpful. Please consider using UF in the demoninator of the AET equation, as is typical.	More clarification is needed with respect to UF, especially in light of recent publications and guidance from other organizations.
Fred Xi	472	484	5.1	An uncertainty factor (UF) is crutial to calculate AET, Please illustrate how to determine UF by examples	
Medicines for Europe	472	472	5.1	chapter 5.1 - there is no further subchapter	adjust chapter numbering

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Sartorius-Stedim Biotech GmbH	472	472	5.1.	We consider an "uncertainty factor" in an E&L study as inadequate, because its numeric value is always arbitrarty and cannot be reasonably justified or defined by a guideline. It strongly depends on analytics. Such factors can variy over several orders of magnitute.	Remove the general requirement for the "uncertanty factor". Better discuss that e.g. GC/MS and GC/FID measurements are sufficiently linear in response, that a "semi-quatification" even for "unknowns" is possible, while for LC/MS justification for quantification of substances without reference and unknowns must be provided. Please consider the discussion of "uncertanty" in E&L and propagation of uncetrtanty in exposure calculation in the scientific literature, e.g.: Hauk, A., et al.: From extractables to exposure data: Sensitivity analysis of extrapolation algorithms with focus on USP 〈665〉. Eur. J. Pharm. Sci. 207, 107026 (2025)
Maven E&L Ltd	473	484	Section 5.1	General Comment on the concept of Analytical Uncertainty Factor use in extractable studies: Where the extractable study is using solvents which remove high quantities in comparison to leachables e.g. A hexane extract when comparing to an aqueous formulation or even 100% Ethanol in comparison to water formulation it would seem un-neccessary to further lower the detection limit by use of a uncertainty factor. So could this not be included in these recommendation. Suggested wording to include in this section: "Where solvent extracts are considered to be extreme in comparison to drug product formulation, it can be possible to exclude the use of the uncertainty factor in these extractable studies". I think there should be a clear difference between use of the factor in screening extractable studies vs. use in leachable screening studies	Where solvent extracts are considered to be extreme in comparison to drug product formulation, it can be possible to exclude the use of the uncertainty factor in these extractable studies
Maven E&L Ltd	473	475	Section 5.1	Suggested rewrite for clarity: …an appropriate uncertainty factor should be applied to account for potential response differences between a detected analyte and the standard compound used for its detect and quantitation. This uncertainty factor should be considered separately for the detection limit - linked to the applied AET, and any subsequent estimate of quantity. Indeed there is opportunity for a two-step application of a factor and a difference in that factor for these different process steps.	…an appropriate uncertainty factor should be applied to account for potential response differences between a detected analyte and the standard compound used for its detect and quantitation. This uncertainty factor should be considered separately for the detection limit - linked to the applied AET, and any subsequent estimate of quantity. Indeed there is opportunity for a two-step application of a factor and a difference in that factor for these different process steps.
AstraZeneca	473	484	Section 5.1	General Comment on the concept of Analytical Uncertainty Factor use in extractable studies: Where the extractable study is using solvents which remove high quantities in comparison to leachables e.g. A hexane extract when comparing to an aqueous formulation or even 100% Ethanol in comparison to water formulation it would seem un-neccessary to further lower the detection limit by use of a uncertainty factor. So could this not be included in these recommendation. Suggested wording to include in this section: "Where solvent extracts are considered to be extreme in comparison to drug product formulation, it can be possible to exclude the use of the uncertainty factor in these extractable studies". I think there should be a clear difference between use of the factor in screening extractable studies vs. use in leachable screening studies	Where solvent extracts are considered to be extreme in comparison to drug product formulation, it can be possible to exclude the use of the uncertainty factor in these extractable studies
AstraZeneca	473	475	Section 5.1	Suggested rewrite for clarity: …an appropriate uncertainty factor should be applied to account for potential response differences between a detected analyte and the standard compound used for its detect and quantitation. This uncertainty factor should be considered separately for the detection limit - linked to the applied AET, and any subsequent estimate of quantity. Indeed there is opportunity for a two-step application of a factor and a difference in that factor for these different process steps.	…an appropriate uncertainty factor should be applied to account for potential response differences between a detected analyte and the standard compound used for its detect and quantitation. This uncertainty factor should be considered separately for the detection limit - linked to the applied AET, and any subsequent estimate of quantity. Indeed there is opportunity for a two-step application of a factor and a difference in that factor for these different process steps.
EfPIA	473	473	5.1	Abbreviate first time that it shows up and not in row 481	uncertainty factor (UF)"
ELSIE	473	473	5.1	Abbreviate first time that it shows up and not in row 481	uncertainty factor (UF)"
EfPIA	475	475	5.1	"reference standard"	"reference standards"
ELSIE	475	475	5.1	"reference standard"	"reference standards"

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EfPIA	476	484	5.1	UF guidance is vague. Clarify basis and provide examples. Otherwise, remove if there is insufficient justification.	Describe the analytical uncertainty with examples, but indicate it is up to the end-user to justify the UF applied. Otherwise, remove the entire secsion 5.1.
ELSIE	476	484	5.1	This section doesn't make sense. Its states that the UF is based on material of construction, expected leachables, and availability of reference standards. This doesn't make sense since analytical uncertainty has nothing to do with these variables and instead if based on the variation in response factor associated with an analytical method. "Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5. Alternatively, an uncertainty factor can be derived from statistical analysis of appropriately constituted response factor database of relevant reference compounds. Justification of UF applied should be included in the extractable/leachable study report" • Editorial correction: "...multiply an uncertainty factor..." • It is not clear under which circumstances a UF of 0.5 is to be used, so clear criteria for applying a UF of 0.5 should be highlighted in the guidline. • Even a UF of 0.5 requires justification — the sentence on line 484 implies that any UF applied, including the default value of 0.5, must be justified in the study report. This reinforces the need for justification requirements for all UF values, including default ones. This portion of section 5.1 is quite vague and needs significant expansion in regard to how a UF should be determined and applied to the data. Currently, it provides no directive other than "a UF of 0.5 may be appropriate, otherwise, justify as you see fit". "Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5". This approach is adequate for some analytical methods but has been demonstrated as not fully adequate for some others like LC/MS. There is a need to clearly mention in the document that the UF must be scientifically justified in association with the analytical methods used It is well established that response factor variability differs between GC and LC techniques. Consequently, applying a uniform value of 0.5 to both methods is not scientifically justified. Moreover, the specific "certain circumstances" under which such an approach might be considered acceptable are subjective and should be explicitly defined. Maybe a couple of examples may be useful to see how the Analytical uncertainty factor can be derived from statistical analysis of response factor database of relevant reference compounds?	Revise this section to better characterize what the UF is a function of and what it pertains to. • Editorial: "...multiply by an uncertainty factor..." •We recommend to include practical examples of situations where a UF of 0.5 is considered appropriate. Sugest to include discussion of the UF and its proposed 0.5 value in the training materials. Training could also include: --Expanding this section to better explain how the UF should be determined. --Clarifying that other, lower values can be justified depending on the analytical method, since some methods require lower UF values (lower than 0.5) --Clarification is needed to ensure that uncertainty associated with different analytical instrumentation is appropriately considered
EfPIA	477	478	5.1	It is not clear how knowledge of the materials of construction should influence the UF, which is related to an analytical response of individual compounds.	Remove 'Prior knowledge and understanding of the materials of construction"
EfPIA	480	481	5.1 Analytical Uncertainty Factor	Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5. It is not clear what circumstances these would be.	Please provide an example for considerations.
Maven E&L Ltd	481	484	Section 5.1	Suggested additional text to add linked to comment on use of separate uncertainty factor application for detection and quantitation step: The multiple used for detection step is linked to how the method detection limit is set. Consideration for choice of standard for this function should be made based on nature of the analysis and the type of substances which may be present. If identity of the detected substances is determined there is opportunity to use this information to select a standard response to further refine the accuracy of the reported substance	The multiple used for detection step is linked to how the method detection limit is set. Consideration for choice of standard for this function should be made based on nature of the analysis and the type of substances which may be present. If identity of the detected substances is determined there is opportunity to use this information to select a standard response to further refine the accuracy of the reported substance
AESGP	481	482	5.1	What are the certain circumstances where an UF of NGT 0.5 can be used? This value is not state-of-the-art. Based on current literature, technique dependant different values are to be applied if not statistical derived database-value is present	Definition / examples missing and correction to commopnly accepeted thresholds is recommended to align approaches

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	481	484	Section 5.1	Suggested additional text to add linked to comment on use of separate uncertainty factor application for detection and quantitation step: The multiple used for detection step is linked to how the method detection limit is set. Consideration for choice of standard for this function should be made based on nature of the analysis and the type of substances which may be present. If identity of the detected substances is determined there is opportunity to use this information to select a standard response to further refine the accuracy of the reported substance	The multiple used for detection step is linked to how the method detection limit is set. Consideration for choice of standard for this function should be made based on nature of the analysis and the type of substances which may be present. If identity of the detected substances is determined there is opportunity to use this information to select a standard response to further refine the accuracy of the reported substance
EfPIA	481	484	5.1	The current wording states that the application of an UF not greater than 0.5 is acceptable "under certain circumstances" and that "alternatively" UF factors derived from statistics can be applied. Can the guidance be more clear ?	Proposed wording/change: An acceptable approach is to consider an uncertainty factor (UF) of no greater than 0.5. An uncertainty factor may also be derived from statistical analysis of appropriately constituted response factor database of relevant reference compounds."
EfPIA	481	484	5.1	Under certain circumstances is unclear. What are the circumstances that require a UF. Is 0.5 the default without other data? Is 0.5 used only when using semi-quantitative methods? Also you can not muliply by no greater than 0.5; only by 0.5 itself.	When semi-quantitative analytical methods are used, then an uncertainty factor of 0.5 should be applied unless otherwise justified. For example…
EfPIA	481	483	5.1	We believe it would be beneficial to detail the uncertainty factor to hamonize the practices and we propose to at least give an example from ISO.	Alternatively, an uncertainty factor can be derived from statistical analysis of appropriately constituted response factor database of relevant reference compounds (e.g. as in the ISO 10993-18).
EUCOPE	481	482	5.1	For the Analytical Uncertainty factor (UF), here it describes UF as a value less than 1 and should be multiplied to arrive at the adjusted AET. However, other guidance documents differ in the definition of UF (i.e., AET should be divided by an UF or should multiply an UF to obtain the adjusted AET). ISO 10993-18 and USP<1664.2> uses the AET (adjusted)= AET/UF, where UF is a value greater than 1.	Propose to clarify on how to determine UF and how to calculate adjusted AET using the UF, align with other available guidance (ISO 10993-18 and USP<1664.2>) to avoid confusion.
IPAC-RS	481	482	5.1	"Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5", this approach is adequate for some analytical methods but has been demonstrated as not fully adequate for some others like LC/MS. There is a need to clearly mention in the doc that the UF must be scientifically justified in associatetion with the analytical methods used	We note that a UF of 0.5 is not suitable in all cases. For example, some analytical methods require lower values. Consider clarifying that other values, including lower values, can be used and justified.
IPAC-RS	481	481	5.1	The choice of words can be improved - perhaps 'utilise' an uncertainty factor rather than 'multiply'	Under certain circumstances an acceptable approach is to ~~multiply~~ utilise an uncertainty factor (UF)
Luye Pharma	481	481	5.1	"Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5. Alternatively, an uncertainty factor can be derived from statistical analysis of appropriately constituted response factor database of relevant reference compounds. Justification of UF applied should be included in the extractable/leachable study report." - When is the UF to be applied?	The guideline should provide more information including examples when the UF is being applied.
Medicines for Europe	481	481	5.1	The guideline states that “under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5” (Line 481) but does not define what those circumstances are. This lack of clarity can lead to inconsistent application of UF and variability in AET calculations across submissions.	The circumstances to apply (or omit) the UF need to be outlined in more detail. Clarification to be added in Section 5.1 (Analytical Uncertainty Factor) to: Provide examples of circumstances where UF ≤ 0.5 is acceptable (e.g., when reference standards represent the majority of expected extractables, or when statistical analysis confirms minimal variability in response factors). Include guidance on documentation requirements for justification of UF selection. Consider adding a decision tree or table summarizing UF ranges based on available data and prior knowledge.

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Medicines for Europe	481	484	5.1	The draft guideline lacks sufficient clarity regarding the determination of uncertainty factors, which may result in significant misinterpretation by both applicants and regulatory authorities. The statistical methodology for deriving uncertainty factors is not defined and the criteria for what constitutes an appropriately constituted response factor database are absent. This ambiguity undermines the reliability and reproducibility of uncertainty assessments. Deriving uncertainty factors based on known response factors for a given analytical method is inherently inappropriate. The selection and adjustment of target analytes for response factor determination can be manipulated, introducing bias. The response of a target analyte is independent of the response of other analytes within the same method. Therefore, it should not be used as a proxy for assessing method uncertainty. Given the virtually infinite number of potential target analytes, any analytical method can be artificially optimized or degraded through selective response factor determination.	Moved to proposed changes: To ensure scientific robustness and regulatory consistency, the guideline should define acceptable approaches for uncertainty factor determination and specify the structural and data quality requirements for response factor databases. The use of target analyte response factors as a basis for uncertainty estimation should be discouraged.
Qualimetrix SA	481	484	5.1	A database of response factors can be used for the selection of internal standards and the justification of a UF. This addresses the preemptive stage. It is not clear, however, whether at the subsequent stage it is required to correct all estimates obtained through response factors for each specific substance. It is also quite improbable considering that many substances observed may be commercially available. It is not clear how these cases are handled. Is it possible/acceptable to justify based on the RFs that an estimate attained can only be “over-estimative/worst-case” of the true concentration?	
EfPIA	482	482	5.1	It is well established that response factor variability differs between GC and LC techniques. Consequently, applying a uniform value of 0.5 to both methods is not scientifically justified. Moreover, the specific "certain circumstances" under which such an approach might be considered acceptable are subjective and should be explicitly defined.	Clarification is needed to ensure that uncertainty associated with different analytical instrumentation is appropriately considered
EfPIA	485	485	6	The QT concept is introduced. It is stated that the QT is based on the assessment of 330 potential leachable permitted daily exposures (PDEs). Where is this body of work published? The QT threshold concept should be supported by peer reviewed work (or at the very minimum included in the supporting information), and referenced in the ICH applicable section. One should not look at a table presenting a new concept and values and wonder where the values come from. More recent related ICH guidances acknowledge the underlying datasets (Q3C, D, M7). The lack of rationale for the selection of the QT and acknowledgment of the underlying dataset is a significant error on behalf of the ICH Q3E authors which risks erroding public confidence in the ICH approach.	Justify the QTs. In additon reference peer-reviewed work supporting the proposed thresholds, or include in the supporting in appendices information at the very minimum
EfPIA	485	689	6	Specific considerations for pediatric assessments – particularly for vaccines intended for neonates, infants, toddlers, and children – are not mentionned in this draft. Toxicokinetic and sentisitivity differences between pediatric and adult population may occur. The TTC and other QTs are established for a 60 or 50-kg adult, respectively. This could involve the use of additional safety factors and/or adjustments based on body weight for the different pragmatic safety thresholds which could improve scientific rigor	Recommend to clarify practices concerning pragmatic safety thresholds for pediatric subpopulation (e.g., additionnal safety factor and/or adjustments based on body weight).
EFPIA Drug-MD ICH STG	485	574	6 Safety Asssessment	Add clarification in Section 6 (Safety Assessment) on how to assess risk when the patient is exposed both to leachables in the drug product and potentially to direct contact with the device material itself . Should exposures be summed? Do different thresholds (e.g., TCL from ISO 10993-17) apply to the direct device contact?	Rationale: DDCPs can present complex exposure scenarios requiring distinct assessment strategies compared to traditional drug products.
ELSIE	485	689	6	In general this draft has limited to no discussion of recommended practices, modifications, or considerations for pediatric assessments (i.e., DPs/vaccines intended for pediatric cohorts such as neonates, newborns, toddlers, children). This may include the introduction of addition of additional relevant uncertainty factors (i.e. to account for metabolic, kinetic, immunologic, PD disparities) and/or modifications of body weight - for which age grouping recommendations would be useful.	Recommend to speak to recommended practice for pediatric subpopulation. Both with regard to recommendations of default assumptions and /or uncertainty factors.
Medicines for Europe	485	495	6	Does this mean that a safety assessment is performed on leachables only? What does this mean for changes in manufacturing components? I understand that for changes in manufacturing components an extraction study can be done to see if all extractables fall below AET (including UF?). What about those exceeding the AET but being below PDE?	Clarify if toxicological evaluation (PDE) can be performed to qualify extractables resulting from quantitative extractable studies of manufacturing components, to avoid leachable studies.
Sartorius-Stedim Biotech GmbH	485	485	6	Some introduction to this chapter is missing - it is focusing on tox, but not on exposure. A reasonable safety assessment needs both, reasonable exposure data and reasonable thresholds.	We propose to add a simple plot which shows the key elements of a saftey assessment and how they are linked; please see Fig. on the right side

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A3P	486	515	6,1	The guideline encourages the use of chemical families and representative tracers to evaluate leachables, but does not explain how to perform a comprehensive safety assessment when a chemical family may consist of tens or hundreds of different compounds with potentially different toxicological profiles. Applying the PDE of a single tracer compound to an entire family may underestimate cumulative exposure or fail to address the possibility that some family members have higher toxicological relevance. More guidance is needed to ensure that family-based assessments are protective, consistent, and scientifically justified.	Provide clarification on: - how to extrapolate toxicological conclusions from one or several tracers to an entire family; - when cumulative exposure within a family should be considered; - criteria for selecting tracers that are toxicologically conservative (i.e., representing the highest safety risk); - when additional toxicological follow-up or identification is warranted for families with very large structural diversity; - examples illustrating acceptable family-based safety assessments.
Bio-Process Systems Alliance	486	511	6.1	Documentation and Regulatory Expectations-There is no standard template for summarizing E&L justification.	Suggest that ICH develops an optional summary table (similar to ICH M7 Appendix A format) for E&L risk documentation to improve reviewer consistency and transparency.
EfPIA	486	515	6.1	In this chapter, TTC classifciation of M7 is used for SCT. In such case, another classification (e.g. TTC Classification by Product Quality Research Institute (PQRI)) is not applicable any longer?	N/A
ELSIE	489	489	6.1	"overall" risk-based evaluation	Remove "overall"
Fred Xi	490	511	6	Please present example how to determine SCT value. PQRI and USP<1664.1> take 0.15µg/day as SCT. FDA and ISO-10993-18 use DBT to replace SCT while selecting value of 1.5µg/day or larger	
AESGP	491	492	6.1 General Principles	As the SCT is designed to consider all toxicological concerns, it would be clearer to state 'toxicological' concerns, rather than, 'mutagenic and non mutagenic', because the latter may mislead the reader so they think it only relates to mutagenicity and canon mutagenic cancer endpoints.	Within this context, the SCT is considered the threshold below which a leachable would have an exposure so low as to present negligible toxicological (including mutagenic) ~~and non-mutagenic toxicity~~ concerns.
Medicines for Europe	491	492	6	While the guideline defines the SCT (Safety Concern Threshold) as a threshold for negligible risk, it would be beneficial to include detailed examples or scenarios illustrating how the SCT is determined for specific leachables.	Providing case studies could help clarify the application and importance of the SCT in real-world assessments.
Maven E&L Ltd	492	495	Section 6.1	It may be helpful to present the inputs to the safety assessment process as a bulleted list to ensure reader understand all of the requirements from the assessment. Suggested reword: "The possible elements to include the safety assessment are: *A review of the certainty of the identifications made for substances presented for safety assessment, and how that might influence the safety assessment *A review to determine if Class 1 leachables may be present and thus require a specific assessment *A review to consider if leachables identified have mutagenic potential and thus a lower threshold *A review to consider if alternative toxicity end-points apply to identified leachables, if may need to be considered *A review to consider route & duration of exposure, and its potential influence on applied thresholds * A consideration of available literature to support any permitted daily exposure calculation	The possible elements to include in the safety assessment are: *A review of the certainty of the identifications made for substances presented for safety assessment, and how that might influence the safety assessment *A review to determine if Class 1 leachables may be present and thus require a specific assessment *A review to consider if leachables identified have mutagenic potential and thus a lower threshold *A review to consider if alternative toxicity end-points apply to identified leachables, if may need to be considered *A review to consider route & duration of exposure, and its potential influence on applied thresholds * A consideration of available literature to support any permitted daily exposure calculation

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AstraZeneca	492	495	Section 6.1	It may be helpful to present the inputs to the safety assessment process as a bulleted list to ensure reader understand all of the requirements from the assessment. Suggested reword: "The possible elements to include the safety assessment are: *A review of the certainty of the identifications made for substances presented for safety assessment, and how that might influence the safety assessment *A review to determine if Class 1 leachables may be present and thus require a specific assessment *A review to consider if leachables identified have mutagenic potential and thus a lower threshold *A review to consider if alternative toxicity end-points apply to identified leachables, if may need to be considered *A review to consider route & duration of exposure, and its potential influence on applied thresholds * A consideration of available literature to support any permitted daily exposure calculation	The possible elements to include in the safety assessment are: *A review of the certainty of the identifications made for substances presented for safety assessment, and how that might influence the safety assessment *A review to determine if Class 1 leachables may be present and thus require a specific assessment *A review to consider if leachables identified have mutagenic potential and thus a lower threshold *A review to consider if alternative toxicity end-points apply to identified leachables, if may need to be considered *A review to consider route & duration of exposure, and its potential influence on applied thresholds * A consideration of available literature to support any permitted daily exposure calculation
EfPIA	492	495	6.1	"The outcome of the safety assessment (…) may be used to set specifications for leachables in the drug product if needed": not clear how the routine inclusion of one or more test attributes for the control of Class 1 leachables on the release and/or end of shelf-life specification would contribute to ensure safety.	In the context of QbD, an approach similar to that described in ICH Q3D for Class 1 and Class 2 elemental impurities would likely be more appropriate. If development studies show that Class 1 leachables are not present above 10% or 30% of the corresponding acceptable intake, as calculated from teh SCT, then their testing does not need to be included in any specifications.
EfPIA	495	497	6.1	The outcome of the assessment is to determine appropriate classification of the leachables, and not just to assign as Class 1	Clarify sentence.
AESGP	496	497	6.1 General Principles	Similar to the comment above, aim is to bring clarty that the SCT covers all endpoints and not just mutagenity and cancer endpoints. Suggesting not to use the word 'alternative' due to possible confusion with animal alternatives and NAMS language.	Since the SCT is defined to be protective of 'all toxicological effects including' ~~both~~ mutagenic and non-mutagenic effects, it must consider 'all ~~both mutagenicity concerns and concerns related to alternative~~ toxicity endpoints and is based on whichever is more limiting with respect to exposure.
EfPIA	498	499	6.1	Typo: " As such, in addition to amount of exposure, the SCT dependent on both route and duration of exposure."	Replace with " As such, in addition to amount of exposure, the SCT is dependent on both route and duration of exposure."
EfPIA	498	500	6.1	Sentence is unclear and open to regulatory debate.	Define alternative toxicity endpoints and clarify "based on whichever is more liminting with respect to exposure".
AESGP	499	499	6.1	typo	…, the SCT is dependant…
AstraZeneca	499	499	Section 6.1	Word missing:The sentence reads: "As such, in addition to amountof exposure, the SCT dependent on both route and duration of exposure." Suggest the word "is" is added so it reads:As such, in addition to amountof exposure, the SCT is dependent on both route and duration of exposure."	Add missing word
ELSIE	499	499	6.1	As such, in addition to amount of exposure, the SCT dependent on both route and duration of exposure.	Editorial correction: "…the SCT is dependent…"
A3P	500	515	6.1	For parenteral drug products, what is the rationale or calculation for defining QT value for non-mutagenic leachable molecules lower than TTC values for mutagenic leachable molecules ? For example : 26µg/day for non-mutagenics aigainst 120µg/day for mutagenics for an exposure below or equal to 1 month.	Review the QT at a value higher or equal than TTC for parenteral, or detail the rationale

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ELSIE	503	505	6.1	It is stated that the lowest value of the TTC or QT in table 5 is used as the SCT for leachable evaluation. Since you choose the lowest of either of these values, shouldn't table 5 just list the single lowest value to be used instead of having a separate column for each? It could cause confusion or misinterpretation if both values are listed. Also, it would seem more logical to call one value systemic and one non-systemic, or whatever is appropriate, instead of calling them a TTC and QT. These terms have other meanings outside this table and otherwise don't accurately convey what each refers to.	Clarify this section and Table 5 to better describe the SCT value to be used.
BioPhorum	504	506	6.1	Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list
EfPIA	504	506	6.1	Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list
EfPIA	504	507	6.1	The derivation of the QT is not transparent. It refers to 330 compounds but details are not provided. The numbers are very precise, and suggest significant precision, however they were a conservative estimate.	Provide details or refer to publication. Suggest rounding QTs: for example 50 instead of 48, etc. so as not to assuming significant precision in the numbers.
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	In keeping with the transparency of other recent ICH guidelines (Q3D and M7) and to support the scientific validity of the QT values, stakeholders should have been provided access to the following information and sufficient time to review and comment before finalizing the guideline.
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	What are the ~330 leachable compounds
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	How were these ~330 leachable compounds identified and selected; Jenke D, et al., 2025 has published a list of commonly detected extractable and leachable compounds from plastics used in packaging systems, manufacturing components and medical devices. Please cross compare the 330 leachable compounds with their respective reporting frequency in the Jenke D, et al., 2025 paper. The dataset used for QT derivation should not only be based on the compound toxcity, but also the frequency of detection in real-world experience.
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	From a statistical and toxicological perspective, is this list representative of the chemical domain of all pharmaceutical leachables, or is it biased towards the most toxic compounds in certain classes of leachables, materials of construction, or processes that might be better addressed in disaggregated QT values, and if not, then the corresponding QT values will be improperly biased and the analysis needs to be conducted properly
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	ICH should provide a tabular compilation listing the all of the leachables compounds it identified (highlighting those it selected for derivation of PDE values), identify their chemical class/classes, frequency of detection (preferably by material of construction or device), and average and high-end concentration values (and corresponding patient dose), and critical effect and study used to derive the PDE. It should then summarize this information. For instance, it would be valuable to know if perhaps only half of the PDE values were derived from in vivo data, 20% from in in vitro data, and 30% from in silico prediction
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	How do these QT values compare to background human exposures to ensure there is not an inordinate risk mitigation mandate in the guideline for an insignificant reduction in total human exposure

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EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	Where are the specific in vivo, in vitro, and in silico data and associated data quality and uncertainty assessments for the selected compounds and how were data integrated across methods, routes of exposure and exposure duration, and data sources to derive the individual PDE values
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	How were the route- and time-adjusted QT values calculated
EfPIA	504	513	6.1 and Table 1	Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs).	The number of significant digits is improperly presented as two and three significant digits. This should be corrected.
EfPIA	504	506	6.1	Reference for 330 PDEs is missing.	Add reference in section 8 or list of reviewed compounds in a new Appendix.
EfPIA	504	507		Insufficient information are provided to evaluate the appropriateness of the QT and local toxicity threshold values specified in the guideline.	Since the QT values for Class 2 leachables are a key aspect of the document, the methods used to derive them should be described in more detail in the guideline or a supplement. In the case of the local toxicity thresholds (which are primarily based on arbitrary historical practice not established by ICH), the basis for each threshold should be described in more detail.
ELSIE	504	506	6.1	There is no reference for "values have been derived by review of approximately 330 potential leachable permitted daily". Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list
IPAC-RS	504	506	6.1	Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list
EfPIA	505	505	6.1	There is no reference for "values have been derived by review of approximately 330 potential leachable permitted daily"	Include reference
AESGP	506	507	6.1 General Principles	The transdermal systemic safety threshold should not also be a 'dermal'systemic safety threshold. Transdermal and topical (dermal) administration are quite different. Transdermal and topical administration both involve applying medication to the skin, but they differ in their intended effects and mechanisms of action. Topical administration is designed to treat local conditions at the site of application, such as skin infections, rashes, or localized pain, with minimal systemic absorption. In contrast, transdermal administration delivers medication through the skin into the bloodstream, resulting in systemic effects throughout the body. As such, the systemic bioavailability from chemicals delivered from topical (dermal) versus transdermal is quite different. Therefor, the systemic safety threshold for transdermal would be too conservative for topical drug prodeucts and would be adjusted for dermal penetration. Without such bioavailability adjustment, the oral systemic safety threshold is more relevant, and even that can be adjusted by at least 50%, in the lack of specific dermal penetration data.	An overview of these systemic safety thresholds (expressed in µg/day) for oral, parenteral, ~~dermal/~~transdermal and inhalation routes of exposure, are provided in Table 1.
ELSIE	507	507	6.1	• Editorial correction: "...and inhalation routes of exposure, are provided in Table 1." (redundant comma before 'are')	"...and inhalation routes of exposure~~,~~ are provided in Table 1." (remove comma)
AESGP	508	510	6.1 General Principles	See detailed comment above. Transdermal and dermal are quite different and should not be linked together. Bioavailability from creams and oinments applied to skin/dermal route (topical)<oral route<transdermal<parenteral.	In addition, local toxicity thresholds for leachable concentrations in drug products for topical ',' ophthalmic, subcutaneous/intradermal, ~~dermal/~~transdermal and inhalation routes of exposure are presented.
EfPIA	508	511	6.1	The local toxicity thresholds seem arbritary, with no scientific justification on how they were derived. Also 5 ug/day was included for inhalation which presumably was from the PQRI derivation. However this was not referenced.	Provide scientific justification, reference or exclude.
ELSIE	508	513	6.1	Although local effects and toxicity play an important role for pharmaceuticals administered via topical ophthalmic, subcutaneous/intradermal, dermal/transdermal and inhalation routes, the ppm numbers seem extremely low, E.g., for an eyedrop of 50 µL, 20 ppm refers to 1 µg. What are these ppm values based on? Especially for topical ocular and SQ route these numbers seem arbitrary.	Proposal: Omit ppm values and change to "compound specific evaluation". Such evaluation should include endpoint evaluation of irritation and sensitization, other endpoints are likely not available.

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ELSIE	512	513	6.1	Where does this info come from? Add appropriate references	
ELSIE	512	512	6.1	Table 1: Systemic and Local Toxicity Thresholds Table 1: Systemic and Local Toxicity Thresholds for DP - clarification on what these thresholds are used for is needed.	
Maven E&L Ltd	513	513	Section 6.1	Table 1: The values for Topical Opthalmic, subcutaneous and intradermal, and Dermal & Transdermal are given in unit of ppm, without further definition of whether this would be a volume / volume or a mass / volume or mass / mass measurement. This needs further clarification via a footnote.	
A3P	513	513	6,1	In Table 1, one would expect the thresholds to be expressed as a quantity/day. The use of ppm (which is a concentration, and not a quantity) seems unappropriate in this table	add in table 1 the reference to the corresponding explanation for the use of ppm in subsections of section 6.4.
A3P	513	513	6.1	Are the SCT values defined for leachables applicable to pediatrics ?	Could you precise if SCT are applicable to all population ?
AESGP	513	0	Table 1: Systemic and Local Toxicity Thresholds	As these are parenteral values, the word, 'Dermal' in the column title, 'Parenteral, Dermal/Transdermal, Inhalation', is misleading, because, considering chemicals in topical creams applied to the skin, the systemic bioavailability can be adjusted wih a dermal penetration estimate (when comparing to a parental threshold). While appendix 5 does talk about modifying exposure considering dermal exposure, this is much further down in the guideline, and it is important to bring clarity upfront in the main section and separate dermal from transdermal to prevent confusion. Chemicals in dermal topical products always have lower systemica bioavailability than oral or transdermal or other parenteral products. Transdermal and topical administration both involve applying medication to the skin, but they differ in their intended effects and mechanisms of action. Topical administration is designed to treat local conditions at the site of application, such as skin infections, rashes, or localized pain, with minimal systemic absorption. In contrast, transdermal administration delivers medication through the skin into the bloodstream, resulting in systemic effects throughout the body, such as hormone replacement, pain management, or nicotine replacement therapy.	Delete the word 'dermal' from the title of the column, i.e. 'Parenteral, ~~Dermal/~~Transdermal, Inhalation'
AESGP	513	0	6.1	The 20 ppm limit listed under “Local toxicity – ophthalmic application” as well as the 50 ppm and 500 ppm limit in Table 1 is not clearly defined with respect to its basis of expression. It is unclear whether the concentration refers to µg of impurity per gram (or mL) of drug product, per gram of drug substance, or per gram of container/closure material.	
AESGP	513	514	Table 1	It would be beneficial to obtain QT values that are also increasing with decreasing exposure duration	Extend Table with additional values
AESGP	513	514	Table 1	It can be expected that values for dermal/transdermal and inhalation routes of administration are different from parenteral one. AS mentioned above dermal and transdermal are quite different and should be separated.	Further differentiation of routes of administration
AstraZeneca	513	513	Table 1	How does Dolan/Cramer/Munro limits fit in to these thresholds since in earlier sections of the document it discusses leveraging prior knowledge with various approaches such as relevant food-contact safety- is there any guidance for this?	
AstraZeneca	513	513	Section 6.1	The values provided in Table 1 are given with no reference as to their derivation, this is wholly inconsisent with ICH Q3D and ICH M7 where detailed references a re made to the source of data used to calculate limits. Also in respect to ICH M7 the TTC is defined as a 'de mininus' limit relfecting a hypothetical risk of 1 in 100,000, what therefore is the basis of QTs below this for Parenteral, Dermal/transdermal and inhalation,	the basis for derivation of limits should be included either in the guideline or an addendum without this context it is impossible to comment on he merit or otherwise of these proposals
AstraZeneca	513	513	Section 6.1	Table 1: The values for Topical Opthalmic, subcutaneous and intradermal, and Dermal & Transdermal are given in unit of ppm, without further definition of whether this would be a volume / volume or a mass / volume or mass / mass measurement. This needs further clarification via a footnote.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addition of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity thresholds subcutaneous? --> For clarification add comment to local toxicity thresholds " Only applicable for certain scenarios - see chapter 6.4"	An addition of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day add some considerations around when requalification of extractables is recommended (align with wording in USP665- comparator with justification)
EfPIA	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addtion of SCT in Table 1 would be helpfull to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity threshholds subcutaneous? --> For clarfication add comment to local toxicity threshholds " Only applicable for certain scenarious - see chapter 6.4"	An addtion of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day
EfPIA	513	513	6.1	What is the rationale for the QT values developped?	Clarification needed
EfPIA	513	514	6.1 Table 1	Align QT with TTC for oral and parenteral routes to match other impurity guidelines	
EfPIA	513	514	6.1 Table 1	What is the appropriate method for determining AET for e.g. intrathecal or intraocular administration where there are no recommendations regarding SCT? Additional clarification on this matter would be beneficial	
EfPIA	513	514	6	Table 1 should mention that the ug/day values correspond to exposures and the ppm values correspond to the concentration in the drug product - This is stated in the text before the table but not in the table itself.	Update Table 1 with an indication about to what the values refer to (exposure or concentration in drug product)
EfPIA	513	514	6.1	Table 1 refers to intracerebral… etc. refer to Section 6.4. All other routes in the table are included in Section 6.4. This should be referenced to 6.4.2, and intraocular should be included in 6.4.2, instead of 6.4.1.	Replace with reference to 6.4.2 for intracerebral…. And include intraocular as part of 6.4.2
EfPIA	513	514	Table 1	Consider specifying in table title that the values are for the SCT selection. To guide the reader further	Table 1: Systemic and Local Toxicity Thresholds for SCT selection
EfPIA	513	514	6.1	Table 1 needs clarification on exposure duration, nasal route, and QT vs TTC, ppm basis and systemic vs local thresholds.	Add definitions of exposure duration, nasal route, and QT vs TTC in a footnote. Add reference to the ppm and systemic/local thresholds.
EfPIA	513	514	6.1	Threshold for ocular injections is missing.	Provide threshold or guidance for ocular routes in line with section 6.4.1.
EfPIA	513	513	Table 1	Without additional details, it is impossible to critically evaluate the scientific and methodological rationale for the QT values for systemic toxicity, which are not aligned with Masuda-Herrera et al. (2022) work, raising concerns about their validity and applicability. In addition, the TTC and other QTs are established for a 60 or 50-kg adult, respectively. Based on specific pediatric recommandation, it is suggest to express the pragmatic safey thresholds in body weight for a better harmonization.	Please include the full derivation of the QT values in an appendix, and indicate all thresholds according to the body weight (expressed as quantity per kg bw).
EfPIA	513	514	6.1	It would be beneficial to explain the methodology used for QT values determination, for example in an Appendix. Indeed, the QT valuaes covered in this text do not cover all the cases encountered and having the methodology described would permit toxicologist to apply the same for new compounds and therefore have coherance. Furthermore, as general comment, these QT values do not consider recent peer-review literature from Masuda-Herrera et al. 2022, PDA Journal of Pharmaceutical Science and Technology September 2022, 76 (5) 369-383; DOI: https://doi.org/10.5731/pdajpst.2021.012693)	NA

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	513	513	Table 1	Insufficient information are provided to evaluate the appropriateness of the QT values specified in the table.	Since the QT values are a key aspect of the document, the methods used to derive them should be described in more detail in the guideline or a supplement.
ELSIE	513	514	6.1	"Table 1: Systemic and Local Toxicity Thresholds" • The fiirst row Expousure duration period should be defined as "10 Years to Lifetime" •Clarification is requested regarding the rationale for applying thresholds to oral drug products, given that the route of administration is equivalent to food. Therefore, it is suggested that food contact statements for container closure systems (CCS) and manufacturing components may be sufficient. This is supported by Table A.1.1., which aligns oral drug products with food exposure • Clarification is nedded if is nasal route of administration is the same as inhalation. • Table 1 - Systemic Toxicity Thresholds for Parenteral, Dermal/Transtermal, and Inhalation: For less-than-lifetime (LTL) exposure durations up to 1 year, the LTL-adjusted TTC value for is much higher than the corresponding QT. The table is somwhat misleading, as the reader might think that a mutagenic leachable present at an exposure level of up to 20 µg/day (> 1 month to 1 year) or 120 µg/day (≤ 1 month) is considered acceptable. In reality, according to the flowchart on page 21 ("Safety Assessment Process for Leachables Using Safety Evaluation Thresholds"), the leachable exposure level should be kept below the QT, even if it is already lower than the TTC. Essentially, the effective threshold in these cases should be aligned to the corresopnding QTs, that is 12 µg/day and 26 µg/day, respectively • Rationale: Local Toxicity Threshold: the units "ppm" can be ambiguous • Clarification is needed regarding the local toxicity threshold of 500 ppm for dermal and transdermal routes. It is necessary to clarify what constitutes the reference product mass for calculating the corresponding absolute limit. Specifically, clarification is needed whether the concentration is based on the total mass of the patch, the mass of the formulation embedded within the patch, or another defined component.	• "> 10 Yyears to Lifetime" • We recommend to complete route of administration with addition of nasal: 'inhalation/nasal' • We recommend adding an asterisk (*) next to the cells with TTC values of 20 µg/day (> 1 month to 1 year) or 120 µg/day (≤ 1 month) and add the following footnote: * The TTC value for this exposure duration is higher than the corresponding QT. Nevertheless, the exposure level of the leachable, whether mutagenic or non-mutagenic, should be kept below the QT. • We recommend to explain how is "ppm" derived.
ELSIE	513	514	6.1	Table 1: What is the rationale for the QT values developped? Please provide how the QTs were derived (reveal the 330 compounds, the point of departure, the applied modifying factors, and data distribution). The numbers appear random and it is impossible to review them. Furthermore, they are not aligned with (Masuda-Herrera et al. 2022). The QTs listed in Table 1 in 6.1 are unacceptable. Provide additional context that the QT values for dermal/transdermal may be higher as the QT is a systemic toxicity threshold. Application of bioavailability can adjust this value based on product specific knowledge Need to have additional clarification on how to calculate the exposure duration for example for antibiotics (liquid) that can be taken more than oone time per year. How do we calculatez the LTL for these elements. Idem for other treatment where the number of treatments during lifetime is not defined in the posology QT proposed are upper than the 5 µg/day describe in PQRI for the sensitizer. How this is justified? It would be helpful to highlight how the information in Table 1 is different from current practices. Please include a remark for the Table 1 directly in the title or at least as a footnote that this table should be applied only for Class 2 and 3 leachables	Clarification needed Provide the derivation of the QTs in an Appendix, so that toxicologists can understand the underlying principles of the QTs. Consider including in line 515 additional statement (the QT values may be adjusted based on product specific/compound specific knowledge on bioavailability). Is it possible to have additional information on the way to calculate the LTL and associated exposure duration when the treatment can be taken more than one time during the lifetime. Need justification to apply a value upper than 5 µg/day for sensitizer Additional text outlining the application of table 1 and any differences with current practices would be helpful

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addtion of SCT in Table 1 would be helpfull to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity threshholds subcutaneous? --> For clarfication add comment to local toxicity threshholds " Only applicable for certain scenarious - see chapter 6.4"	An addtion of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day
ELSIE	513	513	6.1	The proposed parenteral limits in Table 1 are seemingly contridictory to typical toxicological risk assessment practice. Typically the genotoxic endpoint / ascribed thresholds are considered the most conservative and sensitive endpoint / thresholds across all toxicologically relevant endpoints. As seen in multiple prioritization schemas including ICH M7. However, the proposed parenteral QTs in less-than-lifetime scenarios now suggests that non-mutagenic hazard is considered more significant? While this would seemingly make sense for local toxicity considerations to potentially supercede as a critical endpoint in acute risk assessment practice, the notion that systemic toxicity is even more sensitive than mutagenic toxicity would defy conventional practice (i.e. Haber's Law).	We would expect that the TTC and local toxicity endpoints be the primary endpoints of concern for less-than-lifetime scenarios.
ELSIE	513	513	6.1	There are no proposed thresholds for single dose or intermittent dosing regimens (i.e., once per month, etc.).	Propose to add in the footnote that recommended practice for equating dosing regimen to the corresponding less-than-lifetime row to ensure accurate selection of the appropriate TTC & QT.
ELSIE	513	513	6.1	Local Toxicity thresholds for parenteral / intravenous products are not proposed. I've noted that in the text lines 671-675 suggests that this endpoint is not a significant factor for this route of exposure, if so then are we to presume that in practice there is effectively no threshold to account for sensitization induction via the patenteral route of exposure?	Given that this is a significant departure from the current PQRI practice, then it may be useful to clearly state this within Table 1. A suggestion would be to explicitely specify 'n/a', or similar language and/or providing brief reiteration of the context in a footnote of this table.
ELSIE	513	513	6.1	The basis and/or citations to the underlying work justifying how the QT thresholds are derived are currently outstanding.	Please include either citation or appropriate Appendix to capture this information.
ELSIE	513	513	6.1	Can the TTC and/or QT for class 1 leachables be added to the table? It would be helpful to have some guidance for those compounds.	
EUCOPE	513	0	Table 1	As far as we understood, the TTC or the QT are the two options for the SCT settings. If no mutagenic compounds are found in the extractables study above the AET, the QT can be used as baseline for each compound. On the other hand, the TTC is used in case a mutagenic compound is found above the EAT. Is this correct? Table 1 of the guideline includes both systemic and local toxicity thresholds. Could you please provide the data sources from which these thresholds were derived?	
GUERBET	513	513	6.1	Table 1 indicates, for short term products, that the Qualification Threshold (QT) to be used for parenteral is 26 µg/day. Why is this limit much lower than the TTC of 120 µg/day mentioned in ICH M7(R2) for mutagenic impurities ?	Keep 120 µg/day for short term products
Hikma	513	514	6.1	Pyelocaliceal route is not listed in the table. Can the QT and Local Toxicity Thresholds for Dermal Products be applied?	Please specify the QT and local toxicity threshold for pyelocaliceal route.
IPAC-RS	513	515	6.1	Provide additional context that the QT values for dermal/transdermal may be higher as the QT is a systemic toxicity threshold. Application of bioavailability can adjust this value based on product specific knowledge	Consider inlucding in line 515 additional statement (the QT values may be adjusted based on product specific/compound specific knowledge on bioavailability).
IPAC-RS	513	513	6.1	Need to have additional clarification on how to calculate the exposure duration for example for antibiotics (liquid) that can be taken more than oone time per year. How do we calculatez the LTL for these elements. Idem for other treatment where the number of treatments sudring lifetime is not define in the posology	Is it possible to have additional information on the way to calculate the LTL and associated exposure duration when the treatment can be taken more than one time during the lifetime.
IPAC-RS	513	513	6.1	QT proposed are higher than the 5 µg/day describe in PQRI for the sensitizer. How this is justified ?	Need justification to apply a value higher than 5 µg/day for sensitizer

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	513	513	6.1	Table 1: Systemic and Local Toxicity Thresholds: In case you have a systemic toxicity thresholds and a local toxicity thresholds.	In case of both (systemic and local), which toxicity threshold should be used ?
IPAC-RS	513	513	6.1	Table 1: Systemic and Local Toxicity Thresholds: The route of administration "Nasal" is not written in the Table. We note that the nasal or mucosal route is very different from the inhalation route.	We suggest adding "nasal" or "mucosal" to Table 1.
IPAC-RS	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addtion of SCT in Table 1 would be helpfull to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity threshholds subcutaneous? --> For clarfication add comment to local toxicity threshholds " Only applicable for certain scenarious - see chapter 6.4"	An addtion of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day
Luye Pharma	513	513	6.1	The systemic and local toxicity thresholds applied to dermal, transdermal, and inhalation devices are currently derived from parenteral-use limits. This approach seems inappropriate, particularly for transdermal products, which are applied to intact skin—a strong barrier that substantially reduces the risk of systemic exposure. Please also refer to Ph. Eur. chapter "Patches", which defines patches as "flexible preparations intended for application to unbroken skin to deliver active substances to or through the skin for a local or systemic effect over an extended period of time." Furthermore, only very low levels of extractables and leachables, if any, are expected in such preparations. As a result, the chemical potential driving passive diffusion is minimal, leading to negligible systemic exposure. Even the active substance itself is not fully absorbed from those formulations, i.e. a significant fraction remains within the patch. Therefore, classifying transdermal systems as high-risk products requiring compliance with parenteral limits is not justified.	A reassessment of the systemic and local toxicity thresholds applied to dermal and transdermal products is necessary. Such products should be provided with scientifically justified thresholds or, if this is not feasible, temporarily removed from the guideline's scope.
Medicines for Europe	513	513	6.1	To our understanding systemic and local toxicity thresholds for dermals/transdermals and inhalation devices are derived from parenteral application. This appears inappropriate as especially transdermals are applied to intact skin which minimizes risk of systemic effects as skin acts as a strong barrier -> Reference is made to Ph.Eur. chapter "Patches" with the following definition: "*Patches are flexible preparations intended for application to unbroken skin to deliver active substances to or through the skin for a local or systemic effect over an extended period of time.*" In addition, only very low concentrations of extractable/leachables can be expected in the preparation, if any at all, therefore, the chemical potential serving as the driving force for passive diffusion is very low and in consequence systemic exposure of minimal risk only. Even the drug substance itself is not quantitatively absorbed; significant portions remain in the transdermal patch. Therefore, it cannot be concluded that transdermals are classified as high risk and are expected to comply with parenteral limits.	Reconsider systemic and local toxicity thresholds for dermals/transdermals. Dermals/transdermals shall receive scientifically justified thresholds or, alternatively, shall be excluded from the scope of this guideline at this time point.
Medicines for Europe	513	513	6.1	in table 1, can it be further clarified that intravenous and intramuscular are part of parenteral (especially because subcutaneous and other types of injections are called out)?	add a footnote or include in the title that parenteral includes intravenous and intramuscular
Medicines for Europe	513	513	6.1	In Table 1, ppm values for intrathecal and other routes are not identified. Intrathecal data are rarely available, leading to a high amount of animal studies necessary to be performed for epidural products. A concentraion based threshold is therefore highly desirable.	Add threshold for missing local routes
Octapharma	513	515	6.1	Please provide how the QTs were derived (reveal the 330 compounds, the point of departure, the applied modifying factors, and data distribution). The numbers appear random and it is impossible to review them. Furthermore, they are not aligned with (Masuda-Herrera et al. 2022). The QTs listed in Table 1 in 6.1 are unacceptable.	Provide the derivation of the QTs in an Appendix, so that toxicologists can understand the underlying principles of the QTs.
TGA	513	513		We agree with the use of TTC and qualification thresholds depending on the mutagenic potential of the leachable. Having qualification thresholds for non-mutagenic leachable compounds while using the TTC approach for mutagenic leachable compounds (or compounds of unknown mutagenicity) is consistent with the approach taken in other ICH guidelines.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TGA	513	513		It is unclear why topical ophthalmic products are not included in the systemic safety assessment. At the very least there should be options to control for compounds that are mutagenic or potentially mutagenic. Ophthalmic products do not just pose a local safety concern. In Section 6.4 (Route Specific Considerations and Special Cases), prior to discussion of ophthalmic products, it states "when potential local toxicity needs to be considered, the SCT used should be the lowest (on a daily exposure basis) of the mutagenic (i.e., TTC), non-mutagenic (i.e., QT), and local toxicity thresholds (pertinent concentration converted to a maximum daily exposure level)", implying that ophthalmic products should be included in the systemic toxicity thresholds section.	
TGA	513	513		For parenteral, dermal/transdermal and inhalation, it is unclear why a qualification threshold is lower than the TTC when the TTC is defined as the "Threshold of Toxicological Concern". This is at odds with other guidelines and at odds with the definition of "TTC". It seems the QT values were determined from PDE calculations of several compounds.	
TGA	513	513		We agree with maintaining the four TTC thresholds based on exposure duration. This is consistent with the approach outlined in ICH M7, which differentiates TTC values according to the length of exposure. This stratification is scientifically justified because carcinogenicity risk due to mutagenic impurities is influenced by dose and duration of exposure. While this may also be the case for other toxicities—longer periods allow cumulative effects to manifest, whereas shorter exposures typically present lower risk—the time effect differs for different toxicities, and it would be inappropriate to use as many tiers as that for mutagenicity. Two tiers for qualification thresholds are sufficient. Therefore, while simplifying to two TTC categories (acute vs chronic) may improve operational efficiency, retaining four duration-based TTCs aligns more closely with regulatory expectations and toxicological principles, ensuring robust protection across diverse exposure scenarios.	
TGA	513	513		The TTC limits and qualification thresholds in Table 1 only seem to apply to Class 2 leachables. This should be clearly articulated in the document. According to Appendix 4, there are three classes of leachables: •Class 1 – leachables to be avoided – the TTC and QT are not considered sufficiently protective – this implies the TTC values and QTs in Table 1 do not apply to these; compound-specific limits should be determined •Class 2 – leachables to be limited – the values in Table 1 apply •Class 3 – leachables with relatively low toxic potential – considered qualified up to 1.0 mg/day, which implies that the values in Table 1 do not apply to these While we agree with the principles of the classes and the general approach, noting that it is consistent with other ICH guidelines, it seems that the presentation of limits in Table 1 should be presented with the definition of classes of leachables.	
Medicines for Europe	516	526	6.2	In practice, when toxicological information is available, establishing compound-specific safety limits provides a more scientifically sound and risk-based approach than applying generic SCT values specifically for targeted leachable study. Need clarity on how to apply such compound-specific limits during extractables studies for determining AET, since the SCT for Class 1 compounds is lower than 1.5 µg/day.	Lines 315 to 317: "*Specific targeted tests for potential Class 1 leachables (see Section 6.2 Leachables Classification) should be performed based on the understanding of the material of construction and quality; risk analysis should be performed as appropriate*" Clarify if always required to look for class 1 extractables/leachables or only if information available that class 1 extractables/leachables may be present.
ELSIE	517	518	6.2	"Potential leachables from various materials encompass a large variety of chemicals, and thus toxicological characteristics." • While leachables are a large variety of chemicals they are primarily lipophilic in chemical nature as they are derived from synthetic polymers	• We recomment text chage based on the rationale: "Potential leachables from various materials encompass a large variety of lipophilic chemicals, and thus toxicological characteristics."
AESGP	521	523	6.2	CoC compounds usually list a compound class where the specific compounds within might have different AI values and not all will necessarily be 1.5 ug/d, e.g. nitrosamines with very different values.	Rephrasing needed
Maven E&L Ltd	523	524	Section 6.2	Benzo(a)pyrene is a mutagenic carcinogen, so this sentence is incorrect as it implies Benzo€pyrene is not a mutagen or carcinogenic to humans.	
AstraZeneca	523	524	Section 6.2	Benzo(a)pyrene is a mutagenic carcinogen, so this sentence is incorrect as it implies Benzo€pyrene is not a mutagen or carcinogenic to humans.	

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Chiesi Farmaceutici	523	523	6.2	The acronym AI is mentioned for the first time in the guideline but it is not reported what it refers to, as done for all other acronyms in the text, neither in the glossary.	It is suggested to include the meaning of the acronym in Paragraph 6.2 and to include it also in the glossary.
EfPIA	523	526	6.2	Benzo(a)pyrene seems out of place as an example compound with potent non-mutagenic concerns. Benzo(a)pyrene is a potent carcinogen and listed as an IARC Class 1 carcinogen. Is the non-mutagenic effects more sensitive than its carcinogenicity?	If using benzo(a)pyrene as an example, it should be confirmed that the non-mutagenic / carcinogenic effects are the most sensitive, and stated.
EfPIA	523	523	6.2	Editorial comment.	Defined acronym AI for clarity.
AESGP	524	515	6.1 General Principles	As mentioned in several other comments, dermal and transdermal are not the same. The transdermal PDEs are parenteral PDEs. Topical PDEs would be <oral<transdermal/parenteral, so the term, 'dermal' is misleading as it can be confused with topical, so it should not be used here.	...QT values for inhalation and ~~dermal/~~transdermal routes have been established based upon parenteral QT in lieu of available PDE values.
Maven E&L Ltd	526	529	Section 6.2	Suggested reword: "During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.	During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.
AstraZeneca	526	529	Section 6.2	Suggested reword: "During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.	During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.
EfPIA	526	529	6.2	It says that Class 1 leachables should be avoided, but then includes a common leachable (BPA) as stated in the Appendix 6. This seems like an apparent contradiction.	Focus of Class 1 leachables to their compound-specific limit as in Figure 1 should be included versus avoidance.
BioPhorum	527		6.2	Regarding 'class 1 leachables ... Avoid the use of materials which may leach such compounds', the wording could drive fear around materials used in bioprocessing where such as where polycarbonate, polysulfone (undetectable levels of BPA) are used. Suggest augmenting wording	Propose "Materials known to contain Class 1 leachables should be included in the risk assessment considering the process risk and propensity for leaching." Clarify what is meant by class 1 leachables? is it class 1 compounds? Better define class 1 compounds and when they should be measured
Maven E&L Ltd	530	530	Section 6.2	Suggestion to add Class 1, Class2 and Class 3 to Glossary, Class 3 glossary entry would then read, "Class 3 leachables are considered toxicological qualified when exposures are up to 1.0 mg/day, and thus do not need further assessment when found as leachables regardless of route of adminstration. (See Table A.4.1). Class 1 and Class 2 would defined as appropriate in glossary too	
AstraZeneca	530	530	Section 6.2	Suggestion to add Class 1, Class2 and Class 3 to Glossary, Class 3 glossary entry would then read, "Class 3 leachables are considered toxicological qualified when exposures are up to 1.0 mg/day, and thus do not need further assessment when found as leachables regardless of route of adminstration. (See Table A.4.1). Class 1 and Class 2 would defined as appropriate in glossary too	
BioPhorum	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5. Clarify definition of class 3 compounds
EfPIA	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5.
ELSIE	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5.
ELSIE	533	536	NA	"Class 3 leachables would not require further safety qualification if observed at daily exposure levels < 1 mg/day." Please clarify if this limit should be applied also for vaccines and if LTL considerations could be made • Clarification is needed on whether leachables testing is required when extractables data already demonstrate that Class 3 compounds are present at <1 mg/day. This aligns with a risk-based approach, suggesting that if safety concerns are ruled out based on extractables, further leachables testing may not be scientifically justified Recommend discussing Class 2 leachables before Class 3 and a better description would be helpful.	Provide clearer explanation Discuss Class 2 leachables before Class 3 and a better description would be helpful. Also, add a footnote to state that these are not applicable for medical devices
IPAC-RS	533	534	6.2	"Class 3 leachables would not require further safety qualification if observed at daily exposure levels < 1 mg/day." Please clarify is this limit should be applied also for vaccines and if LTL considerations could be made	Provide clearer explanation
EfPIA	535	535	6.2	Please add definition of AI and add to the abbreviations list.	Define or replace with Acceptable Intake
Maven E&L Ltd	537	539	Section 6.3	Suggested Addtional text to re-enforce connection of Safety Assessment to extractable and leachable study: "Safety Assessment should be considered a process step which follows a leachable study or the equilivalent extractable study. i.e. Leachables which are predicted to exceed the drug product AET..."	Safety Assessment should be considered a process step which follows a leachable study or the equilivalent extractable study. i.e. Leachables which are predicted to exceed the drug product AET..."
AstraZeneca	537	539	Section 6.3	Suggested Addtional text to re-enforce connection of Safety Assessment to extractable and leachable study: "Safety Assessment should be considered a process step which follows a leachable study or the equilivalent extractable study. i.e. Leachables which are predicted to exceed the drug product AET..."	Safety Assessment should be considered a process step which follows a leachable study or the equilivalent extractable study. i.e. Leachables which are predicted to exceed the drug product AET..."
BioPhorum	538	539	6.3	In addition to leachables also potential leachables (extractables) should be assessed 1.in order to inform on target leachables 2.in case of abbreviated data package (refer to chapter 3.4 and Appendix 1 Table A.1.2	Add potential leachables
EfPIA	538	539	6.3	It is considered important to clearly distinguish the purposes of the chemical assessment and the toxicological assessment within the overall evaluation framework. The conversion of SCT to AET enables an analytical chemist to address the question of whether a specific E/L needs to be quantified and identified. The AET represents the threshold above which a compound should be quantified and identified as a prerequisite for its potential toxicological assessment.	It is proposed to adapt "Organic leachables exceeding the AET should be identified, quantified, and reported for safety risk assessment. " to "Organic leachables exceeding the AET should be identified and quantified; and those quantified above the relevant SCT should be reported for safety risk assessment"
ELSIE	538	539	6.3	In addition to leachables also potential leachables should be assessed 1.in order to inform on target leachables 2.in case of abbreviated data package (refer to chapter 3.4 and Appendix 1 Table A.1.2)	Add potential leachables
IPAC-RS	538	539	6.3	The SCT should be the threshold above which leachables are assessed for safety. If below SCT, by definition, they do not pose risk. See lines 488-490. Reword to include potential, if they pose a risk or are above the SCT.	Organic leachables exceeding the AET should be identified, quantified, and reported for potential safety risk assessment.
IPAC-RS	538	539	6.3	In addition to leachables also potential leachables should be assessed 1.in order to inform on target leachables 2.in case of abbreviated data package (refer to chapter 3.4 and Appendix 1 Table A.1.2	Add potential leachables
EfPIA	539	539	6.3	How can the statement "Acceptability of partial or incomplete elucidation of the compound structure should be justified from an analytical perspective" be supported? Would this involve demonstrating that there is insufficient mass spectral information to improve the ID level?	Provide examples (as suggested)
EfPIA	539	540	6.3	For confirmation,if the compound structure is partally elucidated for unknown extractables/leachables, a read across approach can be applied for toxicological assessment? For example, if PEG-related unknown compounds are observed as extractables/leachables, the toxicological infromation of PEG can be applied?	N/A

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	539	539	6.3	How can the statement "Acceptability of partial or incomplete elucidation of the compound structure should be justified from an analytical perspective" be supported? Would this involve demonstrating that there is insufficient mass spectral information to improve the ID level?	Provide examples (as suggested)
Maven E&L Ltd	544	544	Section 6.3	Figure 1: See earlier Comment (Section 2) on lack of complete guidance on inorganic leachables	
Maven E&L Ltd	544	544	Section 6.3	Figure1: Consider adding Risk Acceptance Process Step to the flow chart to align with ICH Q9, for example where current flow has "No Further Action" & and as an additional box after "Consider risk mitigation strategy and changes to component leaching this compound"	
Maven E&L Ltd	544	544	Section 6.3	Figure 1: Whilst acceptable Margin of Safety is shown in Figure 1, there is no clear statement in the document of what an acceptable Margin of Safety is. Only what an unacceptable value is (See Appendix 5 & Glossary). I would suggest this is included either in Appendix 5 or Glossary of perhaps in the main body of the document as this is a key process step in Figure 1	
AESGP	544	544	6.3 Safety Assessment Process Figure 1	This flowchart is listed as Figure #1. There is already a Figure #1 and this should be listed as Figure #3.	Correct figure number.
AESGP	544	544	6.3	Typping error: replace "Figure 1" by "Figure 3"	replace "Figure 1" by "Figure 3"
AstraZeneca	544	544	Figure 1	There are 2 x Figure 1's in the guideline, one on page 3 and one on page 21. Figure 1 on page 21 needs to be renamed Figure 3.	Rename Figure1 (page 21) to Figure 3.
AstraZeneca	544	544	Section 6.3	Figure 1: See earlier Comment (Section 2) on lack of complete guidance on inorganic leachables	
AstraZeneca	544	544	Section 6.3	Figure1: Consider adding Risk Acceptance Process Step to the flow chart to align with ICH Q9, for example where current flow has "No Further Action" & and as an additional box after "Consider risk mitigation strategy and changes to component leaching this compound"	
AstraZeneca	544	544	Section 6.3	Figure 1: Whilst acceptable Margin of Safety is shown in Figure 1, there is no clear statement in the document of what an acceptable Margin of Safety is. Only what an unacceptable value is (See Appendix 5 & Glossary). I would suggest this is included either in Appendix 5 or Glossary of perhaps in the main body of the document as this is a key process step in Figure 1	
BioPhorum	544	545	6.3	Figure 3 The starting point is not correct, because the AET based on the SCT is for organic leachables and not for elemental impurities. Only class 1 elemental impurities are considered, while all other elemental impurities are not considered here.	Recommend to revise the workflow: Starting point "List of identified and quantified potential leachable or leachable", then go to decision point "Is the compound an elemental impurity?" if yes go to "Evaluate in accordance with ICH Q3D", if not go to decision point "Compound exceeding AET based on SCT" go on as described in the current flow chart.
BioPhorum	544	545	6.3	Figure 3 In the field „further risk assessment": The duration of use and route of exposure are already considered when selecting the SCT or QT from table 1.	Recommend to remove "duration of use and route of exposure"
EfPIA	544	545	6.3	Figure 3 The starting point is not correct, because the AET based on the SCT is for organic leachables and not for elemental impurities. Only class 1 elemental impurities are considered, while all other elenmental impurities are not considered here.	Recommend to revise the workflow: Starting point "List of identified and quantified potential leachable or leachable", then go to decision point "Is the compound an elemental impurity?" if yes go to "Evaluate in accordance with ICH Q3D", if not go to decision point "Compound exceeding AET based on SCT" go on as described in the current flow chart.
EfPIA	544	545	6.3	Figure 3 In the field „further risk assessment": The duration of use and route of exposure are already considered when selecting the SCT or QT from table 1.	Recommend to remove "duration of use and route of exposure"
EfPIA	544	544	Figure 1	Wrong figure number	Figure 3

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	544	544	Fig.1	In the diagram, “no further action” is recommended for leachable ICH M7 Class 1, 2, or 3 impurities if the level can be reduced to below the AI or TTC. However, the TTC value may be lower than the QT (see Table 1). Consequently, non-mutagenic toxic effects could occur at levels below the TTC.	It is recommended to add an arrow linking “Reduce leachable to < AI or TTC ?” → YES → “Exposure > QT” in the decision flowchart to improve clarity and specify all cases.
EfPIA	544	544	6.3	Typo in the figure numbering	Figure ~~1~~ 3
EfPIA	544	546	6	It is too easy to get confused between the M7 "Class 1" and the "Class 1" leachable. Indeed "Class 1" is used 7 times before getting the definition of Class 1 leachables in Section 6.2, and the discussion on the mutagenic toxic concerns is provided before the classification of leachables.	"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET, see Section 5) applicable to the drug product and no Class 1 leachables are observed (see classification of leachables in Section 6.2)
EFPIA Drug-MD ICH STG	544	549	6.3 Safety Assessment process	Incorporate DDC aspects into the process flow with reference to ISO 10993-17	Rationale: Integration provides clearer linkage for manufacturers familiar with device standards and acknowledges established practices for device material assessment.
ELSIE	544	544	Figure 1	Wrong figure number. Editorial change: "Figure 1. Safety Assessment Process for Leachables Using Safety Evaluation Thresholds" (misnumbered caption)	"Figure ~~1.~~ 3. Safety Assessment Process for Leachables Using Safety Evaluation Thresholds"
ELSIE	544	544	6.3	The schematic view uses the TTC; what about the assessment if the QT has been used in place of the TTC ?	Need clarification
ELSIE	544	544	6.3	Figure 3 - It is not clear how to complete the evaluation if you have leachable class 1 compound.	
ELSIE	544	545	6.3	Figure 3 The starting point is not correct, because the AET based on the SCT is for organic leachables and not for elemental impurities. Only class 1 elemental impurities are considered, while all other elenmental impurities are not considered here.	Recommend to revise the workflow: Starting point "List of identified and quantified potential leachable or leachable", then go to decision point "Is the compound an elemental impurity?" if yes go to "Evaluate in accordance with ICH Q3D", if not go to decision point "Compound exceeding AET based on SCT" go on as described in the current flow chart.
ELSIE	544	545	6.3	Figure 3 In the field "further risk assessment“: The duration of use and route of exposure are already considered when selecting the SCT or QT from table 1.	Recommend to remove "duration of use and route of exposure"
Gedeon Richter Plc.	544	545	6.3	Figure numbering is incorrect: "Figure 1" should modify to "Figure 3".	"Figure 1" should correct to "Figure 3".
IPAC-RS	544	544	6.3	The schematic view use the TTC, what about the assessment if the QT has been used in place of the TTC ?	Need clarification
IPAC-RS	544	545	6.3	Figure 3 The starting point is not correct, because the AET based on the SCT is for organic leachables and not for elemental impurities. Only class 1 elemental impurities are considered, while all other elenmental impurities are not considered here.	Recommend to revise the workflow: Starting point "List of identified and quantified potential leachable or leachable", then go to decision point "Is the compound an elemental impurity?" if yes go to "Evaluate in accordance with ICH Q3D", if not go to decision point "Compound exceeding AET based on SCT" go on as described in the current flow chart.
IPAC-RS	544	545	6.3	Figure 3 In the field "further risk assessment“: The duration of use and route of exposure are already considered when selecting the SCT or QT from table 1.	Recommend to remove "duration of use and route of exposure"
Medicines for Europe	544	544	6.3	change number of figure from 1 to 3	figure 3
TGA	544	544		We note that there are two “Figure 1” diagrams in the document (line 52, 544). The Figure at line 544 should be “Figure 3”.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	545	546	Figure 1: Safety Assessment Process for Leachables Using Safety Evaluation Thresholds	The right diamond to the far right of row 3 states, "reduce leachable to < AI or TTC?". Define AI in this guideline. Also, in the 2 arrows (options) coming out of this diamond box, what is the difference between "reducng the leachable" and "Consider risk mitigation strategy and changes to component leaching this compound"? Aren't they both "mitigation strategies"?	Clarify this point
EfPIA	545	546	Figure 1	The following step "reduce leachables to < AI or TTC" appears inconsistent with table 1 and text in section 6.3, as the AI or TTC might be higher than QT.	"reduce leachables to < AI or TTC or QT, whichever is lower"
EfPIA	545	546	Figure 1		Consider adding local toxicity threshold to the decision three, alternatively add a foodnote that local toxicity should also be consider for specfic routes as described in section 6.4 and table 1.
ELSIE	545	546	6.3	In the Figure: "If exposure is <=QT, no further action." There is situation when a non-target leachable is reported above AET and identified, but its exposure is less than QT therefore does not need safety assessment. For non-targeted leachable analysis, an analytical uncertainty factor is applied to AET. For example, a product with maximum patient exposure of <1 year and MDV of 12mL, SCT=QT=12 µg/day, UF = 2, AET= 0.5 µg/day. A leachable is reported at 0.7 µg/day. The daily exposure is 8.4 µg/day and is less than QT (12 µg/day).	Please clarify for non-target leachable above AET, but its daily exposure is less than QT, if safety assessment is needed.
Hikma	545	546	6.3	In Figure 1: "If exposure is <=QT, no further action." There is situation when a non-target leachable is reported above AET and identified, but its exposure is less than QT therefore does not need safety assessment. For non-targeted leachable analysis, an analytical uncertainty factor is applied to AET. For example, a product with maximum patient exposure of <1 year and MDV of 12mL, SCT=QT=12 µg/day, UF = 2, AET= 0.5 µg/day. A leachable is reported at 0.7 µg/day. The daily exposure is 8.4 µg/day and is less than QT (12 µg/day).	Please clarify for non-target leachable above AET, but its daily exposure is less than QT, if safety assessment is needed.
ELSIE	546	546	6.3	• Figure 3 does not clearly explain how a suitable surrogate is determined.	• We recommend adding the following text: "A suitable surrgoate may be a compound of same empricial formula, or display the same or similar chemical struture".
Maven E&L Ltd	548	549	Section 6.3	Figure 1: Footnote, Attachment 3 of ICH Q3A seems to be the only place where TDI >1mg/day is discussed, and would indicate that TDI > 1 is more than the qualification threshold for impurities in drug substances. This guidance does not consider leachables, and thus why is this considered relevant and true also for leachables? This seems an abitary inclusion	
AstraZeneca	548	549	Section 6.3	Figure 1: Footnote, Attachment 3 of ICH Q3A seems to be the only place where TDI >1mg/day is discussed, and would indicate that TDI > 1 is more than the qualification threshold for impurities in drug substances. This guidance does not consider leachables, and thus why is this considered relevant and true also for leachables? This seems an abitary inclusion	
EfPIA	548	549	6.3	Data on genotoxicity of leachables will likely come from literature. It should be confirmed that this data is acceptable, versus having to generate new data GLP.	Include statement which says, literature data can be used to support the genotoxicity assessment of a leachable.
EfPIA	548	549	6.3	In silico studies are generally used when no toxicity data are available, therefore we propose to add this in the text. We propose to add in vitro micronucleus assay in the examples as it is now a standard.	If daily exposure to leachable is >1 mg/day, in silico and/or genotoxicity studies should be considered, as recommended in ICH Q3A and ICH Q3B (e.g., bacterial mutagenicity study and in vitro chromosomal aberration assay or in vitro micronucleus assay).
EfPIA	548	548	6.3	"Reduce leachable to <AI or TTC?"	Clarify Yes/No

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	548	548	6.3	It is stated that if daily exposure to a leachable is greater than 1 mg per day genotoxicity studies should be considered.	It would be helpful to clarify that if genotoxicity testing is still recommended in cases where the leachable is greater than 1 mg/day but less than the acceptable intake.
ELSIE	548	549	6.3	In silico analysis for mutagenicity should also be an option (see line 1050). Furthermore, in vitro MNT should be mentioned as an alternative to in vitro chromosomal aberration.	If daily exposure to leachable is >1 mg/day, in silico analyis or genotoxicity studies should be considered, as recommended in ICH M7, Q3A and ICH Q3B (e.g., bacterial mutagenicity study and in vitro chromosomal aberration assay or in vitro micronucleus assay).
EfPIA	549	549	6.3	This sentence is not correct. ICH Q3A does not say to perform a chromosome aberration assay. It states "a study to detect chromosomal aberrations". This is an important nuance. A chromosome aberaration assay is a specific microscopic method to score aberrations in fixed chromosomes, whereas a "study to detect chromosome aberrations" is a more broad set of asays and can include, for example, the in vitro micronucleus assay.	Copy Q3A verbatim "A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen."
Maven E&L Ltd	550	553	Section 6.3	This sentence is a near repeat of Lines 526 to Lines 529. I suggest using comment reword there… " During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.	During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.
AstraZeneca	550	553	Section 6.3	This sentence is a near repeat of Lines 526 to Lines 529. I suggest using comment reword there… " During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.	During drug product development, the possibility of class 1 leachables should be considered when material screening and selection is made. Where the use of materals of construction which are known sources of Class 1 leachables is unavoidable, a detailed leachable risk management process may be required, and could lead to a requirement for risk control centred on the class 1 leachable.
ELSIE	550	551	NA	" Potential Class 1 leachables should ideally be identified and avoided during materials and component selection". Please clarify if supplier will need to inform that materials are potentially leaching Class 1 compounds	Provide clearer explanation
IPAC-RS	550	551	6.3	"Potential Class 1 leachables should ideally be identified and avoided during materials and component selection." Please clarify if supplier will need to inform that materials are potentially leaching Class 1 compounds	Provide clearer explanation
EfPIA	551	553	6.3	In analogy with comment left for lines 492-495, how would "lower compound-specific (…) specifications (…) adequately control" the presence of Class 1 leachables, in case such compounds could not be avoided? This would introduce uncertainty in the release of batches, as the risk of OOS would be not negligible, given the analytical challenges with quantitating compounds that are expected at very low levels.	Consider including a tiered approach, similar to the four control strategy otpions descirbed in ICH M7, whereby for Class 1 leachabels a combination of upstream control inputs (such as adquate limits in raw materials, intermediates, etc.) with well-described fate-and-purge studies may be sufficient to ensure that these leachables of concern are not present at levels above the AI in the finsihed product.
Medicines for Europe	551	553	6.3	Related to if specifications to adequately control leachables are required (in terms of any class of leachable compound), I noticed that there is not guidance as to when it is appropriate to set a drug product specification to control leachables in the drug product, for example, being below a specific margin of safety, or results remaining below their specific thresholds or PDE. Will there be a consideration to add information related to this topic (adding a control threshold or other guidance related to when to set a drug product specfication for leachables, similar to guidances for elemental impurities and nitrosamines?	add a section related to specifications or control thresholds, e.g. MoS of >3 for class 2 and 3 compounds, MoS of >10 for class 1 compounds

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Maven E&L Ltd	553	556	Section 6.3	Remove Subsequently from the Sentence. The sentence beginning, "Leachables considered potentially mutagenic.." should be re-written. Suggested re-write: "Leachables flagged as Class 3 (as defined by ICH M7), should be risk controlled as per ICH M7 until such time as reclassified as Class 2 or Class 5, when they should be controlled as outlined in ICH M7.	Remove Subsequently from the Sentence. The sentence beginning, "Leachables considered potentially mutagenic.." should be re-written. Suggested re-write: "Leachables flagged as Class 3 (as defined by ICH M7), should be risk controlled as per ICH M7 until such time as reclassified as Class 2 or Class 5, when they should be controlled as outlined in ICH M7.
AstraZeneca	553	556	Section 6.3	Remove Subsequently from the Sentence. The sentence beginning, "Leachables considered potentially mutagenic.." should be re-written. Suggested re-write: "Leachables flagged as Class 3 (as defined by ICH M7), should be risk controlled as per ICH M7 until such time as reclassified as Class 2 or Class 5, when they should be controlled as outlined in ICH M7.	Remove Subsequently from the Sentence. The sentence beginning, "Leachables considered potentially mutagenic.." should be re-written. Suggested re-write: "Leachables flagged as Class 3 (as defined by ICH M7), should be risk controlled as per ICH M7 until such time as reclassified as Class 2 or Class 5, when they should be controlled as outlined in ICH M7.
ELSIE	553	553	6.2	Typo/Editorial Start new paragraph at "Subsequently…" as this relates to all leachables, and not only to the Class 1 leachables at the beginning of the paragraph.	Start new paragraph at "Subsequently…" as this relates to all leachables, and not only to the Class 1 leachables at the beginning of the paragraph.
BioPhorum	560	564	6.3	Sentence not complete/understandable.	Propose to adjust to: "Conversely, if data do not sufficiently support the safety of the leachable, further action is needed, which can include reduction of the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level."
EfPIA	560	564	6.3	Sentence not complete/understandable.	Propose to adjust to: "Conversely, if data do not sufficiently support the safety of the leachable, further action is needed, which can include reduction of the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level."
ELSIE	560	564	6.3	Sentence not complete/understandable.	Propose to adjust to: "Conversely, if data do not sufficiently support the safety of the leachable, further action is needed, which can include reduction of the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level."
IPAC-RS	560	564	6.3	Sentence not complete/understandable.	Propose to adjust to: "Conversely, if data do not sufficiently support the safety of the leachable, further action is needed, which can include reduction of the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level."
Maven E&L Ltd	570	574	Section 6.3	This paragraph seems to contradict the footnote to Figure 1. Footnote to Figure 1 should be changed or removed	
AstraZeneca	570	574	Section 6.3	This paragraph seems to contradict the footnote to Figure 1. Footnote to Figure 1 should be changed or removed	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Chiesi Farmaceutici	570	572	6.3	Document states that in silico methods could be considered if they can be justified. NAMs and other in silico or in vitro methods should be utilised in the first instance prior to generation of new in vivo data, either by assessment of structural alerts or other suitable methodology	Instead of "New Approach Methologies (NAMS) including in silico and in vitro models may be considered if appropriately justified…", write "New Approach Methodologies (NAMs) including in silico and in vitro models should be considered if appropriately justified..."
EfPIA	570	574	6.3	As written it is unlikely that companies will use NAMs to justify limits since no acceptable framework has been provided and NAMs are currently not validated.	Providing additional brief guidance on what would be sufficient use of NAMs so companies feel confident that they would be accepted from a regulatory perspective would encourage companies utilize NAMs in E&L evaluations.
EfPIA	570	574	6.3	The applicability of NAMs data including in silico and in vitro models to support the safety of exposure is not clearly defined.	Consider indicating that NAMs data including in silico and in vitro data may be considered to generate data for justification of TTC selection or application of read across.
EfPIA	570	572	5.4	Is it the intent of the guideline to recommend extractables testing on every incoming lot of container closure system components for the purpose of evaluating E/L correlation? While this may be the current expectation or practice for OINDP, it is not for components used with parenteral products and would result in an increase in repeat testing of the same materials with little to no value.	Recommend including a consideration of how the components are manufactured and common practices for determining lot numbers since manufacturing may include a large batch size that is then sublotted for inventory purposes, resulting in component lots that are identical. Testing of each lot would then be redundant.
ELSIE	571	572	6.3	"New Approach Methodologies (NAMs) including in silico and in vitro".	Please provide more guidance on the approach, and/or examples or practical cases
EfPIA	572	574	6.3	ICH Q3A/B applies to drug substance-related impurities, and such studies rarely use neat materiall	
AstraZeneca	573	573	Section 6.3	Word missing. The test currently reads as: "Otherwise, a toxicological qualificationstudy(ies) as described in ICH Q3A and Q3B should be considered in order support safetyassessment of the compound(s)." Suggest the word "to" is added so it reads "Otherwise, a toxicological qualificationstudy(ies) as described in ICH Q3A and Q3B should be considered in order to support safetyassessment of the compound(s).	Addition of missing word "to"
ELSIE	573	574	6.3	• Editorial change: "...in order support safety assessment…"	"...in order to support safety assessment…"
EFPIA Drug-MD ICH STG	575	675	6.4. Route specific considerations	Add clarification in Section 6.4 (Route Specific Considerations) on how to assess risk when the patient is exposed both to leachables in the drug product and potentially to direct contact with the device material itself. Should exposures be summed? Do different thresholds (e.g., TCL from ISO 10993-17) apply to the direct device contact?	Rationale: DDCPs can present complex exposure scenarios requiring distinct assessment strategies compared to traditional drug products.
EfPIA	578	578	6.4	"damage to vulnerable tissues". Reads alarmist, especially for leachables at negligible levels relative to drug product doses. Recommend "potential adverse effects in surrounding tissues"	Change to "potential adverse effects in surrounding tissues"
EfPIA	579	583	6.4	Intracerebral administration route is too specific and quite rare, therefore we advise to apply a case-by-case evaluation in this case.	Safety risk assessments for potential systemic toxicity are typically sufficient to support thesafety of exposure to leachables. However, there are certain scenarios where potential local toxicity effects may be pertinent due to the potential for damage to vulnerable tissues relatedto the local concentration of a compound (e.g., pulmonary drug products, ophthalmic drug products, and ~~intracerebral~~/intrathecal/epidural drug products).
EUCOPE	580	583	6.4	The route-specific considerations outlined in the guideline indicate that, in certain scenarios, an assessment of local toxicity for leachables should be performed. Given that non-clinical safety studies already address local toxicity, is an additional safety risk assessment still required?	
EfPIA	581	583	6.4	How should formulation and excipients be considered in the safety assessment of local toxicity related to a leachable? To avoid unclarities, additional guidance would be helpful.	
EfPIA	587	597	6.4.1	Intraocular seems out of place here since the guidance is more in line with 6.4.2, especially when considering Table 1.	Rename to 6.4.1 to Topical Ophthalmic Products, and remove reference to intraocular. Include intraocular to 6.4.2

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Laboratoires Théa	587	597	6.4.1	For ophthalmic local toxicity, only a threshold of 20 ppm is presented. Can you confirm that the limits of 1 and 10 ppm presented in the FDA draft guidance "Quality Considerations for Topical Ophthalmic Drug Products" do not need to be taken into account and that only leachables above this threshold need to be reported and qualified?	
EfPIA	590	597	6.4.1	The limit of 20ppm is concentration based rather than dose derived. This is inconsistent with the entire principle of the guideline - it talks about this being based on historical precedence - this is should not be the basis of the assessment	Re-evaluate appropriate limits for Opthalmic DPs
Maven E&L Ltd	592	592	Section 6.4.1	See earlier comment about use of ppm unit. This needed definition to clarify units are volume / volume	
AstraZeneca	592	592	Section 6.4.1	See earlier comment about use of ppm unit. This needed definition to clarify units are volume / volume	
EfPIA	592	593	6.4.1	You introduce 20ppm as a threshold for opthalmic drug products. You do not support the threshold with the supporting literature. It should not be assumed that all readers know where the values originate from.	Support the 20 ppm limit with peer-reviewed literature and provide in text citation
EfPIA	593	594	6.4.1	Please clarify that irrigation fluids are less critical. Which concentration limit or SCT applies to ocular irrigation fluids?	
EfPIA	594	595	6.4.1	What should be the threshold for drugs used for injection in ocular tissues?	Clarification needed
ELSIE	594	595	6.4.1	What should be the threshold for drugs used for injection in ocular tissues? This statement is interpreted that a complete assessment for every potential leachable is required without a SCT. Guidance is missing how to calculate the AET. Is the proposed PDE calculation intravitreal applying a factor of 1/500 x parenteral PDE deemed applicable (Lovsin-Barle et al 2019)?	Clarification needed Kindly either provide a threshold for injections into ocular tissue or esp. Intraventrial or use 20ppm for all ophthalmic dps.
Maven E&L Ltd	595	595	Section 6.4.1	There is an absence of advice on the expected analytical detection limit for leachables. Include in analytical section some advice on AET for opthhalmics (i.e. limit less than 20ppm)	
AstraZeneca	595	595	Section 6.4.1	There is an absence of advice on the expected analytical detection limit for leachables. Include in analytical section some advice on AET for opthhalmics (i.e. limit less than 20ppm)	
BioPhorum	595	597	6.4.1	This statement is interpreted, that a complete assessment for every potential (is it meant to be every leachable) leachable is required without a SCT. Guidance is missing how to calculate the AET. Is the proposed PDE calculation intravitreal applying a factor of 1/500 x parenteral PDE deemed applicable (Lovsin-Barle et al 2019)?	Kindly either provide a threshold for injections into ocular tissue or esp. Intraventrial or use 20ppm for all ophthalmic dps. Propose removing the word "potential"
EfPIA	595	597	6.4.1	This statement is interpreted, that a complete assessment for every potential leachable is required without a SCT. Guidance is missing how to calculate the AET. Is the proposed PDE calculation intravitreal applying a factor of 1/500 x parenteral PDE deemed applicable (Lovsin-Barle et al 2019)?	Kindly either provide a threshold for injections into ocular tissue or esp. Intraventrial or use 20ppm for all ophthalmic dps.
EfPIA	595	597	6.4.1	In the current wording, the "may be of relevance" cases uncertaity in the interpretation as a specific compound might cause for example a direct chemical effect on the retina or cause an indurect effect on the retina through increased intro-occular pressure.	A qualitative safety assessment of any leachables present should be provided, since such leachables may be of relevance even when present at a concentration below 20 ppm. The relevance can be demonstrated by a direct or indirect effect on targeted organ, e.g a compound might cause for example a direct chemical effect on the retina or cause an indurect effect on the retina through increased intro-occular pressure.
IPAC-RS	595	597	6.4.1	This statement is interpreted, that a complete assessment for every potential leachable is required without a SCT. Guidance is missing how to calculate the AET. Is the proposed PDE calculation intravitreal applying a factor of 1/500 x parenteral PDE deemed applicable (Lovsin-Barle et al 2019)?	Kindly either provide a threshold for injections into ocular tissue or esp. Intraventrial or use 20ppm for all ophthalmic dps.
EfPIA	596	596	6.4.1	Reword "Final to-be-marketed topical ophthalmic products"	topical ophthalmic drug products
Maven E&L Ltd	598	607	Section 6.4.2	As per section 6.4.1, no advice on a suitable analytical limit is included. Suggest inclusion of some text even if it is as low as reasonally practical	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	598	607	Section 6.4.2	As per section 6.4.1, no advice on a suitable analytical limit is included. Suggest inclusion of some text even if it is as low as reasonally practical	
AstraZeneca	598	607	Section 6.4.2	This indicates that in vitro data suggest effects at ppb - where is this evidence and how does this correlate with more specific in vivo data? Has any thought been given to the practicality of achieving such limits ? either analyticality or practically in terms of reduction / avoidance ?	
EfPIA	603	603	6.4.2	If ppm are not defined in row 467, ppb need not to be defined either	Harmonize
ELSIE	603	603	6.4.2	If ppm are not defined in row 467, ppb need not to be defined either	Harmonize
EfPIA	604	607	6.4.2	For intracerebral, etc. leachables there is no QT and a compound-specific risk assessment should include local effects to neuronal tissue (which are not available for most leachables). What tests would be informative, and how can a compound-specific limit be derived from such data? What is the AET based on? Without an AET, how is the analytical limit for identifying compounds derived? Without guidance on these questions it will likely result in a huge burden on biological testing, with little benefit to patients.	Even without a QT, a practical threshold needs to be suggested for the AET. Also, provide more guidance on an acceptable strategy and derivation of compound-specific limits for local effects on neuronal tissue. One suggested approach is to derive based on guidance from Yu et al., 2024 (https://pubmed.ncbi.nlm.nih.gov/39581257/) specifically for intravitreal impurities, but many of the concepts would also apply for other concerning routes, e.g. intracerebreal, etc. routes.
EfPIA	605	607	6.4.2	How can local inflammatory response in CNS be assessed since these data is rarely available for E&Ls? Is there an expectation to conduct in vitro studies for all potential compounds? Additionally, it is known that only low number of immune cells (i.e. dendritic cells) is found in the human cerebrospinal fluid (CSF) (Engelhardt, 2006; Pashenkov et al, 2002); therefore, there is very limited concern for this specific endpoint for E&Ls which are usually detected at very low levels only	Remove ''including an assessment of the potential for a local inflammatory response.''
Maven E&L Ltd	608	617	Section 6.4.3	As per other comment, use of ppm unit is problematic without a further definition of how the concentration is expressed	
AstraZeneca	608	617	Section 6.4.3	As per other comment, use of ppm unit is problematic without a further definition of how the concentration is expressed	
AstraZeneca	610	610	Section 6.4.3	"... the leachable concerns a strong or extremepotency skin sensitizer"Not sure "concerns" is the correct word to use here?	Consider the use of word "concerns"
EfPIA	611	611	6.4.3	No need to use an acronym that is not mentioned anywhere else (HPC)	Remove "HPC"
ELSIE	611	611	6.4.3	No need to use an acronym that is not mentioned anywhere else (HPC)	Remove "HPC"
Luye Pharma	611	617	6.4.3	The conversion of the dermal sensitization threshold (DST) to ppm based on an assumed 0.5 g daily dermal dose originates from the ICH Q3D default dermal exposure assumption. Therefore, the ppm conversion is formally valid only for dermal dosage forms for which this 0.5 g default is scientifically appropriate. For transdermal systems, this default assumption does not hold, because: The applied matrix mass of a transdermal patch needs to be considered (usually less than 0.5 g) and only a very small fraction of the formulation is available for potential transfer into the skin (limited contact area, low chemical potential). Thus, applying the same ppm conversion is not scientifically justified.	Should the scope be broadened to include transdermals, a representative calculation would be appreciated.
Medicines for Europe	611	617	6.4.3	Is the conversion to ppm for the dermal sensitization threshold only valid for dermals (dose of 0.5 g assumed based on ICH Q3D) or also applicable to any dosage form applied to skin tissue (e.g. transdermals)?	If application is widened to transdermals exemplary calculation is highly appreciated.
ELSIE	612	612	6.4.3	No reference for how the 1 µg/cm2/day was derived	Reference needed
EfPIA	613	613	6.4.3	No need to use an acronym that is not mentioned anywhere else (CTCL)	Remove "CTCL"
EfPIA	613	614	6.4.3	Is "when the leachable concerns a strong or extreme potency skin sensitizer" necessary?	
ELSIE	613	613	6.4.3	No need to use an acronym that is not mentioned anywhere else (CTCL)	Remove "CTCL"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	614	617	6.4.3	ICH Q3D identifies 1FTU as being equivalent to 0.5g drug product, usually cutaneous products are designed to apply 1FTU over 250 cm2. The ICH Q3E dermal local toxicity threshold of 500 ppm was based on the DST of 1 µg/cm2/day applied over a surface area of 250 cm2 and product use of 0.5g = 500ppm or 500 µg/g. Are the EWG agreed to apply 500 ppm to all dermal products.	Provide clearer guidance, instead of "can be used", suggest is "recommended to be used"
IPAC-RS	614	617	6.4.3	ICH Q3D identifies 1FTU as being equivalent to 0.5g drug product, usually cutaneous products are designed to apply 1FTU over 250 cm2. The ICH Q3E dermal local toxicity threshold of 500 ppm was based on the DST of 1 µg/cm2/day applied over a surface area of 250 cm2 and product use of 0.5g = 500ppm or 500 µg/g. Are the EWG agreed to apply 500 ppm to all dermal products.	Provide clearer guidance, instead of "can be used," we suggest "recommended to be used"
Rentschler Biopharma SE	618	675	6.4.4	The threshold for irritants and sensitizers for parenteral drug products (5 µg/person/day) stipulated by PQRI (Reference: Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular), PQRI, 28 October 2021, ISBN: 978-1-945584-30-5) is not mentioned in this subchapter. Will the PQRI threshold be outdated after ICH Q3E becomes effective?	
EfPIA	624	624	6.4.4	Editorial comment.	Remove word "potential".
AESGP	639	640	6.4.4	It might be substantially overestimating, that all leachables from a multi-day patch migrate within one day.	This approach should be challenged
EfPIA	639	640	6.4.4	"For multi-day patches it is assumed that all leachables migrate within a day"	What is the rationale for this assumption?
EfPIA	645	650	6.4.4	Applicability of the dermal sensitization data to the respiratory tract should be evaluated on a case-by-case basis as some compounds can be sensitizers in both applications, some others not. this proposal is going along with the subsequent lines in the text.	Consequently, depending on the compound, dermal sensitization data might not be applicable ~~should not be used~~ to estimate the risk for respiratory sensitization. ~~and no threshold for respiratory sensitization can be provided.~~
ELSIE	645	647	6.4.4	"Consequently, dermal sensitization data should not be used to estimate the risk for respiratory sensitization and no thresold for respiratory sensitization can be provided." • The clarification is necessary how and if the Systemic Toxicity Threshld QT for Inhalation could be applied instead of the Local Toxicity Threshold QT	• We propose rewording the sentence or adding detailed clarification regarding when the Systemic Toxicity QT can be used as an alternative to the Local Toxicity QT
Maven E&L Ltd	648	655	Section 6.4.4	It would be helpful to include a recommendation for how irritation and sensitizing properties are to be determined such as a in-silico tool.	
AESGP	648	655	6.4.4	This paragraph is missing a clear statement how to use the different thresholds, especially the local one, if being applied for AET and extractables studies.	E.g. the local threshold is used for AET calculation, the identified compounds are evaluated for structural elements which might irritate or sensitize and if nothing suspicious is found, the systemic QT is applied.
AstraZeneca	648	655	Section 6.4.4	It would be helpful to include a recommendation for how irritation and sensitizing properties are to be determined such as a in-silico tool. As worded it could be interpreted to mean that were any alert triggered based purely on structure, the emphasis would be to prove it was not a concern. Given as stated line 647 that no threshold exists for respiratory sensitisers then it is difficult to see how, if such a compound was observed it would be feasible to define an acceptable limit	
EfPIA	648	655	6.4.4	At written there is no threshold for respiratory sensitisation, instead it stated that specific functional groups are defined as being of concern, including many relatively common structural moeties. In the absence of an actual threshold and announcement of structures of concern this seems to put the onus on the applicant to prove any such impurity is not a sensitiser	reconsider the implications of how this is currently defined and the impact this would have.
EfPIA	650	650	6.4.4	Remove "and no threshold for respiratory sensitization can be provided"?	
IPAC-RS	650	650	6.4.4	Sensitization Potential: Which component is behind the term nitrile?	Consider adding further information or examples of nitriles of concern
ELSIE	668	668	6.4.4	It is unclear why a factor of 10 is used, rather than another value. The rationale behind selecting this specific multiplier should be clarified.	Clarification needed

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ELSIE	669	675	NA	Historically, the PQRI approach was considered for risk assessment of leachable compounds with sensitizing potential (i.e., 5 µg/dose acceptable exposure limit). In this draft of the Guideline there is no mention concerning acceptable exposure limit/safety limit for skin sensitizer administered intramuscularly. Does it mean that according to this guideline, the QT should be considered protective also for this skin sensitization?	Provide clearer explanation
IPAC-RS	669	675	6.4.4	Historically, the PQRI approach was considered for risk assessment of leachable compounds with sensitizing potential (i.e. 5 µg/dose acceptable exposure limit). In this draft of the Guideline there is no mention concerning acceptable exposure limit/safety limit for skin sensitizer administered intramuscularly. Does it mean that according to this guideline, the QT should be considered protective also for this skin sensitization?	Provide clearer explanation
ELSIE	671	672	6.4.4	• Editorial change: "...intramuscular and intravenous administered substances..."	"...intramuscularly and intravenously administered substances..."
EfPIA	673	675	6.4.4	We believe that the potency of the sensitizer should be taken into account and only the concetration, therefore we propose to add this aspect.	Since leachables are present at low concentrations in drug products, it is considered unlikely that sensitization potential will be of concern for drugs administered via intravenous or intramuscular injection, irrespective of the sensitizer potency (i.e. low, moderate, high and extreme).
ELSIE	673	675	NA	"Since leachables are present at low concentrations in drug products, it is considered unlikely that sensitization potential will be of concern for drugs administered via intravenous or intramuscular injection." Do we have a reference to substantiate this statement? It is not clear how to interprete this sentence and what would be the consequence. Should a threshold be defined anyway for those routes of administration or can it be omitted?	Provide reference
IPAC-RS	673	675	6.4.4	"Since leachables are present at low concentrations in drug products, it is considered unlikely that sensitization potential will be of concern for drugs administered via intravenous or intramuscular injection." Do we have a reference to substantiate this statement?	Provide reference
AqVida GmbH	676	682	6.5	The focus of this comment is to highlight the discrepancy between the ICH Q3E draft and current ICH guidelines (M7, S9) regarding the evaluation of impurities for oncology products. For many oncology drug products, the inherent toxicity and often genotoxicity are the primary determinants of patient risk. Patients treated with these products typically face life-threatening diseases with limited therapeutic options, making timely access to effective therapies critical. In this context, the incremental risk from trace levels of leachables over the shelf life of the product is negligible relative to the overall toxicity of the drug product itself. A scientific risk-based approach is required to account for the unique characteristics and therapeutic context of oncology products, to align with ICH M7 and ICH S9 guidelines. ICH M7 states for S9 products: "Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities." The S9 Q&A document details what acceptable levels are: " Therefore, mutagenic impurities in products used for treatment of indications under the scope of ICH S9 should be considered for management consistent with the concepts outlined in ICH Q3A/B."	Suggested edit (in italics) (lines 677-682): For drug products within the scope of ICH S9, extractables and leachables testing can be waived since the exposure to a potential mutagenic extractable or leachable impurity in these cases would not significantly add to the cancer risk of the drug substance. For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, extractables and leachables should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AqVida GmbH	676	682	6.5	[Continued from above] As an example and in current contrast to extractables and leachables, for the assessment of nitrosamines, which is another potential subset of mutagenic impurities, the following is written in the document Questions and answers document for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (EMA/409815/2020): "For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines, as specified in the Q&A document to ICH S9 guideline." This means, nitrosamines are treated as non-mutagenic impurities for S9 products. In the same way, the ICH Q3E draft should address extractables and leachables as non-mutagenic impurities for S9 products. Finally, some nitrosamines are described in ICH M7:"Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkyl- azoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline." Whilst these impurities pose a high potential risk, the strategy outlined in EMA/409815/2020 for evaluation of nitrosamines is as follows: "For products where nitrosamine impurities can be controlled according to ICH Q3A/B principles, see Q&A 10, confirmatory testing is generally not needed if the risk can be sufficiently mitigated based on scientific considerations that demonstrate that the relevant ICH Q3A/B thresholds will not be exceeded. In such cases, the justification should be documented in the risk assessment in the MAH's pharmaceutical quality system." This strategy should therefore also be applied for assessing extractables and leachables in S9 products.	Suggested edit (in italics) (lines 677-682): For drug products within the scope of ICH S9, extractables and leachables testing can be waived since the exposure to a potential mutagenic extractable or leachable impurity in these cases would not significantly add to the cancer risk of the drug substance. For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, extractables and leachables should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines.
AstraZeneca	676	682	Section 6.5	The wording of this section is not consistent with either ICH M7, ICH S9 guideline or recent guidance relating to N-Nitrosamines; all these permit such impurities to be controlled to ICH Q3A/B limits. This is inordinately conservative in comparison	Re-examine this and seek to better align to principals established in the aforementioned guidance
BioPhorum	676	682	6.5	Chapter 6.5 For ICH S9 products, the TTC would not be applicable and the SCT would be defined by the QT. By this statement, only systemic toxicity is addressed for ICH S9 products.	It is proposed to add verbiage that the SCT is derived from QT or local toxicity threshold, whatever is lower.
EfPIA	676	682	6.5	Chapter 6.5 For ICH S9 products, the TTC would not be applicable and the SCT would be defined by the QT. By this statement, only systemic toxicity is addressed for ICH S9 products.	It is proposed to add verbiage that the SCT is derived from QT or local toxicity threshold, whatever is lower.
ELSIE	676	682	6.5	Chapter 6.5 For ICH S9 products, the TTC would not be applicable and the SCT would be defined by the QT. By this statement, only systemic toxicity is addressed for ICH S9 products.	It is proposed to add verbiage that the SCT is derived from QT or local toxicity threshold, whatever is lower.
IPAC-RS	676	682	6.5	Chapter 6.5 For ICH S9 products, the TTC would not be applicable and the SCT would be defined by the QT. By this statement, only systemic toxicity is addressed for ICH S9 products.	It is proposed to add verbiage that the SCT is derived from QT or local toxicity threshold, whatever is lower.
ELSIE	677	682	6.5	For ICH S9 products, the QT can be considered an applicable threshold to be used in the tox evaluation, can this be applied as the SCT for AET?	Provide clearer explanation
IPAC-RS	677	682	6.5	For ICH S9 products, the QT can be considered an applicable threshold to be used in the tox evaluation, can this be applied as the SCT for an AET?	Provide clearer explanation
ELSIE	683	689	6.6	The term "safety assessment" is used in this section.	Please clarify if the safety assessment is the same as the toxicological risk assessment. Using consistent terminology throughout would be helpful.
EfPIA	688	688	6.6	Editorial comment.	Change "is provided" to "are provided".
BioPhorum	690	763	7.	Chapter 7. Glossary Glossary missing abbreviations MDD, NAM, AI	Propose to add definitions

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BioPhorum	690	763	7.	Chapter 7. Glossary Following definitions are not included: packaging, primary packaging, secondary packaging and Container Closure System	Propose to add definitions and ensure the right terms are used throughout the document and not interchangeably
Chiesi Farmaceutici	690	763	7	Acronym AI is not included in the glossary	See above
Chiesi Farmaceutici	690	763	7	It could be useful to include definitions of primary packaging, secondary packaging, delivery device, device constituent part, drug-device combination products, as the interpretation of these definitions are often confunding, while they should be unambiguous.	-
EfPIA	690	763	7.	Chapter 7. Glossary Glossar missing abbrevations MDD, NAM, AI	Propose to add definitions
EfPIA	690	763	7.	Chapter 7. Glossary Following definitions are not included: packaging, primary packaging secondary packaging and Container Closure System	Propose to add definitions and ensure the right terms are used throughout the document and not interchangeably
EfPIA	690	763	7	Throughout the document, the term Safety Assessment (SA) is used in both the analytical and toxicological contexts. In general, the scope of SA and Toxicological Risk Assessment (TRA) are different. SA may include material assessment (MA), TRA, risk/benifite assessment; TRA would focus on compound specific assessment with toxicological data. In the context of this guideline, results of MA would inform if targeted analyses of Class 1 compounds need to be incorporated into study design.	Consider providing clear definition of SA and TRA in the Glossary and apply them consistently throughout the document.
EfPIA	690	763	7	Editorial comment.	Cross-check all glossary definitions with those in Q3A, Q3B, Q3C, Q3D, and M7 for consistency,
EFPIA Drug-MD ICH STG	690	690	7. Glossary	Terminology- lack of definitions for packaging, primary packaging secondary packaging and Container Closure System	add definitions and ensure the right terms are used throughout and NOT interchangeably
ELSIE	690	763	7	The definition of terms is presented in the glossary.	Please include the definitions for drug-device combination product and delivery device component in the glossary.
ELSIE	690	763	7.	Chapter 7. Glossary Glossary missing abbrevations MDD, NAM, AI	Propose to add definitions
ELSIE	690	763	7.	Chapter 7. Glossary Following definitions are not included: packaging, primary packaging secondary packaging and Container Closure System	Propose to add definitions and ensure the right terms are used throughout the document and not interchangeably
IPAC-RS	690	763	7.	Chapter 7. Glossary Glossary missing abbrevations MDD, NAM, AI	Propose to add definitions
IPAC-RS	690	763	7.	Chapter 7. Glossary Following definitions are not included: packaging, primary packaging secondary packaging and Container Closure System	Propose to add definitions and ensure the right terms are used throughout the document and not interchangeably
ELSIE	691	763	7	• A definition of 'extractable' should be added. Clarification is needed, especially given that the scope includes combination products	• A definition of 'extractable' should be added.
ELSIE	691	763	7	• A definition of 'leachable' should be added. Clarification is needed, especially considering that the scope includes combination products	• A definition of 'leachable' should be added.
EfPIA	692	692	7	"The threshold above"	"The threshold at or above"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	692	693	7	It is considered important to clearly distinguish the purposes of the chemical assessment and the toxicological assessment within the overall evaluation framework. The conversion of SCT to AET enables an analytical chemist to address the question of whether a specific E/L needs to be quantified and identified. The AET represents the threshold above which a compound should be quantified and identified as a prerequisite for its potential toxicological assessment.	It is recommended to keep the definition use by medical device regulation and adapt "The threshold above which an extractable or leachable should be identified, quantified, and reported for safety assessment. " to "threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment"
ELSIE	692	692	7	"The threshold above"	"The threshold at or above"
IPAC-RS	692	693	7	We disagree with this definition of AET. Safety assessments should be triggered by SCT, not AET. The definition of AET should align with the definition from PQRI: 'The AET is defined as the threshold at or above which an analytical chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.' The SCT will drive whether the toxicological assessment is undertaken.	The threshold above which an extractable or leachable should be identified, quantified, and reported for potential safety assessment.
EfPIA	694	696	7	This ISO 10993 concept is only used in Figure 1 and causes confusion. Replace in Figure 1 "chemical characterisation" by" E&L testing" and remove this definition	Remove
EfPIA	694	697	6.1	One thing of particular interest would be the route specific local/systemic QTs specifically the 'still to be defined' QT for parenteral DPs (lines 694 - 697). Our major question would be, are these to align with PQRI practice, aligning with the recent suggestions from Masuda-Herrera et al., or proposing a new value altogether?	This section appears to be currently outstanding…awaiting finalization of proposed values/rationale for oral and parenteral DPs.
ELSIE	694	696	7	This ISO 10993 concept is only used in Figure 1 and causes confusion. Replace in Figure 1 "chemical characterisation" by "E&L testing" and remove this definition. The term is primarily used in ISO 10993-18 as a definition and is used in the device world, so its odd to use it here without further explanation and it adds confusion regarding the scope of ICH Q3E	Remove the term "chemical characterization"
ELSIE	708	710	7	The definition of drug subsance as written is not inclusive of biologic products. DS for biologics is usually formulated minus additional excipients and or steps to get to the DP.	The unformulated active pharmaceutical ingredient or bulk formulated biological substance that is further processed to produce the dosage form (or drug product).
Medicines for Europe	715	715	7	it is defined that a leachable profile should be quantitative, however, if a surrogate standards is used for quantitation, wouldn't that be defined as semi-quantitative, and if so, should "semi-quantitative" also be included in the leachable profile definition? Or is quantitative defined as a validated method?	"Qualitative or semi-quantitative/quantitative accounting of leachables present in a drug product."
EfPIA	726	728	7	ICH Q3E introduces the concept of an Acceptable Level for less-than-lifetime exposure. Therefore, the term PDE in the definition of 'Marge of Safety' should be reconsidered to account for the actual dose regimen of the concerned drug product. Patients may be exposed to a leachable via other route than oral . Consequently, the definition of 'Margin of Safety' must be adapted accordingly.	It is proposed to adapt "A correlation between the PDE of the specific leachable and actual patient intake based on the daily dose. " to "A correlation between the safety threshold of the specific leachable and actual patient exposure level based on the daily dose."
EfPIA	728	730	6.3	Additionally, lines 728-730 would suggest that all elements - including those of ubiquitous and even essential nutrients would require the derivation of a PDE (given that the TTC methodology would technically not be an appropriate approach for qualification)?	This section would require clarification in this regard otherwise the value add is quite questionable.
EfPIA	730	730	7	Materials of Construction only applies to Delivery devices (which are mentioned earlier in the document). A more generic definition may be more appropriate	Proposed wording/change: Individual materials (e.g. Polymers) used to construct a packaging / manufacturing / delivery device component or system.
EFPIA Drug-MD ICH STG	730	730	7	Materials of Construction applies to Delivery devices (which are mentioned earlier in the document). A more generic definition may be more appropriate	Proposed wording/change: Individual materials (e.g. Polymers) used to construct a packaging / manufacturing / delivery device component or system.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Sanjay Desai (Cipla Ltd.)	730	730	7	For the overall risk assessment and control of leachables, it is important to consider the risk of leachables contributed from delivery device in addition to manufacturing equipments and packaging components to ensure pharmaceutical quality and safety.	Individual materials used to construct a packaging, manufacturing or delivery device component or system.
ELSIE	733	733	7	"Member State" is a term specific to the European context. To ensure broader applicability of the guideline, using "country" is more inclusive and globally relevant.	"in a region or country"
EfPIA	739	741	7	Patients may be exposed to a leachable via multiple routes of exposure, not exclusively through oral administration. Consequently, the definition of 'Margin of Safety' must be adapted accordingly.	It is proposed to adapt "The maximum acceptable intake per day of a leachable in pharmaceutical products per day (for a lifetime)." to The maximum acceptable exposure level per day of a leachable in pharmaceutical products per day (for a lifetime)."
EfPIA	740	740	7	The definition of PDE sounds weird (" in pharmaceuticals products per day"?). Can we stick to already established definitions e.g. from EMA ?	Proposed wording/change: "A pharmacologically or toxicologically acceptable intake per day of leachable in a pharmaceutical product, that is unlikely to cause an adverse effect if an individual is exposed at or below this level every day for a lifetime"
ELSIE	740	741	7	Check the wording: "The maximum aceptable intake per day of a leachable in pharmaceutical products per day (for a lifetime)".	Suggestion: "The maximum aceptable intake of a leachable in pharmaceutical products per day (for a lifetime)"
ELSIE	743	743	7	Definition of PoD: "it can be derived from the human dose or appropriate animal study." Comment: Leachables are usually not administered to humans.	Delete: "the human dose or"
Maven E&L Ltd	745	747	Section 7	The definition for QT, perhaps needs modification, suggested reword: "The threshold above which a leachable requires to be toxicologically qualified for non-mutagenic toxicity (excludes leachables defined as Class 1 in this guidance, which require qualification at lower bespoke levels).	The threshold above which a leachable requires to be toxicologically qualified for non-mutagenic toxicity (excludes leachables defined as Class 1 in this guidance, which require qualification at lower bespoke levels).
AstraZeneca	745	747	Section 7	The definition for QT, perhaps needs modification, suggested reword: "The threshold above which a leachable requires to be toxicologically qualified for non-mutagenic toxicity (excludes leachables defined as Class 1 in this guidance, which require qualification at lower bespoke levels).	The threshold above which a leachable requires to be toxicologically qualified for non-mutagenic toxicity (excludes leachables defined as Class 1 in this guidance, which require qualification at lower bespoke levels).
Maven E&L Ltd	748	751	Section 7	This definition needs better alignment with language used in Section 6: Suggested reword: "The threshold at or below which a leachable exposure (µg/day) is so low as to present a negligible safety risk to general population of patients from mutagenic and non-mutagenic effects and is thus toxicologically qualified (excludes leachables defined as Class 1 in this guidance and leachables defined as Class 1 or cohort of concern in ICH M7, which require qualification at lower bespoke levels)	The threshold at or below which a leachable exposure (µg/day) is so low as to present a negligible safety risk to general population of patients from mutagenic and non-mutagenic effects and is thus toxicologically qualified (excludes leachables defined as Class 1 in this guidance and leachables defined as Class 1 or cohort of concern in ICH M7, which require qualification at lower bespoke levels)
AstraZeneca	748	751	Section 7	This definition needs better alignment with language used in Section 6: Suggested reword: "The threshold at or below which a leachable exposure (µg/day) is so low as to present a negligible safety risk to general population of patients from mutagenic and non-mutagenic effects and is thus toxicologically qualified (excludes leachables defined as Class 1 in this guidance and leachables defined as Class 1 or cohort of concern in ICH M7, which require qualification at lower bespoke levels)	The threshold at or below which a leachable exposure (µg/day) is so low as to present a negligible safety risk to general population of patients from mutagenic and non-mutagenic effects and is thus toxicologically qualified (excludes leachables defined as Class 1 in this guidance and leachables defined as Class 1 or cohort of concern in ICH M7, which require qualification at lower bespoke levels)
EfPIA	748	751	7	The term 'leachable of high concern' corresponds to Class 1 leachables. For better harmonization across the glossary and the definitions of safety thresholds, the same terminology should be consistently used.	It is proposed to adapt "Threshold at or below which a leachable would have a dose so low as to present negligible safety concerns from mutagenic and non-mutagenic toxic effects unless the leachable is identified as being a leachable of high concern." to "Threshold at or below which a leachable would have a dose so low as to present negligible safety concerns from mutagenic and non-mutagenic toxic effects unless the leachable is identified as being Class 1".

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	751	751	7	What is a "leachable of high concern" in the context of ICH Q3E. Shall Class 1 leachables be mentioned instead ?	
EfPIA	752	752	7	This term (simulated drug product) is introduced only in the glossary. In the document, the related concept of Simulation study / simulated leachables study is addressed but the connection to the "Simulated drug product" is not made	Either delete the term "Simulated Drug Product" or refer to the section on Simualted Leachables study
POLPHARMA	752	754	7	We propose modification of a definition of simulated drug product to specify that its leaching potential should not exceed that of the intended drug product.	Simulated Drug Product: Matrix or solvent that as closely as possible replicates the leaching characteristics of the drug product formulation, ensuring that its leaching potential does not exceed that of the intended drug product
Maven E&L Ltd	761	763	Section 7	For aligment with QT and SCT, suggested TTC reword, "The threshold exposure level (µg/day) at or below which a leachable does not require to be further toxicologically qualified for mutagenic effects (See ICH M7)"	The threshold exposure level (µg/day) at or below which a leachable does not require to be further toxicologically qualified for mutagenic effects (See ICH M7)
AstraZeneca	761	763	Section 7	For aligment with QT and SCT, suggested TTC reword, "The threshold exposure level (µg/day) at or below which a leachable does not require to be further toxicologically qualified for mutagenic effects (See ICH M7)"	The threshold exposure level (µg/day) at or below which a leachable does not require to be further toxicologically qualified for mutagenic effects (See ICH M7)
Ferring Pharmaceuticals	764	777	8	Consider the addition of ICHQ12 Guideline	
Maven E&L Ltd	789	789	Appendix 1	Suggestion that title of the section is: Typical workflows for Leachable Risk Management	Typical workflows for Leachable Risk Management
AstraZeneca	789	789	Appendix 1	Suggestion that title of the section is: Typical workflows for Leachable Risk Management	Typical workflows for Leachable Risk Management
Maven E&L Ltd	790	792	Appendix 1	Suggestion that first sentence is changed to read. "The following diagrams illustrate typical workflows and process steps for leachable risk management including risk assessment and risk control of leachables derived from both manufacturing systems and packaging.	The following diagrams illustrate typical workflows and process steps for leachable risk management including risk assessment and risk control of leachables derived from both manufacturing systems and packaging.
AstraZeneca	790	792	Appendix 1	Suggestion that first sentence is changed to read. "The following diagrams illustrate typical workflows and process steps for leachable risk management including risk assessment and risk control of leachables derived from both manufacturing systems and packaging.	The following diagrams illustrate typical workflows and process steps for leachable risk management including risk assessment and risk control of leachables derived from both manufacturing systems and packaging.
EfPIA	790	792	Appendix 1	"manufacturing components/system packaging", as it referes to Figure 4, and "packaging and dleivery device components/systems", as it refers to Figure 5: terminology is ambiguous, unclear what it specifically entails in both cases, and is not aligned with the captions of the two figures.	Recommend removing slashes, replacing with appropriate prepositions and expanding or splitting the sentence to add clarity.
ELSIE	790	790	Appendix 1	E&L "overall" risk assessment	Remove "overall"
EfPIA	791	791	Appendix 1	Delete "packaging" when referring to Figure 4	"The following diagrams illustrate typical workflows for E&L overall risk assessment and risk control, for component qualifications for manufacturing components/systems ~~packaging~~ (Figure 4) and packaging and delivery device components/systems (Figure 5)."
ELSIE	791	791	Appendix 1	"for component qualifications for manufacturing components/systems" - "components" used twice	Reword for clarity
Merck KGaA, Darmstadt, Germany	791	791	Appendix 1	Delete "packaging" when referring to Figure 4	"The following diagrams illustrate typical workflows for E&L overall risk assessment and risk control, for component qualifications for manufacturing components/systems ~~packaging~~ (Figure 4) and packaging and delivery device components/systems (Figure 5)."
EfPIA	792	794	Appendix 1	This sentence suggests that leachables testing for manufacturing components is "expected". This is not aligned with USP<665> and practically not doable at least for most manufacturing components due to the impossibility to pull controls that could be used as blanks for the related analytics.	Proposed wording/change: "Under most circumstances, a safety assessment of leachables is expected."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	794	794	Appendix 1	Grammar is not correct. A "safety assessment of leachables studies..." cannot be performed. I guess "saftey assessment of leachables..." is meant.	
Maven E&L Ltd	802	804	Appendix 1	Figure 4: It is suggested that figure 4 would start with a risk identification step, and a risk analysis and risk evaluation before any suggestion that extractable studies would be required. That is it is possible to define a system without leachable risk before conducting a extractable study or to conclude that existing data is sufficent for no further testing.	
A3P	802	812		In Figure 4: Is the approach with a preliminary risk assessment considering duration of contact of drug product with some parts of manufacturing equipment an acceptable approach to potentially priorize the extractable and leachable studies only on the materials with significant duration of contact ? Risk assessment as decribed in figure 2 (lines 83 to 96) is not included in figure 4.	Could you please update the figure 4 including preliminary risk assessment before extractables studies on manufacturing equipment ?
AESGP	802	805	Appendix 1: Typical workflows for E&L risk assessment and risk control Figure 4: Typical workflow for E&L assessment related risk identification and mitigation for manufacturing components/ systems	This chart is confusing to me based on the rest of the document. If I have packaging components which have sufficient vendor data to be cleared without the need for physical extractable/leachable testing this flowchart does not show a route where that is possible. All options in this flowchart show the need for extractable AND leachable testing. In my mind there need to be “off ramps” after determining if there is sufficient data existing already such that extractable and/or leachable testing is not needed.	Add“off ramps” after determining if there is sufficient data existing already such that extractable and/or leachable testing is not needed, e.g. simple oral dose, nasal preparation, topical creams/ointments for skin application made under GMP with compendial grade contact materials.
AstraZeneca	802	804	Appendix 1	Figure 4: It is suggested that figure 4 would start with a risk identification step, and a risk analysis and risk evaluation before any suggestion that extractable studies would be required. That is it is possible to define a system without leachable risk before conducting a extractable study or to conclude that existing data is sufficent for no further testing.	
AstraZeneca	802	804	Appendix 1	In addition to Jason's comment above, include a risk identification step linked to the Section 3.2 risk matrix.	
BioPhorum	802	802	Appendix 1	Figure 4 In case of any extractables above the AET, two options are described: Identify extractable(s) above AET and quantify against proper standards as described in 4.3.2: "For the quantification of identified extractables ABOVE the AET standards with identical or similar analytical response should be used." or Conduct a leachables study according to 4.4: using "reference standards, if available". However, in case of unavailability of reference standards, e.g., for oligomers, one can only apply estimated analytical responses in both types of studies, which always include analytical uncertainty. So one can neither fully quantify these compounds as extractables nor as leachables, only semi-quantitative extractable or semi-quantitative leachable studies are possible.	Proposal: Allow the option to use uncertainty factors for quantitative extractables studies in case of unavailability of reference standards in section 4.3.2. Or allow this option in Appendix 1, figure 4. Clarify whether to tie to TTC or AET Include request for indication or justification of which standards or surrogates have been used to identify tentatively identified/unknown compounds

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
BioPhorum	802	802	appendix 1/Fig 4	(Figure 4) additional step needed between topmost box ("selection…), and next box "Does the semi-quant data…").	Add step, "does Initial risk ranking warrant extractables/leachables data, taking into account process risk and conditions, such as those listed in USP <1665> and BioPhorum Leachables best practice (2020), with the output to establish whether only basic safety (compendial tests) or extractables evaluation (or in high risk cases, full leachables testing) are required? "
Bio-Process Systems Alliance	802	804	Appendix 1	The flowchart does not include the risk assessment, scaling or clearance prior to assessing the individual extractables vs. the AET.	Suggest to limit scope of Guidance to final drug product primary packaging container and/or device only or revise flowchart to include an upfront estimation of PERLs contribution to the final drug product leachables using extractables data, plus scaling via surface area or equilibrium prior to the assessment of individual extractables vs AET
EfPIA	802	803	Figure 4	What happens if there is quantitative extractables data as prior knowledge?	Make connection with the 1st box
EfPIA	802	804	Figure 4	Figure 4 title says "Typical workflow for E&L assessment related risk identification and mitigation for manufacturing components/systems", however the risk identification step is missing in this flowchart. We suggest to add risk evaluation before the first rhombus. It should be highligthed that what is depicted here will be done for medium-high risk components only, not for the low risk ones. As an alternative, the title might be modified as indicated here	"Figure 4: Typical workflow for E&L assessment ~~related risk identification~~ and mitigation for medium - high risk manufacturing components/systems"
EfPIA	802	804	Figure 4	Especially for the process components assessment Product Manufacturers frequently use external labs/Suppliers data and evaluate them with respect to the specifcic product/process. External labs/Suppliers methods cannot be AET-based as they not product/process specific. For example, instead of considering AET, extractables data when converted into Patient Daily Exposure, may also be compared to the Safety concern Treshold (SCT).	>AET or above safety concern threshold
ELSIE	802	803	Figure 4	"vendor provided information"	"Vendor information"
ELSIE	802	803	Figure 4	What happens if there is quantitative extractables data as prior knowledge?	Make connection with the 1st box
ELSIE	802	804		fig 4, suggests that extractable data is required for every component as part of assessment. This is not in alignment with USP665/1665 and current industry practice for risk assessment	Need alignment with BPOG/USP665 etc
ELSIE	802	804		Fig 4 does not result in the risk being designated as High/Low or medium. Low risk is mentioned through out Q3E document	need to define low risk to provide consistancy with best practice described in other part of the document.
ELSIE	802	804		fig 4 prior knowledge cannot be used in the assessment of risk, but why is this acceptable in fig 5 for final container	risk assessment for manufacturing components and packaging should be similar. The final risk score may be different
ELSIE	802	804	Figure 4	Agency may require some extractables conditions (e.g., high organic) that are not relevant for the manufacturing processes and are believed to be "for information only". Therefore, such conditions should not be used solely to determine the requirement for a leachable study.	Revise to "conduct leachables study based on extractable testing knowledge/conditions that are relevant to manufacture or container closure system.
ELSIE	802	804	Appendix 1	Extractable and Leachable risk assessment for manufacturing process change: if leachable study is needed, can it be done on process validation sample? Can leachable testing be done at GLP condition with methods qualified not validated? Is testing at one time point, e.g. time zero or 3M long term storage condition sufficient?	Please comment in the guideline.
ELSIE	802	804	Appendix 1	"Figure 4. Typical workflow for E&L assessment related risk identification and mitigation for manufacturing components/systems" • Figure 4 implies that further testing is triggered solely by detection above AET, even if the extractables pose no toxicological risk or patient safety concern. Clarification is needed if additional testing should be conditional on safety relevance, not just analytical detection	• We recommend rewording title - change "Typical" to "Example", to allow for other approaches and ensure not interpreted as prescriptive "Figure 4. Typical Example workflow for E&L assessment related risk identification and mitigation for manufacturing components/systems"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	802	802	Appendix 1	Figure 4 In case of any extractables above the AET, two options are described: Identify extractable(s) above AET and quantify against proper standards as decribed in 4.3.2: "For the quantification of identified extractables ABOVE the AET standards with identical or similar analytical response should be used." or Conduct a leachables study according to 4.4: using "reference standards, if available". However, in case of unavailabilty of reference standards, e.g., for oligomers, one can only apply estimated analytical responses in both types of studies, which always include analytical uncertainty. So one can neither fully quantify these compounds as extractables nor as leachables, only semi-quantitative extractable or semi-quantitative leachable studies are possible.	Proposal: Allow the option to use uncertainty factors for quantitative extractables studies in case of unavailability of reference standards in section 4.3.2. Or allow this option in Appendix 1, figure 4.
Hikma	802	804	Appendix 1	Extractable and Leachable risk assessment for manufacturing process change: if leachable study is needed, can it be done on process validation sample? Can leachable testing be done at GLP condition with methods qualified not validated? Is testing at one time point, e.g. time zero or 3M long term storage condition sufficient?	Please comment in the guideline.
IPAC-RS	802	804	Appendix 1	Figure 4. Agency may require some extractables conditions (e.g., high organic) that are not relevant for the manufacturing processes and is believed to be "for information only". Therefore, such conditions should not be used solely to determine the requirement for a leachable study.	Revise to "conduct leachables study based on extractable testing knowledge/conditions that are relevant to the manufacturing or container closure system."
IPAC-RS	802	804	Appendix 1	fig 4, suggests that extractable data is required for every component as part of assessment. This is not in alignment with current industry practice for risk assessment	Need alignment with industry practice; can also look at BPOG or potentially USP665, etc
IPAC-RS	802	804	Appendix 1	Fig 4 does not result in the risk being designated as High/Low or medium. Low risk is mentioned throughout Q3E document	need to define low risk to provide consistancy with best practice described in other part of the document.
IPAC-RS	802	804	Appendix 1	fig 4 prior knowledge can not be used in the assessment of risk, but why is this is aceptable in fig 5 for final container	risk assessment for manufacturing components and packaging should be similar. The final risk score may be differant
IPAC-RS	802	802	Appendix 1	Figure 4 In case of any extractables above the AET, two options are described: Identify extractable(s) above AET and quantify against proper standards as decribed in 4.3.2: "For the quantification of identified extractables ABOVE the AET standards with identical or similar analytical response should be used." or Conduct a leachables study according to 4.4: using "reference standards, if available". However, in case of unavailabilty of reference standards, e.g., for oligomers, one can only apply estimated analytical responses in both types of studies, which always include analytical uncertainty. So one can neither fully quantify these compounds as extractables nor as leachables, only semi-quantitative extractable or semi-quantitative leachable studies are possible.	Proposal: Allow the option to use uncertainty factors for quantitative extractables studies in case of unavailability of reference standards in section 4.3.2. Or allow this option in Appendix 1, figure 4.
Medicines for Europe	802	208	8	Figure 4: Shouldn't the diagram include a step "Conduct semi-quantitative extractables study"?	Add a step for initial extractables study. Or add "start" and "end" steps for clarity.
AESGP	803	804	Figure 4	In the box with reference to section 4.4, it is proposed to perform a leachable study. However, a simulation study might be an appropriate alternative	Include simulation study as alternative to leachables study
EfPIA	803	804	Figure 4	First box, listing sources of information for the selection of materials: "vendor provided information" is vague and can be misleading.	An Applicant would usually have limited control on what information a vendor of equipment components or system may be willing to share regarding the specifics of potential leachables, even less so than from excipients vendors. Suggest removing this item from the list (could be incorporated under the broader "prior knowledge").
EfPIA	803	804	Figure 4	The word "typical" can imply a standard approach. Lines 321 to 324 describe a scenario where a leachable study following semiquantitative extractable studies is an approach. This can be the standard for companies focusing on leachables, making "typical" inappropriate. Suggest changing "typical" to "example."	Change typical to example.
ELSIE	803	804	Appendix 1	Figure 4. Figure seems to be conveying that if all extracts are < AET and no cumulative leachable risk is foressen, there is no need to perform a leachable study. Is this correct?	Clarify

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	803	803	Appendix 1	As indicated in Figure 4: 'Selection of manufacturing equipment component/system is based on: Formulation,manufacturing condition, vendor provided information, prior knowledge'	Selection of manufacturing equipment, component/system is based on: formulation, manufacturing condition, and/or provided information, prior knowledge'
Ferring Pharmaceuticals	803	803	Fig. 4	Is there reason, why the criteria for a semi-quantitative study doesn't cover desk-top evaluation of PCI-vendors extractable data? Comment: neither Figure 4 and as described in Section 4.3.1 mention the possibility.	Please reevaluate.
Merck KGaA, Darmstadt, Germany	803	804	Appendix 1	Figure 4, Workflow manufacturing equipment: The logic of first decision of "Does the semi-quantitative extractables data meet the criteria described in Section 4.3.1" is not clear. If the answer is "No" and a quantitiative extractables study would need to be performed this is in contradiction of the example provided in Table A.1.1, Line 819, Scenario 3, where components may be considered qualified if no extractables are above the AET in a semi-quantitiative extractables study. The quantitative extractables study is required if any individual extractables are above the AET as indicated in the workflow at a later step.	Modify as shown in the attached pdf document (cell N22). Step 1: "Selection of manufacturing equipment……." (keep as is) Step 2: "Conduct semi-quantitative extractables study (Section 4.3.1)*" and delete YES and NO and add a foot note below the the graph: "*Vendor provided semi-quantitative data may be used if they meet the riteria described in Section 4.3.1"
POLPHARMA	803	804	8	In line with the Risk Assessment described in section 3, and Table A.1.1 which allows in justified cases to rely on compliance with relevant regional food-contact safety regulations etc. (mild manufacturing conditions, oral drug products etc.), we propose the following amendment of Figure 4:	After the first step <Selection of manufacturing equipment component/system is based on: Formulation, manufacturing condition, vendor provided information, prior knowledge> it is proposed to add 2nd step: <Are components considered qualified without additional E&L testing (see Section 3.2)>. If the answer to the 2nd step is YES the arrow should lead directly to: <Manufacturing equipment component/system is qualified from leachables perspective. No further assessment required**>. If the answer to the 2nd step is NO the arrow should lead to <Does the semi-quantitative extractables data meet the criteria described in Section 4.3.1>.
AstraZeneca	808	808	Appendix 1	Consider adding "Safety Threshold" to the glossary. It is an over arching term and it would be good to have it spelled out in the glossary what this covers.	Consider adding "Safety Threshold" to the glossary
EfPIA	808	809	Figure 4	It should be put a distinction in the case there are known identified extractables above AET but below PDE (where known) before saying that it is necessary to go for leachable study.	* Amount of extractable(s) or leachable(s) are below the applicable safety threshold but below PDE (when known) for each compound
AstraZeneca	810	810	Appendix 1	Word missing. The sentence reads: "For manufacturing process employing multiple components constructed with the same orsimilar material, cumulative leachables risk should be assessed for the final drug product (seeSection 3.4.1)."	Suggest to add the word "a" so it reads "For a manufacturing process...."
ELSIE	810	812	Appendix 1	Cumulative leachables risk is not defined Provide guidance on how to determine cumulative leachables risk	
Maven E&L Ltd	815	816	Appendix 1	Figure 5: The decison question , "Does any individual component pose unacceptable risk for E/L based on prior knowledge of the material/components understanding" should be reworded, "Does the leachable risk management process accompanying material / component selection identify a significant leachable risk which cannot be further reduced through gaining more uncertainty" Yes - change materials / system to reduce or remove risk. No - New Process gain more certainty of the risk with supplier information or knowledge -> Add Another decision question - Has this reduced the risk? - No (development and perform extractable studies based on identified leachable risk - branch at this point to quality or safety risk	
A3P	815	818		In figure 5 : the approach described in lines 333 to 348 are not reprensented in this figure describing the typical workflow.	Could you please update the figure to include the approach/case where quantified extractables can be sufficent to assess the quality and safety risk ?

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AESGP	815	817	Figure 5: Typical workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components	This flow chart not accept any path towards using Paper-based assessments? (i.e., no E&L study performed). There should be a path for scenarios where there is no E&L risk from manufacturing and container closure systems (GMP, simple oral, topical cream for skin, nasal preparations using compendial grade packaging) where the chart states, 'No further assessment required'. On this point, the flow chart cannot be followed for the low risk scenarios in the table.	Add to the flow chart these low risk scenarios for manufacturing and container closure systems where the chart states, 'No further assessment required'
AstraZeneca	815	816	Appendix 1	Figure 5: The decison question , "Does any individual component pose unacceptable risk for E/L based on prior knowledge of the material/components understanding" should be reworded, "Does the leachable risk management process accompanying material / component selection identify a significant leachable risk which cannot be further reduced through gaining more uncertainty" Yes - change materials / system to reduce or remove risk. No - New Process gain more certainty of the risk with supplier information or knowledge -> Add Another decision question - Has this reduced the risk? - No (development and perform extractable studies based on identified leachable risk - branch at this point to quality or safety risk	
BioPhorum	815	816	Appendix 1	Figure 5 In several sections of this guideline abbreviated data packages (without leachables studies) also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
BioPhorum	815	816	Appendix 1	Figure 5 The impact of leachables on the product quality should already be assessed by information about extractables i.e. potential leachables, e.g., to inform compatibility studies. However , it should be considered that E&L studies are triggered by safety levels. Also levels below safety thresholds can impact the drug product quality. In those cases the workflow is often the other way round, first an impurity or degradation product is detected in a stability study and then leachables are assessed as one potential source.	The product quality assessment should be described in a separate workflow

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	815	816	Appendix 1	Figure 5 In several sections of this guideline abbreviated data packages (without leachables studies) also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
EfPIA	815	816	Appendix 1	Figure 5 The impact of leachables on the product quality should already be assessed by information about extractables i.e. potential leachables, e.g., to inform compatibility studies. However , it should be considered that E&L studies are triggered by safety levels. Also levels below safety thresholds can impact the drug product quality. In those cases the workflow is often the other way round, first an impurity or degradation product is detected in a stability study and then leachables are assessed as one potential source.	The product quality assessment should be described in a separate workflow
EfPIA	815	816	Figure 5	The complexity of certain packaging systems—due to the high number of components—often makes individual component testing impractical. Furthermore, testing at the component level overlooks potential interactions between materials during sterilization and storage. Therefore, this decision point should be considered optional	"Develop and perform extratable studies on individual components (if applicable) and/or the final finished product to identify targeted leachables and conduct safety assessment" as "to inform leachable studies" is unnecessary
EfPIA	815	817	Figure 5	The middle section states "Develop and perform extractables studies on individual components...". This is not aligned with the text in Section 4.3 where it is stated "Testing is performed on components or an assembled system". Text shopuld be aligned	Proposed wording/change: "Develop and perform extractables studies on individual components or assembled system..."
EfPIA	815	819	Appendix 1	Figure 5: Workflow should be updated to include scenario 1 under Table A.1.1.Otherwise, it warrants ALL packaging must go through extractables/leachables and safety assessment study	Figure 5: Add to the box "Selection of packaging/delivery components or system" an arrow to "solid oral products..." and directly to bottom box indicating "No further testing/assessment"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA Drug-MD ICH STG	815	816	Appendix 1 Figure 5	in several sections of this guideline abbreviated data packages also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
ELSIE	815	816	Figure 5	The complexity of certain packaging systems—due to the high number of components—often makes individual component testing impractical. Furthermore, testing at the component level overlooks potential interactions between materials during sterilization and storage. Therefore, this decision point should be considered optional	"Develop and perform extractable studies on individual components (if applicable) and/or the final finished product to identify targeted leachables and conduct safety assessment." Also, "to inform leachable studies" is unnecessary text
ELSIE	815	816	Figure 5	the middle part (on the bottom) of the diagram has connections both ways, so it’s not well defined in which direction we should go there	Provide clearer explanation
ELSIE	815	817	Figure 5	The chart should allow for no leachables study if the extractable study evaluation deems the risk to be low, e.g., if all extractables are below the safety limit. In such cases, an extractable-leachable correlation is not performed or warranted.	Update the chart to include this scenerio.
ELSIE	815	817	Appendix 1	The flow chart in Figure 5 describes a process where extractables are determined and assessed, leachables are selected after performing an assessment of the extractables data, and leachables are monitored via validated leachable methods. This process misses a path where extractables are assessed and either no extractables are found or those found are well within the acceptable limits established by the safety assessment. In such situations, what is the path forward? Is leachable monitoring not required? Are only non-targeted methods required for "unexpected leachables"? This is a notable omission since a properly designed extraction study (i.e., represents a worst case for leaching) often either does not uncover leachables above the AET, or they are well below a level that would cause a safety concern.	Consider and explain the process for this important scenario.
ELSIE	815	817	Appendix 1	Figure 5 is really difficult to read and comprehend. Why creating two sides, one for safety assessment and one for product quality. More explanation would be necessary in order to comprenhend this scheme better. Amend figure 5 or add context and explanation.	
ELSIE	815	816	Appendix 1	Per Figure 5, to evaluate extractables and leachables, one has to determine if the concentration is > the AET	a double arrow is needed to connect the box "evaluate extractables and leachables…" to "are individual leachables > AET" box. And the figure itself is complicated, the start is not very clear

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ELSIE	815	816	Appendix 1	Figure 5 In several sections of this guideline abbreviated data packages (without leachables studies) also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
ELSIE	815	816	Appendix 1	Figure 5 The impact of leachables on the product quality should already be assessed by information about extractables i.e. potential leachables, e.g., to inform compatibility studies. However , it should be considered that E&L studies are triggered by safety levels. Also levels below safety thresholds can impact the drug product quality. In those cases the workflow is often the other way round, first an impurity or degradation product is detected in a stability study and then leachables are assessed as one potential source.	The product quality assessment should be described in a separate workflow
IPAC-RS	815	816	Appendix 1	Figure 5. The middle part (on the bottom) of the diagram has connections both ways, so it's not well defined in which direction we should go there	Provide clearer explanation
IPAC-RS	815	817	Appendix 1	Figure 5. The chart should allow for no leachables study if the extractable study evaluation deemed the risk to be low e.g. if all extractables are below the safety limit. In such case, an extractable-leachable correlation is not performed or warranted.	Update the chart to include this scenerio.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	815	816	Appendix 1	Figure 5 In several sections of this guideline abbreviated data packages (without leachables studies) also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
IPAC-RS	815	816	Appendix 1	Figure 5 The impact of leachables on the product quality should already be assessed by information about extractables i.e. potential leachables, e.g., to inform compatibility studies. However , it should be considered that E&L studies are triggered by safety levels. Also levels below safety thresholds can impact the drug product quality. In those cases the workflow is often the other way round, first an impurity or degradation product is detected in a stability study and then leachables are assessed as one potential source.	The product quality assessment should be described in a separate workflow
Medicines for Europe	815	820	Appendix 1	Section explains work flow for E&L risk assement, which is product specific. Also it is described that for solid dosage forms E&L might be qualified without testing.	It would be benefitial if matrixing and brackating can be included especially for solid forms in order not to generate high numer of non necessary risk assesments
Medicines for Europe	815	820	Appendix 1	Section explains work flow for E&L risk assement, which is product specific, also there is different level of risk and actions clarified for different type of products.	As the proces of intodution of specific product risk analysis for all type of products will be very demanding is there posibility to deine different effective times for gudeline for different forms, e.g. first to be efective with forms with highest risk (liquids) and last for forms with lower risk (solids).
AESGP	816	817	Figure 5	In the third box of the middle part, it is stated that extractable studies are to be performed on individual components. But also complete systems are allowed based on the proposed text parts before, like e.g. a vial-stopper-system can be tested as intact packaging material instead of testing the vial and the stopper seperately	Allow for testing of assembled systems
ALK (HJODK)	816	817	8	PTFE film-coated stoppers and plungers provide effective protection of the rubber/elastomer by preventing leaching compounds into the drug product, as the drug product has no direct contact with the rubber/elastomer. In such a case, Extractable profiles tend to show no detectable compounds above the limit of quantitation (LOQ), and no compounds will exceed the analytical evaluation threshold (AET). Figure 5 does not offer guidance for the described scenario. No targeted compounds have been identified, making the development of leachable analytical methods unnecessary, as illustrated in "C" - see figure attached below.	Proposal: Incorporate the alternative flow shown below in position “B” (see figure below): “Perform a simulation study using screening methods for detection of possible non-targeted leachables not detected in the extractables study”

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AstraZeneca	816	816	Figure 5	Under Product Quality Assessment, the lower box currently says: "The packaging/delivery components is acceptable from leachable quality perspective. No further assessment required." Suggest is is changed by swapping the word "is" with "are", and adding the word "a".	"The packaging/delivery components are acceptable from a leachable quality perspective. No further assessment required."
AstraZeneca	816	816	Figure 5	Under "Safety Assessment" the bottom box currently reads: "The packaging/delivery components are acceptable from leachable safety perspective. No further assessment required" Consider adding the word "a"	"The packaging/deliverycomponents areacceptable from a leachable safety perspective.No further assessment required"
EfPIA	816	817	Figure 5	Remove a box for: evaluate correlation profiles between extractables and leachables	Correlation should be presented additional tool to evaluate the E&L data, but not a requirement to be complied and presented as a primary parameter for successful E&L study package. In the present form it obtains far too much weight.
ELSIE	816	817	Figure 5	Remove a box for: evaluate correlation profiles between extractables and leachables	Correlation should be presented/considered as an additional tool to evaluate the E&L data, but not a requirement to be complied and presented as a primary parameter for successful E&L study package. In the present form it obtains far too much weight.
Ferring Pharmaceuticals	816	816	Fig. 5	Comment to the box three in the midle about extractable studies: Individual extractable assessment (> AET or < AET) should be performed. If extractables are > AET a safety assessment should be performed. Decision 'yes' or 'no' with respect to extractables should be performed.	Propose to include assessment of extractables with respect to AET and safety assessement including decision tree possibilities (yes/no).
Luye Pharma	816	816	Appendix 1	Figure 5 needs to be adapted with reference to comments regarding lines 161 - 163 section 3.4.	We propose to revise Figure 5 to include the scenario in which extractables do not exceed the AET, leading to the conclusion that the packaging and device components are qualified from a leachables perspective and no further assessment is required.
Medicines for Europe	816	816	Appendix 1	Figure 5 appears incomplete with reference to comments regarding lines 161 - 163 section 3.4.	Figure 5 needs to be adjusted to reflect the case where extractables are NOT > AET to result in the conclusion that the packaging and device components are qualified from leachables perspective and no further assessment is required.
POLPHARMA	816	817	8	In line with the Risk Assessment described in section 3, and Table A.1.1 which allows in justified cases to rely on compliance with relevant regional food-contact safety regulations etc. (mild manufacturing conditions, oral drug products etc.), we propose the following amendment of Figure 5:	Below < Selection of packaging/delivery components or system> we propose to add 2nd step: <Are components considered qualified without additional E&L testing (see Section 3.2)>. If the answer to the 2nd step is YES the arrow should lead directly to: <The packaging/delivery components is acceptable from leachable quality perspective. No further assessment required>. If the answer to the 2nd step is NO the arrow should lead to < Does any individual component pose unacceptable risk for E/L based on prior knowledge of the material/components understanding? >.
AESGP	819	820	Table A.1.1: Manufacturing Equipment Components /Systems Scenarios	Scenario 1- Add liquid drug products and topical drug products to the scenario 1. It is relevant to treat all oral drug products and topical drug products in the same way because the manufacturing process is such that is does not pose risk to patients due to exposure to leachables. Manufacturing of these drugs involves very short contact time, often in stainless steel (or equivalent), at non-elevated temperatures.	Under the column 'Risk Scenario, Scenario 1: ~~Solid~~ Oral 'and topical' drug product's' manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements (See Section 3.2).'

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AESGP	819	820	Table A.1.1: Manufacturing Equipment Components /Systems Scenarios	Add a new Scenario to the table - nasal preparations (which includes solutions, sprays and drops intended for nasal administration). Calling Scenario 1b for now. For nasal preparatios produced under GMP manufacturing coditions it does not pose risk to patients due to exposure to leachables. This is because the manufacturing process involves very short contact time, often in stainless steel (or equivalent), at non-elevated temperatures. In addition systemic exposure would be negligible as the drug volumes administerd to the patient are very small and not respired into the deep lung. A large proportion of the small volume is expelled out the nose (following patient blowing the nose) and/or swallowed and, therefore, absorption across the mucosal membrane in the nasal cavity is minimal and toxicological risk from a leachable is not realised.	Under the column 'Risk Scenario' add ' Scenario 1b: nasal preparations manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements (See Section 3.2). Potential Outcome Components considered qualified without additional extractables or leachables testing'
EfPIA	819	819	Table A.1.1.	Unclear what is meant by "the leaching propensity of the drug product is not greater than identified in the relevant regulation" in Scenario 2 and how that can be demonstrated	Provide at least one example
EfPIA	819	820	8 References, Table A1.1.	add additional scenario similar to Table A1.2.(scenario 3):	Add scenario 5: Equipment components with very short /transeint contact with oral drug products (.e.g, or o-rings/valves etc…. By describping the minimal surface area and limited contact time: -> Potential oucome: componets may be considered qualified without additional extractables or leachables testing.
ELSIE	819	819	Table A.1.1.	Scenario 1: Solid oral drug product manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements (See Section 3.2).	USP665 is not risk assessing solid dosage form. Is this a discrepancy?
ELSIE	819	819	Table A.1.1.	Unclear what is meant by "the leaching propensity of the drug product is not greater than identified in the relevant regulation" in Scenario 2 and how that can be demonstrated	Provide at least one example
ELSIE	819	819	Appendix 1	Table A.1.1 Scenario 2 - is this scenario dependent on the patient population? E.g. If the population is infants, would food contact regulation compliance be sufficient?	
ELSIE	819	819	Appendix 1	Scenario 4: uses safety threshold (TTC/QT or compound-specific AI/PDE)	Consider using SCT to be consistent
Ferring Pharmaceuticals	819	819	Table A.1.1	First column, second row (Scenario 1): "product manufactured using equipement components..." Anticipate that the word 'polymeric' should be added as it is in 'Scenario 2'?	Propose: "product manufactured using polymeric equipement components..."
Ferring Pharmaceuticals	819	819	Table A.1.1	First column, forth row (Scenario 3): "No manfacturing compoents/systems extractables above..."	Propose: "No extractables, originating from polymeric manufacturing *equipement* , above..."
Ferring Pharmaceuticals	819	819	Table A.1.1	First column, forth row (Scenario 4): The term 'polymeric' is missing in hte sentences.	Propose to include the term "polymeric" in Scenario 4 and/or include it in the name of Table A.1.1.
GUERBET	819	8220	Appendix 1	Table A.1.1 mentions as scenario 1 the solid oral drug product : can those principles be used to consider the E&L for solid Active Pharmaceutical Ingredients ?	Include the case of solid API

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AESGP	822	833	Figure 5: Typical workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components	The following statement is misleading, 'In general, comprehensive extractable and leachable data should be provided for all primary packaging components/systems and delivery device components.' As discussed in other comments, there are many low risk scenarios where E&L studies would not be required such as for manufacturing and container closure for simple oral, topical cream for skin, nasal preparations, manufactured using GMP in compendial grade materials.	Delete '~~In general, comprehensive extractable and leachable data should be provided for all primary packaging components/systems and delivery device components~~.' And add, 'For low risk scenarios including simple oral, topical cream for skin, nasal preparations, documentation of compendial grade requirements can be suffiecient. For other' ~~However, for overall~~ lowrisk scenarios (see Figure 2, Section 3.2) an abbreviated data package that includes a quantitative extractables study may be adequate with justification.
ELSIE	822	822	Appendix 1	extractable and leachable	E&L
ELSIE	822	827	Appendix 1	•The requirement to perform extractable and / or leachable studies of Dry Powder Inhalation products (DPI's) is not clear in this guideline. Currently the requirements are different for different markets (e.g. EMA - generally not required if food contact and compendial compliance of inhaler/packaging system components is established c.f. FDA - generally required). DPI's are a low risk scenario as per Fig 2, Section 3.2 since DPI's are a solid dosage form. The text (lines 823 to 824) states for this low risk scenario that an abbreviated data package that includes a quantitative extractables study may be adequate with justification. It is not clear if this abbreviated package requirement is applicable to DPI's.	•Clarify for Dry Powder Inhalation Products that an abbreviated data package that includes a quantitative extractables study may be adequate with justification and if this requirement is in addition to or in the absence of food contact and compendial compliance of the constituent parts of the dry powder inhaler device / packaging system
Chiesi Farmaceutici	823	827	Appendix 1	From Examples reported in Table A.1.2, it is not clear if in those cases a quantitative extractable study is actually performed in addition to already existing data package reported. For this reason, the sentence reported from line 823 to line 825 is not clear.	It is suggested to modify the sentence as follows: "However, for overall low risk scenarios (see Figure 2, Section 3.2) an abbreviated data package that includes a quantitative extractables study may be adequate with justification. See Section 3.4 for situations where a leachable study should be conducted to address the specific concerns and demonstrate acceptability of the components."
ELSIE	823	823	Appendix 1	"overall" low-risk scenarios	Remove "overall"
ELSIE	823	823		Specific mention of low risk scenario, yet there is no clear cut off for low risk scenario in fig 2	clearer definition of low risk
IPAC-RS	823	823		Specific mention of low risk scenario, yet there is no clear cut off for low risk scenario in fig 2	clearer definition of low risk
ELSIE	825	825	Appendix 1	an abbrevidated data package can, in many instances, include only semi-quantitative data.	Remove "quantitative" or at least allow for semi-quantitative data
BioPhorum	829	838	Appendix 1	Table A.1.2 Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these examples should be added in the table.	It is proposed to include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.

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EfPIA	829	838	Appendix 1	Table A.1.2 Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these eamples should be added in the table.	It is proposed to include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.
EfPIA	829	830	Appendix 1, Table A.1.2	There is no example or guidance provided for lyophilized drug product	Add guidance on risk and expectations for lyophilized drug for IV
EFPIA Drug-MD ICH STG	829	830	Appendix 1 Table A.1.2	Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these eamples should be added in the table.	Include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.
EFPIA Drug-MD ICH STG	829	830	Appendix 1 Table A.1.2	in example 3: short/ transient contact is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	provide definition of short/ transient contact; perhaps add another example of an abbreviated data package for a parenteral drug product e.g. administered using a CSTD
ELSIE	829	839	Table A.1.2	• Example 2 - Leachables testing should be prioritised over quantitive extractables testing, as leachables are more representative of actual patient use.	
ELSIE	829	838	Appendix 1	Table A.1.2 Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these eamples should be added in the table.	It is proposed to include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.
GUERBET	829	830	Appendix 1	Table A.1.2 mentions 3 examples : Could another example be included for Abbreviated data package? We propose the case where a packaging component is well-known and already broadly used for similar product Or where a change is proposed for several similar drug products	Add this example in Table A.1.2

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GUERBET	829	830	Appendix 1	Table A.1.2 mentions 3 examples : Could another example be included for Abbreviated data package? We propose the case where a change is proposed for several similar drug products, especially using extractables / leachabmes correlation	Add this example in Table A.1.2
IPAC-RS	829	838	Appendix 1	Table A.1.2 Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these eamples should be added in the table.	It is proposed to include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.
AESGP	830	831	Table A.1.2: Examples For Abbreviated Data Package for Packaging and Delivery Device Components	Suggest calling these 'examples' 'scenarios' to be consistant with table A.1.1. Add topical drug products to the example as systemic exposure from drug products is lower than from oral drug products, so the same logic applies. Delete 'fabrication, testing results, and in-use limitations specified therein' as it is unclear what these additional points that is not already confirmed by the material being compliant with 'either regional food contact regulations or compendial standards including composition.	~~Example~~ 'Scenario' 1: Container closure system components for oral drug products 'and topical drug products' are compliant with 'either'regional food contact regulations 'or compendial standards' including composition 'and' ~~fabrication,~~ specification~~, testing results, and in-use limitations specified therein~~ (See Section 3.2).
AESGP	830	831	Table A.1.2: Examples For Abbreviated Data Package for Packaging and Delivery Device Components	Add a new Scenario to the table - nasal preparations (which includes solutions, sprays and drops intended for nasal administration). Calling Scenario 1b for now. Systemic exposure would be negligible as the drug volumes administerd to the patient are very small and not respired into the deep lung. A large proportion of the small volume is expelled out the nose (following patient blowing the nose) and/or swallowed and, therefore, absorption across the mucosal membrane in the nasal cavity is minimal and toxicological risk from a leachable is not realised.	Add 'Scenario 1b: Container closure system components for nasal preparations are compliant with eitherregional food contact regulations or compendial standards including composition and specifications (See Section 3.2). Potential Outcome Components may be considered qualified without additional extractables or leachables testing.'
BioPhorum	830	830	Appendix 1	Refer to Table A.1.2, in example 3: "short/ transient contact" is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	Suggest to provide a definition of "short/ transient contact" Propose to add another example of an abbreviated data package for a parenteral drug product e.g., administered using a CSTD
EfPIA	830	830	Appendix 1	Refer to Table A.1.2, in example 3: "short/ transient contact" is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	Suggest to provide a definition of "short/ transient contact" Propose to add another example of an abbreviated data package for a parenteral drug product e.g., administered using a CSTD

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	830	830	Table A.1.2.	What qualifies as a "delivery device"? Wouldn't it be simpler to refer to everything as "packaging component" instead even if they have a delivery functionality?	Clarification needed
EfPIA	830	830	Table A.1.2	It is not clear why, if we have a "well-characterized packaging system" with a bolus of prior knowledge, there would be any need to perform any extraction studies. As an example, this would seem to be overly restrictive.	Rework example 2.
EfPIA	830	831	Appendix 1	For the "E&L of the Delivery device components with very short/transient contact with drug product", it was only mentioned for oral drug product in Example 3 of Table A.1.2. The topic of the E&L for Delivery device components with very short/transient contact with drug product needs to be included and discussed in the main context of ICH Q3E for all forms of drug product (e.g. the parenteal drug products, etc.)	
ELSIE	830	830	Table A.1.2.	Why a quantitive and not semi quantitative extraction is included in example 2?	Do not specifiy the estimation technique
ELSIE	830	830	Table A.1.2.	What is considered a "well-characterized packaging system" ? One that has E&L data with a favorable TRA? Prior knowledge provided by the applicant must be favorable for safety and quality risk assessments	Clarification needed
ELSIE	830	830	Table A.1.2.	What qualifies as a "delivery device"? Wouldn't it be simpler to refer to everything as "packaging component" instead even if they have a delivery functionality?	Clarification needed
ELSIE	830	831	Appendix 1	Example 3: Delivery device components with very short/transient contact with oral drug products (e.g., oral syringes, oral dosing cups) are compliant with regional food contact regulations. Syringes may be considered medical device. Delivery medical devices are covered by ISO 10993 and for ISO 8536-4: Infusion Equipment for Medical Use - Infusion Sets for Single Use, Gravity Feed. In the EU, when the medical device is not physically combined with the medicinal product the device will need to be CE marked. EU: If the device's primary action is drug delivery (like pre-filled syringes), it is regulated as a medicinal product under Directive 2001/83/EC.	Remove this example, use Combination products as example i.e. https://www.fda.gov/combination-products "Examples may include prefilled drug or biologic delivery devices (e.g., syringes, auto-injectors, (line 283) metered-dose inhalers, dry powder inhalers, nasal sprays, pumps, and transdermal systems), solid (line 284) oral dosage form drugs embedded with sensors, and contact lenses coated with drugs.
ELSIE	830	830	Appendix 1	Refer to Table A.1.2, in example 3: "short/ transient contact" is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	Suggest to provide a definition of "short/ transient contact" Propose to add another example of an abbreviated data package for a parenteral drug product e.g., administered using a CSTD
Ferring Pharmaceuticals	830	830	Table A.1.2	Example 1: Is it common standard to take volatile and semi-volatile migrants / extractables into account?	If so, please incoorporate in the sentence.
IPAC-RS	830	830	Appendix 1	Refer to Table A.1.2, in example 3: "short/ transient contact" is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	Suggest to provide a definition of "short/ transient contact" Propose to add another example of an abbreviated data package for a parenteral drug product e.g., administered using a CSTD
AstraZeneca	834	834	Table A.1.2 notes	Letter missing: "recommendation" should be "recommendations"	Consider changing to "recommendations"
EfPIA	835	835	Appendix 1	"No" and "few" extractables assume different risk levels. One can have only one compound above the AET that might be toxic, so the concept that just a few extractables might justify an abbreviated data package is not scientifically sound	Remove "or few"
ELSIE	835	835	Appendix 1	"No" and "few" extractables assume different risk levels. One can have only one compound above the AET that might be toxic, so the concept that just a few extractables might justify an abbreviated data package is not scientifically sound	Remove "or few"
Medicines for Europe	840	845	Appendix 2	Filter suppliers agreed on common diluents/solvents for the extraction of filters (BPOG data) to improve comparability of the data. Would it be preferable to propose extraction media in the guideline as well instead of stating „ a range of solvents that are representative of the drug product formulation are used“?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TGA	840	840		The title of Appendix 2 “Types of studies” should be more specific, for example "Purpose of Extractables and Leachables studies"	
Maven E&L Ltd	841	841	Appendix 2	Table A.2.1 : It should be made clear that Simulated Leachable Study is a type of extractable study (Designed). It should also be made clear whether placebo drug product can form leachable studies. Leachable studies can also be used for quality risk assessment (not currently listed under leachable study purpose). Indeed leachable study is only formation which can directly address leachable quality risk (comparison to leachable specification as an acceptance criteria). The validation / qualification status of the analytical methods deployed should be added as a column to the table. Extractable studies as surrogates for leachable studies needing more qualification than those not used for that purpose.	
AESGP	841	842	Appendix 2: Types of Studies Table A.2.1: Summary of Extractable, Leachable and Simulated Leachable Studies	Simulated Leachable: Simulated-use Extractables or Simulated Leachables. Might be good to include both terminologies as I've seen both be prevalent. With regard to the statement, 'Quantify and monitor target leachables over long-term storage and in-use. Identify and characterize unanticipated (non-target) leachables > AET. In rare circumstances when justified and concurred by regional regulatory authority, may be used in lieu of a leachable study for toxicological risk assessment.' Disagree with 'In rare circumstances' as for more complex formulations this may be done more regularly.	Add 'or Simulated Leachables' Delete 'In rare circumstances'
AstraZeneca	841	841	Appendix 2	Table A.2.1 : It should be made clear that Simulated Leachable Study is a type of extractable study (Designed). It should also be made clear whether placebo drug product can form leachable studies. Leachable studies can also be used for quality risk assessment (not currently listed under leachable study purpose). Indeed leachable study is only formation which can directly address leachable quality risk (comparison to leachable specification as an acceptance criteria). The validation / qualification status of the analytical methods deployed should be added as a column to the table. Extractable studies as surrogates for leachable studies needing more qualification than those not used for that purpose.	
BioPhorum	841	844	Appendix 2	Leachable - Experimental conditions - "Testing .... over shelf-life and in-use stability." in-use stability is not always applicable In-use stability is not relevant/out of scope for E&L. Need clarity on definition of in-use study in context of multi-dose products	Proposal to describe: Testing .... over shelf-life and in-use stability (if applicable for container closure) Need clarity on definition of in-use study in context of multi-dose products
EfPIA	841	842	App 2, table A.2.1	Under "Extractable", first row, the recommendations provided on the experimental conditions to be attempted are vague and ambiguous. Also, not clear what "a range of solvents that are reporesentative of the drug product formulation" would mean, given that most drug product formulation do not include solvents, or if they do such solvents are typically limited to a small subset of solvents that may be used in manufacturing.	Suggest either providing a more quantifiable target set (for instance: subject materials to a pH range that is one log wider than what is intended or typically measured in the final product; or target a measurable degradation of at least x% of the components, similarly to what is usually adopted in practice for forced degradation studies), or, perhaps preferably, just provide general guidance that speaks to a reasoned and well justified scientific approach.
EfPIA	841	842	App 2, table A.2.1	Under "Leachable", second row, "experimental conditions", general recommendation is made about testing over shelf-life and in-use. This seems too restrictive in the evolving landscape of expectations on how to set up stability studies.	Recommend replacing the two sentences under "experimental conditions" with a more general sentence along the lines of "Testing for leachables should be included in stability study plans that are defined in line with the recommendations and principles of [the now under revision] ICH Q1."
ELSIE	841	841	Table A.2.1	"hazard assessment" is not aligned with Figure 1	"hazard identification"

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ELSIE	841	841	Table A.2.1	"quality risk"	"risk"
ELSIE	841	841	Table A.2.1	The AET is a critical concept for both E&L studies. However, in the current guideline, it is primarily emphasized in the context of leachables.	Include AET in the extractables portion of the table
ELSIE	841	842	Appendix 2	The definition of what extraction studies are requires more clarification in table A.2.1 and likely throughout the document. Here at least, it described extractables as being determined from relatively aggressive extraction conditions with the goal of representing actual use conditions without degrading the material. There are many ways that can be interpreted. It also describes the use of multiple solvents to represent the drug product without further elaborating what the purpose of using multiple solvents to represent a single matrix is.	Clarify what the ICH team believes an extraction study is trying to do and how that needs to be done. There is a big difference between using pH buffered water to represent an aqueous drug product vs using water, IPA, and hexane, as some will interpret the directive here to imply.
ELSIE	841	842	Appendix 2	Again, the definition of leachable studies in table A.2.1 doesn't cover all scenarios. Specifically, it mentions the monitoring of leachables over the shelf life of the product as if it is a universal outcome. What if there are no leachables identified as being of concerned via the safety assessment, which is part of the process described in this document. Similarly, it states that unexpected leachables greater than the AET should be characterized. Monitoring expected leachables using validated targeted methods and uncovering unexpected leachables are to completely separate activities requiring different tactical approaches, but the current document make it seem as though they happen simultaneously through the same efforts of monitoring targeted leachables.	Clarify throughout the document the specific requirements for how extractables are assessed to determine what leachables need to be monitored in targeted leachable studied (e.g., if all leachables are shown to be acceptable in the safety assessment do they still require monitoring) and how targeted and non-targeted (e.g., for unexpected leachables) analyses should be performed and coexist.
Ferring Pharmaceuticals	841	841	App. 2	Is the table content supposed to include: - qualitative extractable study - quantative extractable study - screening leachable study - real leachable study - simulated leachable study ?	If so - please specify.
Ferring Pharmaceuticals	841	841	App. 2	Extractable: The description doesn't include description of semi-quantiative and quantitative calculations. Here the term 'safety assessment' used. For leachable studies 'tox. Risk assessment' is use.	Propose to include calculations. Propose to align wording and definition about assessment (safety/tox. Risk/ tox. / risk...).
Ferring Pharmaceuticals	841	841	App. 2	Simulated leachable: ...(pH, temperature and duration)... Is there a reason, why ionic strength not is included?	Please reevaluate.
Medicines for Europe	841	841	Appendix 2	In Table A.2.1 the experimental conditions citing leachable testing may be performed for in-use conditions, will there be further clarification on what the in-use duration would be that would warrant specific in-use leachable testing? What does in-use stability mean? What data and testing conditions are expected here for leachables?	
EfPIA	843	843	Appendix 2	extractable and leachable study	E&L studies
ELSIE	843	843	Appendix 2	extractable and leachable study	E&L studies
Medicines for Europe	845	845	Appendix 2	Unanticipated leachables: If they are unanticipated (non-targeted) how are they detected? Does this mean additional unidentified peaks in the chromatograms?	
AESGP	846	0	Appendix 3	An example calculation of the potential uptakes of an extractable or leachable compound might be beneficial. The UF is considered for use while converting an SCT to an AET. Using an analytical result with the same unit as the AET for the calculation of the daily update (equivalent to SCT) raises the question if the UF or any other factor needs to be considered.	Add example calculation of daily uptake from E&L data.

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Chiesi Farmaceutici	846	921	Appendix 3	Examples of AET calculations are performed for individual sources separately, i.e. filters, manufacturing equipment, container closure components. What about the collective contribution? Allowing the full AET for each separate component (equipment, materials, and container closure) could result in exceeding the overall AET in the final drug product, since the total represents the sum of contributions from all sources.	It is proposed to integrate the sentence as follows: "Each of the examples provided are based upon using the applicable SCT (µg/day) for the drug product. In some instances, an alternative starting point may be pertinent (such as for a potential Class 1 leachable). In all calculations, worst-case assumptions such as maximum approved dosing of the drug product should be assumed. Common examples for both extractables and leachables studies are provided. Calculation of the AET should clearly indicate what the units are and how the calculation was performed. Regardless of the units used to express the AET, the final value for a given study should always equate to the same patient exposure level (i.e., the SCT multiplied by the analytical uncertainty factor [UF]).For a complete risk assessment it is recommended to include an evaluation of the combined effects of all leachables above the AET level, derived from the different sources."
Medicines for Europe	846	846	Appendix 3	Add colon to ensure a consistent presentation of appendices	Appendix 4:
EfPIA	847	847	Appendix 3	Unclear which examples the text refers to when starting to read the section	"Each of the examples provided in this Appendix"
ELSIE	847	847	Appendix 3	Unclear which examples the text refers to when starting to read the section	Revise to read, "Each of the examples provided in this Appendix"
ELSIE	848	849	Appendix 3	In some instances, an alternative starting point may be pertinent (such as for a potential Class 1 leachable).	In some instances, the potential for Class 1 leachable as an alternate starting point may be relevant
EfPIA	851	851	Appendix 3	extractables and leachables	E&L
ELSIE	851	851	Appendix 3	extractables and leachables	E&L
ELSIE	856	860	Appendix 3	Would it be possible to include an example of AET calculated considering presence of BPA in a material/container used for vaccines?	Provide additional example
ELSIE	856	860	Appendix 2	Considering the MDD and SCT and how they pertain to the AET, how are patient populations other than adults covered? For example, children and neonates. Does the TTC and QT specified in the document cover all patient populations? Or are they only intended to apply to adults?	Clarify to which patient populations the TTC and QT values apply to and how the MDD should be used to calculate the AET when the product is used for multiple patient populations.
ELSIE	856	860	Appendix 3	"The MDD is the maximum approved dose of a drug administered in a single day" --> Challenge the definition of MDD? for some drugs this may lead to an extreme worst case? e.g., Some drugs could be given at a higher dose acutely, but a much lower dose could be expected for repeated doses. (e.g. Electrolytes could be injected IV at 2 L/day, but it is unlikely that this dose will be maintained for more than 7 days?)	The concept of MDD is of high importance, a more clear definition, with acute and chronic application format as well as the importance of keeping the scenarios close to the patient treatment practice. A clear process of calculation would be appreciated. Why not stick with ICH Q3D and limit the MDD to 2L/d? Regarding MDD maybe it could be extended to include different exposure scenarios, e.g. short term and long term (this is commonly the case for large volume parenterals), and based on this different safety margins could be derived for a drug based on exposure duration. Give guidelines or example on how to define MDD
EUCOPE	856	858	Appendix 3	For Analytical Evaluation Threshold (AET) calculation, in terms of the Maximum Daily Dose (MDD), elaboration or consideration on the calculation of MDD if dosing is patient body weight-based is not provided.	Propose to add clarifying information to Appendix 3 on the calculation of MDD and corresponding AET when dosing regimen is patient body weight-based (e.g., please clarify if the sponsor should use average body weight for weight-based dosing)

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IPAC-RS	856	860	Appendix 3	Would it be possible to include an example of AET calculated considering presence of BPA in a material/container used for vaccines?	Provide additional example
Laboratoires Théa	856	860	Appendix 3	Which MDD do we need to consider for an OTC product where no posology is indicated (i.e. ophthalmic product used for dry eye)?	
BioPhorum	862	866	Appendix 3	Intermittent dosing: Many monoclonal antibodies are administered at a once every three weeks (q3w) schedule. Assuming daily dosing and using the daily QT would also not be adequate in this case.	Please include a suggestion for q3w (or q2w) dosing or allow ≤ 1 month QT as well.
EfPIA	862	866	Appendix 3	Intermittent dosing: Many monoclonal antibodies are administered at a once every three weeks (q3w) schedule. Assuming daily dosing and using the daily QT would also not be adequate in this case.	Please include a suggestion for q3w (or q2w) dosing or allow ≤ 1 month QT as well.
ELSIE	862	862	Appendix 3	"for derivation of the applicable TTC ICH M7 is followed (e.g., when total number of dosing days is ≤30, the TTC = 120 µg). "	for derivation of the applicable TTC ICH M7 is followed …..ADD "to determine the SCT:
ELSIE	862	866	Appendix 3	Intermittent dosing: Many monoclonal antibodies are administered at a once every three weeks (q3w) schedule. Assuming daily dosing and using the daily QT would also not be adequate in this case.	Please include a suggestion for q3w (or q2w) dosing or allow ≤ 1 month QT as well.
Luye Pharma	868	875	Appendix 3	Unlike the approach in the ICH M7 guideline for mutagenic impurities—which uses average daily exposure—the default assumption for non-mutagenic impurities in multiday products is that migration occurs entirely within one day. This assumption is made without rationale or justification and does not consider that exposure-free days would consequently follow.	Average daily exposure should be calculated over the entire application period and used as the relevant metric for comparison against toxicity thresholds, reflecting the continuous drug release throughout this timeframe. This approach is already conservative, given that certain dosage forms—such as transdermal patches—do not result in quantitative absorption of all components, with significant amounts remaining within the dosage form.
Medicines for Europe	868	875	Appendix 3	Multiday products: Deviating from mutagenic impurities guideline ICH M7 (average daily exposure) the default assumption for non-mutagenic impurities is migration within one day without rationale/justification or taking into account that in consequence exposure-free days would follow.	Average daily exposure should be calculated based on application period and represent the relevant value to be compared against the thresholds in line with the continuous drug release over the application period. This is already a conservative approach, as components are not quantitatively absorbed from certain dosage forms, as transdermal patches, where significant amounts remain within the dosage form.
AESGP	871	872	Appendix 3	It might be substantially overestimating, that all leachables from a multi-day product migrate within one day.	This approach should be challenged
ELSIE	871	872	Appendix 3 AET Calculations, Multi-Day Products	For AET calculation for multi-day products it is stated that for mutagenic impurities, per ICH M7 an average daily exposure should be used whereas for non-mutagenic leachable the default assumption is that all leachables migrate within a day. Does this assumption also apply to the safety assessment of non-mutagenic leachables from multi-day products or can an average daily exposure be assumed taking into account the days of use?	
ELSIE	871	872	Appendix 3	"For non-mutagenic leachable, the default assumption is that all leachables migrate within a day. In this case, the applicable QT is defined by the total number of applications"	"For non-mutagenic leachable, the default assumption is that all leachables migrate within a day. In this case, the applicable QT is defined by the total duration of applications"
EfPIA	872	872	Appendix 3	Editorial comment.	Change "leachable" to "leachables" after mutagenic.
ELSIE	874	874	Appendix 3	• Editorial change: "...decrease the daily dose to a non-mutagenic leachable..."	"decrease the daily dose ~~to~~ of a non-mutagenic leachable"
ELSIE	878	888	Appendix 3	It would be helpful to include an example of how the AET would be adjusted if a scaled down version of the filter (compared to the size used in the manufacturing process).	
ELSIE	881	882	Appendix 3	Having an AET in units of mcg/g filter is impractical. How would this be applied if a scaled down version of the filter compared to the commercial manufacturing scale is used for testing?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	882	882	Appendix 3	Extraction solvent "volume" should be considered	Proposed wording/change: "(3) AET (µg/mL extraction solvent volume) = AET (µg/filter) ÷ Extraction solvent volume (mL)/filter"
Medicines for Europe	887	887	Appendix 3	"batch size in 1 kg"	Change in to is
EfPIA	894	894	Appendix 3	Need to add calculation for ug/cm2 for stoppers as whole (and even cut up) stoppers are extracted, but only the product-contact surface of stoppers are exposed to the formulation.	AET (ug/cm2) = AET (ug/stopper) x Extracted stopper/surface area (cm2). For this sectionmake it clear these are scenarios and alternative appraches may be justified. Include in training materials
ELSIE	901	903	Appendix 3	Not clear how to derive an AET for intermittent dosing.	Provide an example using intermittent dosing.
ELSIE	903	910	Appendix 3	It would be hlepful to include AET calculation examples in units of mcg/component or mcg/cm^2	
EfPIA	905	905	Appendix 3	The units as given in the right part of the equation into brackets do not match with the unit given in the left part	Proposed wording/change: "(2) AET (µg/mL drug product) = SCT (µg/day) × UF ÷ Maximum dose (mL drug product/day)
ELSIE	921	921	Appendix 3	It would be helpful to have also a Leachable scenario for large volume parenterals	Include leachable scenario for large volume parenterals
EfPIA	929	929	Appendix 4	Class 1 compounds are not really part of an e/l program. They are considered special case compounds or compounds of concern. We should have some wording regarding how they are generally investigated when there is a potential for them to be formed either from the component or a chemical reaction with potential leachables/excipients/active ingredient.	Insert as second sentence, something like, "Due to these lower thresholds, these compounds are not generally part of the e/l process; they are compounds that are targeted in addition to the e/l process." Again, something like that.
EfPIA	935	935	Appendix 4	Definitin of "AI" missing. Shows up later in row 1062	Include definition
ELSIE	935	935	Appendix 4	Definition of "AI" missing. Shows up later in row 1062	Include definition
AstraZeneca	936	936	Appendix 4	It states this throughout the guideline and in Table A.4.1 that leachables are assigned to a Class based on their calculated parenteral PDE. i.e.the parenteral route of exposure is the key aspect.Perhaps this should be made clearer in Appendix 4. For example in line 936 consider adding "parenteral" so it reads "... derived parenteral Permitted Daily Exposure (PDE)..."	Consider adding the word "parenteral"
BioPhorum	939	942	Appendix 4	"Class 2 is the default leachable classification and includes compounds for which the chronic parenteral administration thresholds for mutagenicity (TTC) and systemic toxicity (QT)." It is not only the default for parenterals.	Remove "parenteral"
ELSIE	939	942	Appendix 4	"Class 2 is the default leachable classification and includes compounds for which the chronic parenteral administration thresholds for mutagenicity (TTC) and systemic toxicity (QT)." It is not only the default for parenterals.	Remove "parenteral"
IPAC-RS	939	942	Appendix 4	"Class 2 is the default leachable classification and includes compounds for which the chronic parenteral administration thresholds for mutagenicity (TTC) and systemic toxicity (QT)." It is not only the default for parenterals.	Remove "parenteral"
ELSIE	943	949	Appendix 4	Class 3 leachables are a very interesting concept that helps assessing substances with low toxic potency. Is there a way to assign Class 3 to a leachable in a toxicological evaluation? E.g., a substance which is well-studied, with no alerts for any specific toxicity endpoint, NOAEL in the 1000 mg/kg bw/day, could you simply assign 1 mg/day yourself, or is this only approach limited to the Class 3 substances from the guideline list (Line 957ff)?	Proposal: Define toxicity endpoints/properties which would allow to assign Class 3 to a leachable.
Maven E&L Ltd	952	953	Appendix 4	Table A.4.1: It is unclear who will define Classes 1-3? Who will decide the data set which confirms the PDE and AI, which appears to classify. Is ICH going to do this? What will be the process to submit leachables for classification?	
Maven E&L Ltd	952	953	Appendix 4	Table A.4.1:It would appear from what is written here that only non-mutagens, which have parenterally derived PDEs are subject to Class 1 classification. Is that the intent? This seems to contradict the definition written in Lines 935 to 938.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	952	953	Appendix 4	Table A.4.1: It is unclear who will define Classes 1-3? Who will decide the data set which confirms the PDE and AI, which appears to classify. Is ICH going to do this? What will be the process to submit leachables for classification?	
AstraZeneca	952	953	Appendix 4	Table A.4.1:It would appear from what is written here that only non-mutagens, which have parenterally derived PDEs are subject to Class 1 classification. Is that the intent? This seems to contradict the definition written in Lines 935 to 938.	
ELSIE	952	952	Table A.4.1	"Class 1 – Leachables to be avoided Mutagens/Predicted Mutagens Leachables that are part of the ICH M7 cohort of concern (aflatoxin-like-, N-nitroso-, and alky azoxy compounds)." How low should the AET be to screen for Class 1 leachables?	Provide clearer explanation
ELSIE	952	952	Table A.4.1	"Class 1 – Leachables to be avoided Leachables meeting criteria for ICH M7 Class 1 impurities and an AI < 1.5 µg/day." To be clarified if the AI mentioned in this table are the PDEs for mutagenic compounds described in ICH M7	To be clarified if the AI mentioned in this table are the PDEs for mutagenic compounds described in ICH M7
ELSIE	952	952	Table A.4.1	"Class 1 – Leachables to be avoided Non-mutagens/Predicted Non-Mutagens Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety". Is this sentence applicable also to vaccines? Is less than lifetime (LTL) approach applicable?	To be clarified if LTL could be applicable; also is the current text applicable to vaccines?
ELSIE	952	952	Table A.4.1	Per Table A.4.1: Non-mutagens/Predicted Non-Mutagens: Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety (see list below). The inclusion of this group into the Class 1 is very confusing, since the list of such compounds might be long and uncertain. On the other hand, the question would be, why those compounds were not included in the QT derivation? Since there are no details on how the QT was derived, no judgement can be made, for which compounds this cannot be implemented (of course it is clear that CoC and mutagens are excluded). When considering the initial screening study to identify extractables, then anyway the lowest possible limit is to be considered for the AET derivation, e.g., 1.5 µg/day (once the presence of CoC is excluded). Even if the mutagenicity could be excluded via testing, still the indicated above group of 'Class 1' compounds cannot be excluded and hence, the lowest possible limit of 1.5 µg/day should be considered for the AET calculation. On the other hand, when considering the ≤ 1 Month use, then according to current ICH Q3E the Systemic Toxicity Thresholds for ≤ 1 Month provided in Table 1 cannot be used, since again for the initial screening extractable study the presence of the above-mentioned group cannot be excluded. And if the QT is not protective, the mutagenic TTC of 120 µg/day will also not be protective. And then the question would be what threshold should then be used for the AET calculation. Should this be again 1.5 µg/day? Please consider the above-mentioned especially for cases where the application route is IM or IV, where the impact of local effects is considered to be negligible as stated in the current ICH Q3E. This table could use some clarification. The threshold to be used in all cases is the lowest TTC or QT defined in Table 1, depending on exposure duration. But, it is true that these thresholds are not covering to my understanding the Class 1 leachables, for which the AI < 1.5 ug/day. Then the open question is, how to ensure that no class 1 leachables are present at a low enough amount if no threshold is defined for this group and if no comprehensive list of compounds is available?	Clarify the 'Non-mutagens/Predicted Non-Mutagens: Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety' from the Class 1 compounds Provide more clarity with real-world use examples on which thresholds should be considered for the AET calculation especially for the initial screening studies
ELSIE	952	952	Appendix 4	The definition of Class 3 compounds as 'Non-mutagenic leachables established to have a chronic parenteral PDE in excess of the levels at which leachables are typically observed' is quite unclear/confusing. There might be non-mutagenic compounds that would typically leach in small amounts, but those compounds might not be of low toxicity concern.	Proposed change: Class 3 – Leachables with relatively low toxic potential Non-mutagenic leachables established to have a chronic parenteral PDE greatly exceeding 1 mg/day limit

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	952	952	Appendix 4	Table A.4.1: "Class 1 – Leachables to be avoided Mutagens/Predicted Mutagens Leachables that are part of the ICH M7 cohort of concern (aflatoxin-like-, N-nitroso-, and alky azoxy compounds)." How low should AET be to screen for Class 1 leachables?	Provide clearer explanation
IPAC-RS	952	952	Appendix 4	Table A.4.1: "Class 1 – Leachables to be avoided Leachables meeting criteria for ICH M7 Class 1 impurities and an AI < 1.5 µg/day." To be clarified if the AI mentioned in this table are the PDEs for mutagenic compounds described in ICH M7	To be clarified if the AI mentioned in this table are the PDEs for mutagenic compounds described in ICH M7
IPAC-RS	952	952	Appendix 4	Table A.4.1: "Class 1 – Leachables to be avoided Non-mutagens/Predicted Non-Mutagens Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety". Is this sentence applicable also to vaccines? Is less than lifetime (LTL) approach applicable?	To be clarified if LTL could be applicable
Maven E&L Ltd	955	955	Appendix 4	Acute and Chronic have not been defined in the table. Nor are there values for inhalation exposure. Add link to Appendix 5	
AstraZeneca	955	955	Appendix 4	Acute and Chronic have not been defined in the table. Nor are there values for inhalation exposure. Add link to Appendix 5	
AstraZeneca	955	955	Table A4.1	it is unclear given the apparent low toxicity the reason as why Bis-phenol A is defined as Class 1	
BioPhorum	955	956	Appendix 4 Class 1 Leachables	Values for Benzo(a)pyrene considered to be too high, Refer also to comment to line 1173ff, Appendix 6: Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	please justify the thresholds indicated in Class 1 table, or include reference/documenation on how threshold classifications were derived. Clarify that the componunds indicated are only examples, it is not a comprehensive list.
Chiesi Farmaceutici	955	955	Appendix 4	It is suggested to integrate the title of the table in coherence with the sentence reported from line 528-529 and the content of Table A.4.1	It is suggested to integrate the title of the table as follows. "Class 1 Leachables to be avoided *(when practically feasible)* "
ELSIE	955	955	Appendix 4	It would be helpful to highlight that BPA and benzopyrene are just examples of leachables to avoid and not the only leachables to avoid.	Please clarify that the leachables presented in "Class 1 Leachables to be avoided" are examples and that this list is not comprehensive.
ELSIE	955	955	Appendix 4	No mention or examples of class 2 leachables	greater clarity
ELSIE	955	959	Appendix 4	There are only a handful of compounds listed in the tables here for class 1 and class 3 extractables. Will this be expanded on as the document moves toward finalization?	If possible, add other Class 1 and Class 3 leachables do these can be better understood.
ELSIE	955	956	Appendix 4 Class 1 Leachables	Values for Benzo(a)pyrene considered to be too high, Refer also to comment to line 1173ff, Appendix 6: Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	
ELSIE	955	955	Appendix 4	Table of Class 1 leachables - please include the ICH M7 cohort of concern compounds	
ELSIE	955	955	Appendix 4	Why is Bisphenol A considered Class 1 if the parenteral PDE is 4 mcg/day and not < 1.5 mcg/day?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	955	1233	Appendix 4 and 6	Values for Bisphenol A oral Accute and Chronic do not align between Appendix 4 and 6	Align Bisphenol A Oral values
IPAC-RS	955	955	Appendix 4	No mention or examples of class 2 leachables	greater clarity
IPAC-RS	955	956	Appendix 4	Class 1 Leachables: Values for Benzo(a)pyrene considered to be too high, Refer also to comment to line 1173ff, Appendix 6: Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	
AESGP	957	959	Appendix 4	Will there be a public database for Class 3 leachables?	Available (online) database (public) of Class 3 compounds would be helpful
BioPhorum	957	959	Appendix 4 Class 3 Leachables	What is the rationale for selection of these Leachables? Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020), see also ELSIE database	Consider to include more substancesplease. Justify the thresholds indicated in table, or include reference/documenation on how threshold classifications were derived.
BioPhorum	957	959	Appendix 4	Is the PDE only for parenterals? Is the interpretation correct, that parenteral is worst case and e.g., for inhalative or oral dosage, higher amounts may be tolerated.	Please include explanation how this table should be used.
EfPIA	957	959	Appendix 4 Class 3 Leachables	What is the rationale for selection of these Leachables? Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020), see also ELSIE database	Consider to include more substances
EfPIA	957	959	Appendix 4	Is the PDE only for parenterals? Is the interpretation correct, that parenteral is worst case and e.g., for inhalative or oral dosage, higher amounts may be tolerated.	Please include explanation how this table should be used.
EfPIA	957	959	Appendix 4 Class 3 Leachables	Class 3 leachables list is limited. Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020).	Consider to include more substances, or a footnote that these are examples and not a comprehensive list.
ELSIE	957	959	Appendix 4	"Table 3. Class 3 Leachables With Relatively Low Toxic Potential (Chronic Parenteral PDE ≥ 1 mg/day)…" This table lists Rubber Oligomer C21H40. Please consider listing the common variants of these rubber oligomers in the Class 3 leachables table, including the cis and trans diastereomers of C21H40, and C13H24 (please see additional document sent with these comments). Other homologs/fragments (e.g., C25H48) are also known. Given their overall structural similarly, the read across should rely on the very same surrogate (i.e., 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone) for PDE derivation.	Can the table be expanded to include other rubber oligomers, e.g., the cis form using read across based on structure.
ELSIE	957	959	Appendix 4	The proposed PDE for Irganox 1310 is based on a surrogate compound due to an assumed lack of compound-specific data. However, at least two studies are available for Irganox 1310. We propose re-evaluating the PDE using compound-specific data.	Propose to re-evaluate the PDE using compound-specific data
ELSIE	957	959	Appendix 4 Class 3 Leachables	What is the rationale for selection of these Leachables? Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020), see also ELSIE database Should a footnote be included to say these are only examples and that there may be other class 3 compounds? And that these are provided as examples?	Consider to include more substances, or note that these are examples and not a comprehensive list

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	957	959	Appendix 4	Is the PDE only for parenterals? Is the interpretation correct, that parenteral is worst case and e.g., for inhalative or oral dosage, higher amounts may be tolerated.	Please include explanation how this table should be used.
Hikma	957	959	Appendix 4	The proposed PDE for Irganox 1310 is based on a surrogate compound due to an assumed lack of compound-specific data. However, at least two studies are available for Irganox 1310 (attached in rows 71 and 72). We propose re-evaluating the PDE using compound-specific data.	
IPAC-RS	957	959	Appendix 4	Is this an example list - not exhaustive (many compounds similar to those listed are not listed) - suggest to amend the title to indicate this is an example list	Example Class 3 Leachables With Relatively Low Toxic Potential (Chronic Parenteral PDE ≥ 1 mg/day). Monographs In Supporting Documents.
IPAC-RS	957	959	Appendix 4	Class 3 Leachables: What is the rationale for selection of these Leachables? Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020), see also ELSIE database	Consider to include more substances
IPAC-RS	957	959	Appendix 4	Is the PDE only for parenterals? Is the interpretation correct, that parenteral is worst case and e.g., for inhalative or oral dosage, higher amounts may be tolerated.	Please include explanation how this table should be used.
Medicines for Europe	957	957	Appendix 4	incorrect CAS for Lauric acid in the table	Change CAS of Lauric acid from ~~57-10-3~~ to 143-07-7
AstraZeneca	958	959	Class 3 Leachables Table	Typo - please check the CAS no. for caprylic acid, it should be 124-07-2	
EfPIA	958	958	Supporting Documentation: Class 3 leachable monographs; cis-1,1,5,5-Tetramethyl-2-(1-methylethenyl)-3-(2,2,4-trimethylpentyl)-cyclohexane (Rubber Oligomer C21H40)	On the US EPA website regarding the AIM tool, it is mentioned tha "*Experimental data sources identified by AIM are not endorsed by EPA; nor does EPA vouch for the quality or accuracy of the data. Furthermore, professional judgement is needed to determine adequacy of analogs identified by AIM. Note that the AIM software has not been supported or updated since 2012.*" (available at: https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool). Based on this statement, the choice of surrogate used in the read-across approach for the rubber oligomer $C_{21}H_{40}$ can be reasonably questioned without additional data.	It is recommended to provide a more detailed scientificc rational to ensure transparency and consistency with the regulatory expectation for the use of read-across approach.
EfPIA	958	958	Appendix 4	Wrong CAS for lauric acid, CAS 143-07-7 is correct	~~57 10 3~~ 143-07-7
ELSIE	958	959	Appendix 4	• Lauric acid (C12) is listed with a wrong CAS number (57-10-3), which is actually the CAS number for Palmitic acid (C16).	• The correct CAS number for Lauric acid (C12) is 143-07-7 ~~57 10 3~~. And this should be corrected
EfPIA	961	1171	Appendix 5	Entire appendix would be better placed if merged with analogous Appendix 3 of ICH Q3C in one location only (could be an addedum to all ICH Q3 sequence)	As positioned now, it may be confusing as to which guideline (ICH Q3C vs ICH Q3E) an Applicant should refer to for guidance on how to establish exposure limits for any organic substance of concern, regardless of point of entry (solvents, volatile reagents, leachables).
ELSIE	961	961	Appendix 5	Appendix 5: Methods for Establishing Exposure Limits	Change to: Appendix 5: Methods for Establishing Safe Exposure Limits

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	963	963	Appendix 5	Why specify the leachables class if all are already included in the sentence? This adds no apparent value	"For leachables exceeding"
ELSIE	963	963	Appendix 5	Why specify the leachables class if all are already included in the sentence? This adds no apparent value	"For leachables exceeding"
ELSIE	969	969	Appendix 5	extractables and leachables	E&L
AstraZeneca	973	973	Appendix 5	Change "establishing" to "establish"	Consider changing the word"establishing" to "establish"
ELSIE	973	973	Appendix 5	grammer - "to appropriately "	Grammer: change to "for appropriately"
BioPhorum	980	982	Appendix 5	Substances classified as class 3 in ICH Q3C should also be mentioned as examples for class 3 leachables	Include ICH Q3C class 3 compounds as class 3 leachables. Clarify what is meant by class 3 compounds or elements
EfPIA	980	982	Appendix 5	Substances classified as class 3 in ICH Q3C should also be mentioned as examples for class 3 leachables	Include ICH Q3C class 3 compounds as class 3 leachables.
ELSIE	980	982	Appendix 5	Substances classified as class 3 in ICH Q3C should also be mentioned as examples for class 3 leachables	Include ICH Q3C class 3 compounds as class 3 leachables, or simply make reference to ICH Q3E, as appropriate
IPAC-RS	980	982	Appendix 5	Substances classified as class 3 in ICH Q3C should also be mentioned as examples for class 3 leachables	Include ICH Q3C class 3 compounds as class 3 leachables.
AstraZeneca	984	984	Appendix 5	Remove 'still' (should read, 'In other scenarios' rather than 'In still other scenarios')	
ELSIE	984	986	Appendix 5	"In still other scenarios, the dose ratio between a well defined, supported and justified NOAEL and the anticipated patient exposure may be so large (e.g., >10,000) that a detailed derivation may not be necessary". Can this be clarified?	Provide clearer explanation
IPAC-RS	984	986	Appendix 5	"In still other scenarios, the dose ratio between a well defined, supported and justified NOAEL and the anticipated patient exposure may be so large (e.g., >10,000) that a detailed derivation may not be necessary." Can this be clarified?	Provide clearer explanation
AstraZeneca	985	985	Appendix 5	Is the ratio described in this sentence i.e. the ratio between the NOAEL and the patient exposure the "Margin of Exposure"? If so, please can "Margin of Exposure" be added here and also to the Glossary?	Consider adding "Margin of Exposure"
Maven E&L Ltd	988	991	Appendix 5	This paragraph seems to contradict the footnote to Figure 1. Footnote to Figure 1 should be changed or removed	
AstraZeneca	988	991	Appendix 5	This paragraph seems to contradict the footnote to Figure 1. Footnote to Figure 1 should be changed or removed	
EfPIA	996	997	Appendix 5	Suggestion to include examples illustrating how specific in vitro studies can support the safety justification of E&L levels	
AESGP	1007	1013	Appendix 5 F6 factor derivation and supporting documentation Class 3	According to Appendix 5 is it reported that "Safety assessments incorporating a surrogate compound should provide clear justification for the selection of the surrogate(s)". This seems not the case for the reported leachable within Class 3 supporting documentation. The explanation of F6 selection is not always clear (e.g. Erucamide, Rubber oligomer)	Clarification for F6 selection within supporting document should be added. Aaccording to appendix 5, the choice of the surrogate should be based on various attributes (e.g. including mode of action, the principal toxicophore and surrounding chemical environment, presence of functional groups that may impact biological activity, overall structural similarity, toxicokinetic properties, physicochemical properties) if known, and not just one.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	1007	1013	Appendix 5	"Safety assessments incorporating a surrogate compound should provide clear justification for the selection of the surrogate(s). There are various attributes that should be considered (if known) during the selection of a suitable surrogate, including mode of action, the principal toxicophore and surrounding chemical environment (e.g., presence of functional groups that may impact biological activity), overall structural similarity, toxicokinetic properties, physicochemical properties (e.g., polarity, solubility, ionizability, and molecular weight)." To be clarified if discussion and rationale concerning mode of action of surrogate/read-across candidates is a mandatory requirement, or if it is optional	Provide clearer explanation if discussion and rationale concerning mode of action of surrogate/read-across candidates is a mandatory requirement, or if it is optional Add "biological similarity", eventually refer to Echas RAAF (Read Across Assessment Framework)
IPAC-RS	1007	1013	Appendix 5	Safety assessments incorporating a surrogate compound should provide clear justification for the selection of the surrogate(s). There are various attributes that should be considered (if known) during the selection of a suitable surrogate, including mode of action, the principal toxicophore and surrounding chemical environment (e.g., presence of functional groups that may impact biological activity), overall structural similarity, toxicokinetic properties, physicochemical properties (e.g., polarity, solubility, ionizability, and molecular weight). To be clarified if discussion and rationale concerning mode of action of surrogate/read-across candidates is a mandatory requirement, or if it is optional	Provide clearer explanation
ELSIE	1010	1010	Appendix 5	Definition of "toxicophore" missing	Include definition glossary
ELSIE	1020	1059	Appendix 5	Section: Data to be evaluated and incorporated into the safety assessment. This section points out all studies available should be summarized, this makes the assessments long and not succinct. Would a tabulated summary be enough? Are there any examples/suggestions as to how this information should be provided?	
EfPIA	1032	1036	Appendix 5	Bioaccumulation potential, differences between absorption and bioavailability, and data on endocrine disruption are often lacking for E&L compounds. Are there recommended computational tools for incorporating these factors into a Weight of Evidence assessment?	
ELSIE	1047	1047	Appendix 5	• Editorial change: "...should evaluated and included..."	"...should be evaluated and included..."
EfPIA	1051	1051		It seems there is no scientific basis for excluding mutagenicity data from an API or process intermediate when such data is relevant to a specific leachable	Delete "Note: ICH M7 Class 4 is not applicable to leachables"
ELSIE	1057	1057	Appendix 5	• Editorial change: "..heath-based..."	"...health-based..."
Gedeon Richter Plc.	1062	1062	Appendix 5	Abbreviations should be defined in the text when they appear first time in the text. AI=Acceptable Intake appears first time in line 523.	AI as abbreviation should be defined in line 523 as it appears first time in the guideline.
Maven E&L Ltd	1070	1136	Appendix 5	ICH Q3E and ICH Q3D have differences in modifying factors listed. Therefore it is unclear how ICH Q3D would be applied to elemental leachables and this should be further discussed and included in ICH Q3E	
AstraZeneca	1070	1136	Appendix 5	ICH Q3E and ICH Q3D have differences in modifying factors listed. Therefore it is unclear how ICH Q3D would be applied to elemental leachables and this should be further discussed and included in ICH Q3E	
BioPhorum	1072	1074	Appendix 5	"...the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose": Why maximum daily dose? Rather route of administration is assumed to be correct reference here.	Please provide further explanation - should both max (or permissible) daily dose & route be considered
EfPIA	1072	1074	Appendix 5	"...the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose": Why maximum daily dose? Rather route of administration is assumed to be correct reference here.	Please provide further explanation
ELSIE	1072	1074	Appendix 5	"...the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose": Why maximum daily dose? Rather route of administration is assumed to be correct reference here.	Please provide further explanation

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	1072	1074	Appendix 5	"...the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose": Why maximum daily dose? Rather route of administration is assumed to be correct reference here.	Please provide further explanation
ELSIE	1074	1074	Appendix 5	replace "maximum daily dose" by MDD	Abbreviation
ELSIE	1079	1080	Appendix 5	Typo ", if justified…": separate with a semi-colon or a period	"...; if justified…"
AESGP	1080	1083	Appendix 5 acceptable exposure calculation	Details about factor F1 to F5 values should be cleary reported. Factor values to be applied for acute and chronic PDE should also be clarified (e.g. F3 of 1 for acute PDE if the PoD is from short term studies as in the supporting document). additionally, a reference to ICH Q3D might be made to avoid additional discussions and different interpretation of the values.	add explanation of all factor F1 to F5 or clear reference to ICHQ3D
ELSIE	1092	1093	Appendix 5	Not all readers may be familiar with the F1–F5 classification	Make cross reference
BioPhorum	1095	1131	Appendix 5	Impurity profiling by toxicologists is common practice in pharma industry that does not require this additional guidance	refer to established standard procedures
EfPIA	1095	1131	Appendix 5	Further to overarching comment above on the entire Appendix 5, why wouldn't F6 be applicable to extraneous solvents or organic volatile impurities that are not leachables?	Same suggestion as provided above on merging discussion into one document addressing any organic substance of concern is given here.
EfPIA	1100	1102	Appendix 5	"If a radiolabelled study is used… it is not clear if the radiolabel is the parent, a metabolite, or a combination of both". I understand that you mean the detected radiation in the tissues/feces/urine/carcas is the parent or its metabolites?	Replace "if the radiolabel is…" with "if the detected radiation is…"
BioPhorum	1107	1107	Appendix 5	The given Range ("≥ 1% and <50% (divide by a modifying factor of 10)") is considered a wide range….	Propose to allow adjustment of factors depending on the bioavailability.
ELSIE	1107	1107	Appendix 5	The given Range ("≥ 1% and <50% (divide by a modifying factor of 10)") is considered a wide range.	Propose to allow adjustment of factors depending on the bioavailability.
IPAC-RS	1107	1107	Appendix 5	The given Range ("≥ 1% and <50% (divide by a modifying factor of 10)") is considered a wide range.	Propose to allow adjustment of factors depending on the bioavailability.
Lhasa Limited	1111	1114	Appendix 5	More information on how NAM approaches can be used to assess bioavailability would be helpful. This could be in the form of examples or references to studies where these approaches have been successfully applied.	
EfPIA	1112	1112	Appendix 5	PBPK not defined	Include definition
ELSIE	1112	1112	Appendix 5	PBPK not defined	Include definition
EfPIA	1114	1116	Appendix 5	Have any alternatives, rather than just assuming a default F6 of 100, been considered? For example adjusting based on low, moderate, or high oral toxicity as outlined by IGHRC.	Consider principal outlined in: Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals. IGHRC Guidelines. Prepared by the Interdepartmental Group on Health Risks from Chemicals. April 2006.
ELSIE	1114	1116	Appendix 5	"Alternatively, a default modifying factor of 100 is suggested for F6, with smaller values requiring justification (e.g., reasoning based on the physicochemical characteristics of the compound)". A factor of 100 to account for limited information concerning bioavailability is more conservative compared to previously accepted factor 10. Is this too strict compared with previous recommendations? A default modifying factor (MF) of 100 for F6 is way too conservative, especially in view of all the MFs that need to applied.	Provide clearer explanation Default MF for F6 should be 10, unless there is clear indication of extremely low bioavailability.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IPAC-RS	1114	1116	Appendix 5	"Alternatively, a default modifying factor of 100 is suggested for F6, with smaller values requiring justification (e.g., reasoning based on the physicochemical characteristics of the compound)". A factor of 100 to account for limited information concerning bioavailability is more conservative compared to previously accepted factor 10. Is this too strict compared with previous recommendations?	Provide clearer explanation
Octapharma	1114	1114	Appendix 5	A default modifying factor (MF) of 100 for F6 is way too conservative, especially in view of all the MFs that need to applied.	Default MF for F6 should be 10, unless there is clear indication of extremely low bioavailability.
ELSIE	1123	1124	Appendix 5	Not sure what this sentence means.	Please elabraote
Hikma	1123	1124	Appendix 5	Not sure what this sentence mean.	Please elabraote
AESGP	1124	1128	Appendix 5	It would be good to include a description of a default absorption factor for extrapolation from oral to parenteral route of exposure, as this is a case which happens often due to a huge amount of oral toxicity data available. Physicochemical properties are used in parenteral PDE calculation examples (Erucamide (CAS#112-84-5); Benzo[a]pyrene (CAS# 50-32-8); Rubber Oligomer C21H40) (CAS# 114123-73-8)) to justify a default absorption factor of 10% for oral to parenteral extrapolation. Currently only a description of extrapolation from dermal to parenteral route is included.	
EfPIA	1124	1114	Appendix 5	w	Many of the concepts have been derived from Masuda-Herrera et al., 2023, (https://pubmed.ncbi.nlm.nih.gov/37748702/), we suggest in the absence of additional description to reference this paper.
ELSIE	1124	1126	Appendix 5	Please be more specific. Is 50% for water-based or dispersed dilutes, or both?	
Hikma	1124	1126	Appendix 5	Please be more specific. Is 50% for water-based or dispersed dilutes, or both?	
Lhasa Limited	1124	1127	Appendix 5	A default value for dermal absorption is provided for most organic solvent-based dilutes and water-based or dispersed dilutes. Where do these values come from? Could a reference be provided?	
BioPhorum	1125	1127	Appendix 5	"… a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes, respectively": please clarify: 70% for organic, 50% for water-based or dispersed dilutes? 50% for water-based dilutes would be relatively high and not considered "sufficiently conservative" when extrapolating from dermal to parenteral administration (see e.g., https://pmc.ncbi.nlm.nih.gov/articles/PMC7027575/), only if extrapolating from parenteral to dermal.	Please provide further explanation. Remove or clarify the use of arbitrary numbers. (cite sources if applicable)
EfPIA	1125	1127	Appendix 5	"… a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes, respectively": please clarify: 70% for organic, 50% for water-based or dispersed dilutes? 50% for water-based dilutes would be relatively high and not considered "sufficiently conservative" when extrapolating from dermal to parenteral administration (see e.g., https://pmc.ncbi.nlm.nih.gov/articles/PMC7027575/), only if extrapolating from parenteral to dermal.	Please provide further explanation
ELSIE	1125	1127	Appendix 5	"… a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes, respectively." Please clarify: 70% for organic, 50% for water-based or dispersed dilutes? 50% for water-based dilutes would be relatively high and not considered "sufficiently conservative" when extrapolating from dermal to parenteral administration (see e.g., https://pmc.ncbi.nlm.nih.gov/articles/PMC7027575/), only if extrapolating from parenteral to dermal.	Please provide further explanation
IPAC-RS	1125	1127	Appendix 5	"… a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes, respectively": please clarify: 70% for organic, 50% for water-based or dispersed dilutes? 50% for water-based dilutes would be relatively high and not considered "sufficiently conservative" when extrapolating from dermal to parenteral administration (see e.g., https://pmc.ncbi.nlm.nih.gov/articles/PMC7027575/), only if extrapolating from parenteral to dermal.	Please provide further explanation

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EfPIA	1127	1128	Appendix 5	The origin of the criteria is unclear: "If both the molecular weight exceeds 500 and the logPow is either below –1 or above 4, a default absorption factor of 10% is assumed". Rationale needed	Incldue ratioale or incldue reference
ELSIE	1127	1128	Appendix 5	The origin of the criteria is unclear: "If both the molecular weight exceeds 500 and the logPow is either below –1 or above 4, a default absorption factor of 10% is assumed". Rationale needed	Include rationale or include reference
Lhasa Limited	1127	1128	Appendix 5	A physicochemical rule is provided for dermal absorption. How was this rule derived? Is there a reference which could be provided to give the reader more information?	
EfPIA	1132	1136	Appendix 5	There is limited guidance on application of the F7 value in terms of the level of similarity for the surrogate. Recommend providing more details or highlight from a publication.	Many of the concepts have been developed in Masuda-Herrera et al., 2023, (https://pubmed.ncbi.nlm.nih.gov/37748702/), we suggest in the absence of additional description to reference this paper.
Lhasa Limited	1132	1136	Appendix 5	Make F7 (read-across uncertainty) quantitative and reproducible Current: “Up to 5” based on (dis)similarity; F7=1 possible when surrogate is highly similar. Improvement: Provide guidance for mapping evidence to F7. For example: Include optional quantitative similarity metrics as examples (not requirements), paired with expert justification (alerts, TK, MoA). This converts F7 from a “black box” into an evidence-weighted choice.	F7=1 (high confidence): strong mechanistic concordance, common toxicophore and highly similar metabolic fate, high structural similarity and TK/physchem comparability. F7=2–3 (moderate): good structural similarity and/or partial TK/physchem alignment; single high-quality surrogate; limited MoA information. F7=4–5 (low): surrogate differs on metabolism/alerts; structural similarity is low; conflicting data; read-across used as placeholder pending data.
EfPIA	1133	1136	Appendix 5	In the paragraph describing the F7 safety factor, it is stated that a value of 1 may be applicable when the surrogate is considered sufficiently similar. The read-across approach is commonly used for assessing E/L in the absence of toxicological data to derive an acceptable exposure level. Therefore, applying an additional safety factor F7 different from 1 could be interpreted as an indication that the surrogate is not adequately representative.	It is purposed to delete safety factor F7 or to provide additional details on the criteria and rationale for assigning an F7 value different from 1
EfPIA	1135	1135	Appendix 5	Unclear what the criteria are for "considered similar"	Clarification needed
ELSIE	1135	1135	Appendix 5	Unclear what the criteria are for "considered similar"	Clarification needed
EfPIA	1136	1136	Appendix 5	Since F7 is a new factor introduced for PDE calculation, it is advisable to add the existing explanations (lines 1007-1018) in the same section to ease reading, i.e. after line 1136	Safety assessments incorporating a surrogate compound should provide clear justification for the selection of the surrogate(s). There are various attributes that should be considered (if known) during the selection of a suitable surrogate, including mode of action, the principal toxicophore and surrounding chemical environment (e.g., presence of functional groups that may impact biological activity), overall structural similarity, toxicokinetic properties, physicochemical properties (e.g., polarity, solubility, ionizability, and molecular weight). When properly justified, in silico tools and data from NAMs may be used to support the selection of surrogates and inform the read-across approach, but the above-mentioned criteria need to be considered. How a surrogate is incorporated into the safety assessment for the leachable of interest should be scientifically justified. Potential uncertainties related to the read-across approach should also be indicated and appropriately accounted for, such as when using for an acceptable exposure level determination"
EfPIA	1137	1139	Appendix 5	Requirement to provide all references supporting PDE derivation is overly burdensome to industry and HA reviewers.	Remove
ELSIE	1138	1139	Appendix 5	"Copies of articles (or other documents referenced to support a proposed PDE should be provided." --> copies of all references? Or only the ones selected as PoD and that support the UFs?	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	1143	1143	Appendix 5	• In toxicology textbooks, the Margin of Safety (MOS) is defined as the NOAEL (or PoD) divided by Potential patient exposure. In some variations of this definition, the NOAEL is further divided by an allometric scaling factor to account for the extrapolation between animals and humans. No further assessment factor needs to be applied. However, in the MOS formula provided in the ICH Q3E draft guideline, the numerator is set to the PDE or Acceptable exposure level, as opposed to the traditional definition of the MOS, where the NOAEL (or PoD) is used instead.	
EfPIA	1145	1146	Appendix 5, Margin of Safety	Not clear what additional information would bring the calculation of a "Margin of Safety" to the risk assessment, based on the statement given at these lines. The overall description of the risk assessment, starting already from Section 3 of the draft guideline, indicates that "risk mitigation measures" should be undertaken in case the patient is potentially exposed to levels of leachables that are above the established AI values.	Recommend rephrasing the introductory sentences and the title of this section without mention of the MOS. This should be about recommendations on how to justify exposure that is potentaillly above the compound-specfic PDE.
EfPIA	1154	1154	App 5	A clarification (addition of a note) would be useful to explain why an acceptable exposure level to a leachable higher than the PDE may be acceptable for a "limited patient population (e.g., adult males only) " Is it linked to bodyweight? Would it not be more appropriate to indicate "specific patient population"?	
ELSIE	1154	1154	Appendix 5	A clarification (addition of a note) would be useful to explain why an acceptable exposure level to a leachable higher than the PDE may be acceptable for a "limited patient population (e.g., adult males only) " Is it linked to bodyweight? Would it not be more appropriate to indicate "specific patient population"?	Consider indicating "specific patient population" as per comment
EfPIA	1156	1158	Appendix 5, Margin of Safety	For drugs administered for less than lifetime to the patient, a lower value of F3 is conceivable. This seems to be already included in the definition of F3, as provided in ICH Q3C. Unless a less-than-lifetime concept (as per ICH M7) is considered here.	Recommend alignment with ICH Q3C, appendix 3, or with ICH M7, whichever is applicable here.
EfPIA	1156	1161	Appendix 5	The different F3 values are described in ICH Q3D / Q3C. These values are defined for establishing Permitted Daily Exposure (PDE) for lifetime treatment. The current ICH Q3E draft introduces the concept of deriving an Acceptable Exposure Level for short-term exposure, where the safety threshold results from an adaptive F3 factor as mentioned in lines 1165–1166. However, no specific F3 values are provided to account for acute, subacute, or subchronic exposure, which could lead to inconsistencies and lack of harmonization in the calculation of Acceptable Exposure level. In the past, certains health authorities did not consider available subacute study (e.g., combined 28-day repeat-dose and DART study OECD 422) suitable for a comprehensive systemic toxicity evaluation for E/L short-term exposure, which is inconsistent with the derivation of an Acceptable Exposure level based on a short-term study as stated in this paragraph.	It is recommended to provide additional details on the criteria and scientific rationale for assigning the relevant adaptive F3 value, such as those proposed by Masuda et al. (2022), and ensure consistency with the acceptance criteria of the different health authorities.
TGA	1156	1159		F3 is a factor used in the PDE calculation to accommodate uncertainties in the NOAEL for a toxicity study of shorter than ideal duration. This adjustment assumes chronic lifetime exposure to the chemical in human subjects. The proposed adjustment of F3 depending on duration of clinical exposure seems reasonable, and is consistent with approaches that have been taken in the past. Any adjustment would need to be clearly justified. Likewise, any adjustment of F2 for intermittent dosing would need to be clearly justified.	
EfPIA	1165	1165	Appendix 5	"Alternatively, the value for F3 can be modified."	Add example?
TGA	1167	1170		Table A.5.1. states that “Qualification study(ies) as described in ICH Q3A and Q3B” need to be considered for “General systemic toxicity assessment”. This implies only endpoints that can be gained from repeat-dose toxicity studies of 2 weeks to 90 days duration need to be considered. Other systemic endpoints such as effects on fertility, embryofetal development and non-mutagenic carcinogenicity should be considered, consistent with other guidelines such as ICH Q3C and Q3D that discuss deriving PDEs for compounds that are not related to the API. The text in Table A.5.1. should be amended to reflect this.	
AstraZeneca	1169	1169	Table A.5.1	The Table is missing a horizontal line to separate Local Toxicity from Genotoxicity.	Update the Table to separateLocal Toxicity from Genotoxicity.

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Chiesi Farmaceutici	1169	1170	Appendix 5	No reference to DART safety assessment	Add a line for DART assessment underneath general systemic toxicity, including read across for non-animal methods and qualification studies as per ICH Q3A and Q3B, regional guidance as per the proposed methods for general systemic toxicity.
EfPIA	1169	1170	Table A.5.1	"Genotoxicity" should be replaced by "Mutagenicity"	ICH M7 and the purpose of in silico models therein discussed are about prediction of mutagenicity, not of genotoxicity.
ELSIE	1169	1169	Appendix 5	Add OECD 439, 492 and 492B	
Medicines for Europe	1169	1170	Appendix 5	Include line to separate the table row prior "Genotoxicity"	format table
AstraZeneca	1172	1215	Appendix 6		
Medicines for Europe	1172	1300	Appendix 6	It would be more consistent to list the leachable monographs in one document.	Include class 1 monographs in supporting documentation.
BioPhorum	1173	1215	Appendix 6: Benzo[a]pyrene	Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), a PDE/AI for mutagenic endpoints should also be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to be used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	Add calculation of PDE/AI for mutagenic endpoints based on carcinogenicity data according to ICH M7.
ELSIE	1173	1215	Appendix 6: Benzo[a]pyrene	Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	Add calculation of PDE/AI for mutagenic endpoints based on carcinogenicity data according to ICH M7.
IPAC-RS	1173	1215	Appendix 6	Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	Add calculation of PDE/AI for mutagenic endpoints based on carcinogenicity data according to ICH M7.
AstraZeneca	1178	1178	Appendix 6	The PDEderived in Appendix 6 for benzo(a)pyrene is fornon mutagenic endpoints. Please can this be made clear in the title, otherwise the nuance might be missed	Consider adding "non-mutagenic" to the title in line 1178
AstraZeneca	1194	1194	Appendix 6	onsider adding "neuro" to the sentence so it reads "Based on critical non-mutagenic effects of BaP, the non-GLP oral neurodevelopmental toxicity study...."This is important since the POD is a behavioural.	Consider adding "neuro" to the sentence
Medicines for Europe	1198	1198	Appendix 6	typo in administered dose	Remove "0,"
AstraZeneca	1199	1199	Appendix 6	Missing letter: "... postnatal day.." should be ".. postnatal days..."	Missing letter "s"
AstraZeneca	1207	1207	Appendix 6	Remove the word "Taking" so the sentence reads better.	
EfPIA	1208	1209	Appendix 6	An F1 for benzo(a)pyrene of 7 was applied for a juvenile rat. Juvenile rat F value has not been included in Q3C or this guideline. A reference to how the F1 was calculated would be helpful as other PDEs could be based on juvenile animals.	Provide details of how the F1 factor for juvenile rats (7) was conducted.

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ELSIE	1208	1209	Appendix 6	F1 (juvenile rat) = 7, F4= 5 (Behavioural effects). These are not in Q3C or Q3D. Need more examples of circumstances where F1/F4 value is not in Q3C/Q3D.	
Hikma	1208	1209	Appendix 6	F1 (juvenile rat) = 7, F4= 5 (Behavioural effects). These are not in Q3C or Q3D. Need more examples of circumstances where F1/F4 value is not in Q3C/Q3D.	
ELSIE	1211	1211	Appendix 6	• Editorial change: "...POD..."	"P~~O~~oD"
ELSIE	1212	1214	Appendix 6	Would appreciate explanation on setting F6 based on MW and LogP.	
Hikma	1212	1214	Appendix 6	Would appreciate explanation on setting F6 based on MW and LogP.	
AESGP	1213	1214	Appendix 5, parenteral calculation table of BaP and Supporting document - Erucamide parenteral PDE derivation	According to the text, for BaP F6 (=10) was selected based on logP of 3.0. Similarly, for in supporting document class 3 monographs, for Erucamide, the same factor was selected for the substance considering a logP of 8.8. It is not clear if a cut off value (e.g. logP>3, Factor of 10 should be used) could be considered for this approach in order to harmonized the selection. Similar values as for oral bioavailability should be established for logP.	approach could be challenged. Add reccomandation/explanation e.g. F of 10 for logP > 3; F of 5 for logP between 0 and 3;F of 1 for logP<1
ELSIE	1213	1213	Appendix 6	• Editorial change: "...physiochemical..."	"…physicochemical..."
ELSIE	1234	1234	Appendix 6	Ln 1179 / 1234: Acute Acceptable Exposure value is applicable to ≤1-month daily administration Ln 1153 Short term administration (i.e., 30 days or less); Ln 84 Fig 2 has Accute / Chronic (intermittent) / Chronic ICH Q3C and Q3D use Short term	Align or Clarify references for Acute/Short term and Intermittent/Chronic (intermittent) within the guidance.
AstraZeneca	1243	1243	Appendix 6	Missing word "as". The sentence should read: "ECHA listed BPA as capable..."	
AstraZeneca	1244	1244	Appendix 6	Typo: "or" should be "of"	
AstraZeneca	1253	1253	Appendix 6	Missing word"A". The sentence should read "A concurrent.."	
AstraZeneca	1265	1265	Appendix 6	It states thatNo BPA-related effects at any dose were observed for adult mating, fertility orgestationalindices, ovarian primordial follicle counts, estrous cyclicity, pre-coital interval, offspringsexratios or post-natal survival, sperm parameters or reproductive organ weights or histopathology(including the testes and prostate). Therefore, if there were no effects at any dose for the repro tox endpoints - why isn't the NOAEL for reproductive toxicity 3500ppm (~600 mg/kg/day)? There is no explanation as to why it is300 ppm (~50 mg/kg/day) in the text.	Reconsider the NOAEL for repro toxicity.
ELSIE	1265	1265	Appendix 6	no BPA-related effects at any dose was observed for reproduction. Why the NOAEL is at 300ppm.	
Hikma	1265	1265	Appendix 6	no BPA-related effects at any dose was observed for reproduction. Why the NOAEL is at 300ppm.	
ELSIE	1267	1268	Appendix 6	• Editorial change: In table: "F3 (POD study duration: 4 months)"	"F3 (P~~O~~oD study duration: 4 months)"
ELSIE	1270	1270	Appendix 6	• Editorial change: "...POD..."	"P~~O~~oD"
ELSIE	1274	1275	Appendix 6	• Editorial change: In table: "POD"	"P~~O~~oD"
ELSIE	1274	1275	Appendix 6	• Editorial change: In table: "F3 (POD study duration: 4 months)"	"F3 (PoD study duration: 4 months)"
ELSIE	1286	1287	References	• Editorial change: "Accessed April: 2025"	"Accessed: April÷ 2025"

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ELSIE	1292	292	References	• Editorial change: "Accessed April: 2025"	"Accessed: April÷ 2025"
ELSIE	1299	299	References	• Editorial change: "Accessed April: 2025"	"Accessed: April÷ 2025"
Pharmapol-Arzneimittelvertrieb-GmbH	35	35	2	It is stated that this guideline is not intended for products used in clinical research stages. Question:At which point of time during developing of a new drug product shall E&L assessment be conducted?	Add an exploratory note.
Pharmapol-Arzneimittelvertrieb-GmbH	84	85	3.2	Absorption via mucous membranes respectively sublingual route is missing.	Add missing routes
Pharmapol-Arzneimittelvertrieb-GmbH	89	91	3.2	Is the compliance with relevant regional food-contact safety regulations only accepted for polymeric substances? Why not for all kind of materials?	Add examples for other materials
Pharmapol-Arzneimittelvertrieb-GmbH	166	170	3.4	To our understanding "prior knowledge" could be the comprehensive safety assessment of the supplier of the packaging component/system with certificates of compliance to food packaging regulations and/or pharmaceuticals. In this case E&L studies should be considered as not necessary.	Certificates of compliance of the supplier of packaging components/systems are condsidered as appropriate data package.
Pharmapol-Arzneimittelvertrieb-GmbH	181	182	3.4.1	Why is a cumulative assessment only described for multiple manufacturing systems? The same could be addressed when multiple changes are applied in the packaging system, e.g. container closure system. The possibe leachables of all changes (manufacturing and packaging components) could be assessed together, respectable could be investigated in one cumulative leachables study.	Rephrase accordingly.
Pharmapol-Arzneimittelvertrieb-GmbH	237	241	3.6	Does this mean that, when intending to change an excipient next to the necessary stability and compatibility testing additional leaching studies with multiple batches over the complete life span are necessary? Was the feasability considered? This would mean, that if a specific excipient is no longer purchasable and need to be exchanged to a different excipient with the same function, that production can only be continuend after several years until the shelf-life long leachable study is completed? This would mean that a specific drug product cannot be sold for multiple years resulting in underprovisioned patients.	If an excipient is exchanged with a different well-established excipient, but of same action (e.g. binder, filler, and lubricant etc.) and comparable purity a theorectical risk assessment of possible leachables will be sufficient.
Pharmapol-Arzneimittelvertrieb-GmbH	242	248	3.6	Does this mean, when a container closure system, a delivery device or manufacturing component need to be changed leaching studies with multiple batches over the complete life span are necessary? Was the feasability considered? This would mean, that if a specific item is no longer purchasable and needs to be ordered from a different supplier or need to be exchanged to a different item with the same function, that the production can only be continuend after several years until the shelf-life long leachable study is completed? This would mean that a specific drug product cannot be sold for multiple years resulting in underprovisioned patients.	If the supplier of an item (e.g.container closure system etc.) is changed, or if an component (e.g. container closure system etc.) is exchanged with a different well-established system, but of same quality a theorectical risk assessment of possible leachables will be sufficient.
Pharmapol-Arzneimittelvertrieb-GmbH	244	244	3.6	Does this mean, when a component (excipient, container closure system or manufacturing system) needs to be ordered from a different supplier leaching studies with multiple batches over the complete life span are necessary? Was the feasibilty considered? This would mean that the production can only be continuend after several years until the shelf-life long leachable study is completed? This would mean that a specific drug product cannot be sold for multiple years resulting in underprovisioned patients.	If the supplier of an item (e.g.container closure system etc.) is changed, or if an component (e.g. container closure system etc.) or an excipient is exchanged with a different well-established system, but of same quality a theorectical risk assessment of possible leachables will be sufficient.
Pharmapol-Arzneimittelvertrieb-GmbH	249	253	3.6	Changes in the manufacturing process might be applied to improve the product quality, increase the yield, due to limited availability of raw materials, to safe engery and/or to protect worker and the environment. The guideline requires for smaller changes which do not influence the product quality & purity shelf-life long leachables studies as necessary. Please consider, that several smaller changes might be applied within a certain timeframe, which would lead to ongoing shelf-life studies and the fact, that a specific drug product will not be available for a long time resulting in underprovisioned patients.	For changes in the manufacturing process, for which can be proven by using appropríate analytical techniques, that the quality and purity of the drug product remains the same, a theorectical risk assessment of possible leachables will be sufficient.
Pharmapol-Arzneimittelvertrieb-GmbH	355	358	4.4	It is stated, that multiple batches shall be used within stability respectively leachable testing. How many batches are needed?	For a new container closure system, the number of studies should be comparable to the number (2) as requested by the variation guideline Commission Regulation (EC) No 1234/2008.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Pharmapol-Arzneimittelvertrieb-GmbH	490	490	6.1	The explanatation of the abreviation "SCT" is missing	Please add the explanation.
Pharmapol-Arzneimittelvertrieb-GmbH	513	514	6.1	Threshold values for sublingual application route is missing.	Add missing values.
Pharmapol-Arzneimittelvertrieb-GmbH	705	705	7	The word "DART" and its explanation is missing	Add missing information
Pharmapol-Arzneimittelvertrieb-GmbH	731	731	7	The word "NAM" and its explanation is missing	Add missing information
Pharmapol-Arzneimittelvertrieb-GmbH	988	991	Appendix 5	What does it mean that toxicity studies for a leachable may be deemed as last resort? Was the feasibility considered? It might be difficult to either extract a sufficent amount of the leachable substance or to produce the molecule needed for animal testing. And what kind of toxicity study will be needed?	In the case a toxicity study is considered for an unknown leachable molecule, an acute oral toxicity study delivering an LD50 value shall be sufficient. In the case that the conduction of a toxicological study is considered, but no reference substance for the identified leachable is purchasable other evaluation tools may be used to derive an acceptable exposure level.
Pharmapol-Arzneimittelvertrieb-GmbH	1037	1047	Appendix 5	A large number of computational tools have been published, focusing on Read-Across, (quantitative) Structure–Activity Relationship ((Q)SAR) models, and Physiologically Based Pharmacokinetic (PBPK) models. There are free platforms for computational toxicology assessment, e.g. OECD QSAR Toolbox, Toxtree, EpiSuite and OncoLogicTM, Cefic´s AMBIT Read across tool as well as commercial platforms e.g. DEREK Nexus, SARAH Nexus, CASE Ultra. Therefore, the use of in silico methods should mentioned for the endpoints systemic toxicity and DART as well.	If data are not available, computational toxicity assessment with free or commercial platforms (e.g. OCED Toolbox, Toxtree, EpiSuite, DEREK/SARAH) can be used for evaluation.
PDA	2	4	1	PDA proposes expanding the statement by adding "clinically relevant conditions" to improve clarity and alignment with current standards. Leachables can be released during clinical use and not only under storage or manufacturing.	PDA suggests the following addition: "Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions, and clinically relevant conditions."
PDA	4	6	1	PDA recommends removing "intentionally" and expanding the statement to add clarity and avoid potential misinterpretation. Extractables are obtained under exaggerated extraction conditions to simulate degradation, aging, etc. Perhaps consider discussing compromised extracts and how far or how aggressive the extracts should be replicated in order to still remain realistic to worse case conditions.	PDA proposes the following edits: "Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions that are replicating worst-case scenarios or/and exaggerated extraction conditions and thus are potential leachables."
PDA	35	37	2	Section 2 states that clinical research stage products are out of scope, but principles may apply in high-risk cases.	PDA recommends providing guidance regarding how sponsors should determine when these principles are applicable during early development.
PDA	38	39	2	As stated, it is unclear why radiopharmaceuticals are listed as out of scope for this gudiance document. PDA suggests clarifying why radiopharmaceuticals are not considered in scope and/or highlighting what would raise a concern. The risk factors for radiopharmaceuticals should follow those of other pharmaceutical products based on route of administration.	If it is not feasible to provide requested clarification and guidance for the reader, PDA recommends the following addition: "Generally, radiopharmaceuticals are not considered in scope, unless there is a specific cause for concern based on the risk factors identified in this guideline."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PDA	73	74	3.2	PDA suggests adding "polarity" because it is an important factor for consideration and should be noted.	PDA recommends the following addition: "The leaching propensity of the formulation, including but not limited to API, **polarity**, pH, organic co-solvents and surfactant/chelating agents."
PDA	86	89	3.2	References to USP Chapter <1665> Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biohparmaceutical Drug Substances and Products and Biophorum's 2018 document Leachables: Best practices guide for evaluating leachables risk from polymeric single-use systems should be included because these resources provide risk-based testing guidance which would be beneficial to the reader.	PDA suggests the following additions to the text: "Depending on the anticipated risk and leveraging prior knowledge, various approaches can be adopted ranging from compliance with relevant food-contact safety or pharmacopeial standards/regulations (e.g., USP <1665>, "Biophorum Leachables Best practice (2018)" (see Table 1)) to an appropriate risk based level of more extensive E&L characterization and safety risk assessment (See Appendix 1)."
PDA	89	89	3.2	PDA recommends updating the statement to be more inclusive so all formulations of oral drug products are addressed. Semi-solid oral products are often not considered with regards to extractables and leachables. If the statement is not updated, readers may assume that this only refers to liquid or solid oral products and not consider other forms such as semi-solids.	PDA proposes the following edits: "For **all dosage forms of** oral drug products, compliance with…"
PDA	94	96	3.2	PDA suggests expanding the statement to include guidance that a risk assessment should determine the appropriate actions to take.	PDA recommends the following addition: "For all other drug products, or for oral products that do not comply with the regulations for food contact in terms of composition, specification, and in-use limitations, extractable/leachable assessments are typically warranted. An initial process based risk assessment should be conducted to determine whether extractables or leachables data are required."
PDA	112	113	3.3	PDA proposes clarifying how to quantitate the "potential occurrence of leachables". Proposed sentence provides guidance that the potential occurrence of leachables comes from extractables data. What is typical is that the highest amount of an extractable observed could be the potential amount as a leachable, as a worst case.	PDA recommends adding the following sentence: "Quantitate the potential occurrence of leachables in the drug product and assess the patient exposure to leachables. This is performed using well-designed extractables studies following the principles in this guideline and the maximum observed extractables."
PDA	151	151	3.4	During extractables screening, compounds are identified and semi/quantified if they are above the Safety Concern Threshold (SCT) for the drug product, using the lowest detection limit possible for the analytical instrumentation used. If the Analytical Evaluation Threshold (AET) is greater than the SCT, then Class 1 leachables could be present but missed if below the AET. For this reason, PDA suggests that the SCT should be used.	PDA proposes the following update: "For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Safety Concern Threshold (SCT) Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5)."
PDA	160	163	3.4	If an authentic reference standard does not exist for an identified extractable, then one cannot fully determine its response factor (RF). If one does not have an RF, then picking a compound with a similar response is left up to too many variables and subject to too much interpretation, depending on the method used. PDA proposes that it would be better to give a protective (overestimated) semi-quantitative result in such cases until a reference standard is available.	PDA suggests the following edits: "However, if authentic reference standards do not exist, compounds with a similar analytical response responses reasonably believed to be lower than the extractables in question should can be employed. This is a protective approach due to not being able to determine the response factor of the extractables in question. If extractables concentrations quantified in this manner are then below the relevant acceptable safety level (see Section 6), then safety concern associated with leachables risk is considered negligible."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PDA	181	182	3.4.1	As written, when the statement is applied to all single-use/multi-use materials that touch the bioprocess could lead to the expectation that this is costly and difficult to achieve comprehensively. If scope or focus is limited to materials downstream of final clearance step, this becomes more practically acheivable. PDA proposes augmenting the wording to keep focus on final container or bioprocessing steps downstream of final clearance step.	PDA recommends the following addition: "When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should be assessed for components downstream of the final clearance step."
PDA	192	194	3.4.1	Particulate formation is a common challenge observed in both legacy and new biological drug products. Leachables can pose significant risks to biological drug products through chemical interactions, potentially leading to secondary toxicity effects. These interactions might result in the formation of particulates, compromising drug safety and efficacy. It is also recommended to be more inclusive to any container made of glass not just pre-filled syringes.	PDA proposes the following changes: "If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered (such as denaturation, aggregation, or degradation, or particulate formation in primary packaging pre-filled syringes)."
PDA	199	201	3.5	Based on the statement from lines 488-490 in this guidance which indicates the following: "A risk-based scientific evaluation is needed to provide confidence that any potential leachables in the drug product are at levels where they pose negligible risk to the patient. Within this overall risk-based evaluation, the focus of the safety assessment is the toxicological evaluation of leachables in the drug product exceeding a predefined SCT for that drug product."; any extractable/leachable below the SCT, by definition, does not present risk. Therefore, PDA proposes updating the statement to say "at or above the SCT" for correctness.	PDA suggests the following edits: "Registration applications should include the justification for the extractable/leachable studies conducted, the associated study reports, the safety assessment of substances at or above the AET SCT and any requisite risk control strategy."
PDA	212	216	3.5	The text suggests different requirements are needed for the submission of extractables and additional data for leachables. Although supporting information such as analytical method and extraction condition selections along with justifications (solvents, temperature, duration, surface/volume ratio, etc.) and a description of the sample preparation and analytical procedures are needed for both extractables and leachables studies; leachables studies must be included. PDA proposes rewording the statement to offer clarity and avoid confusion.	PDA recommends the following update: "A list of extractables and leachables studies conducted should be included along with an assessment report which will typically include analytical method, and extraction condition selections along with justifications (solvents, temperature, duration, surface/volume ratio, etc.), for extractables studies and a description of the sample preparation and analytical procedures for extractables and leachables studies."
PDA	216	218	3.5	PDA proposes adding a reference to the International Council for Harmonisation's *Q2(R2) Guideline on Validation of Analytical Procedure to provide readers a resource that provides specific* recommendations regarding method validation procedures.	PDA suggests the following edits: "In addition, the quantification procedure(s) should be described including the suitability of the procedures used for quantification (e.g., limit of detection (LOD), limit of quantification (LOQ), specificity, linearity, accuracy, and repeatability). Refer to ICH Q2 (R2) for additional guidance."
PDA	218	221	3.5	As proposed in the comment to lines 199-201, PDA recommends evaluating this statment to verify that "AET" is the correct term versus "SCT". Based on the statement from this guidance from lines 488-490 which indicates the following: "A risk-based scientific evaluation is needed to provide confidence that any potential leachables in the drug product are at levels where they pose negligible risk to the patient. Within this overall risk-based evaluation, the focus of the safety assessment is the toxicological evaluation of leachables in the drug product exceeding a predefined SCT for that drug product."; any extractable/leachable below the SCT, by definition, does not present risk. Therefore, PDA proposes updating the statement to say "at or above the SCT" for correctness and referring the reader to Section 6 on SCT content.	PDA suggests the following edits: "All extractables and leachables peaks **at or** above the ~~AET~~ **SCT** (see Section ~~5~~ **6**) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level."

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PDA	224	227	3.5	Manufacturers only collect data post-mitigation therefore the recommendation to collect data before and after implementions is not applicable to all formats. PDA recommends deleting the last portion of the sentence to make the statement more representative of current industry practice.	PDA encourages the following deletion: "Finally, the adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation, where this is appropriate for the container closure system and dosage format."
PDA	249	253	3.6	It is important to address reprocessing and/or reworking steps. Reprocessing/rework steps like re-filtration in the event of mechanical failures or failure of filter integrity during filtration of final drug substance and drug product need to be addressed as a process change. PDA recommends calling this out explicitly, as reprocessing can be proactive or reactive to an event.	PDA proposes the following edits: "Changes to a manufacturing process: Changes to process conditions may cause different leachables or different amounts of leachables from the existing formulation contact material. For example, change in solvent system, duration, temperature, pressure, pH, cleaning/sterilization process, surface area/volume ratio, pre-operation preparation (e.g., flushing), amongst others can affect both the composition and amount of leachables. In addition, any reprocessing of drug substance or drug product (e.g., rework or additional processing steps following an initial manufacturing run) should be considered a process change that may add additional leachables alter the leachables profile and and therefore warrants re-evaluation. A detailed assessment shouldall be performed before proceeding to the next process steps."
PDA	273	273	4.1	PDA suggests expanding the bullet to include clarification that biological reactivity testing is not part of typical extractables and leachables testing and can be performed by the drug product manufacturer, if applicable.	PDA recommends the following addition: "• Biological reactivity testing **(can be performed either by the component supplier or by the drug product manufacturers)**"
PDA	292	293	4.3	PDA proposes expanding the definition of extractable study to add more context and clarity for the reader.	PDA encourages the following update: "An extractable study is a process by which chemical entities are extracted from a test article under a worst-case scenario and/or exaggerated extraction conditions in order to simulate degradation, aging, storage conditions, etc., and potential leachable substances that can be released."
PDA	296	297	4.3	For component extractables data, referenced in Section 4.2, there may only be a reporting limit at the time the data is generated; application of the AET by the sponsor would come at the time the sponsor is trying to use the component/system. PDA recommends changing the wording of line #296-297 to reflect this to avoid potential confusion.	PDA recommends the following edits: "Key **considerations** ~~characteristics of an adequate extraction study~~ **for the generation and application of extractables studies include:**"
PDA	308	308	4.3	For single-use, extractables as a function of "shelf-life" is not generally considered a significant risk or expectation for additional data representing end of shelf life. As written, this language may create an undue expectation for data.	PDA proposes removing single-use from the scope of this guidance. If not feasible, PDA proposes the following change of wording to improve clarity: "• Represents the drug product specific worst-case scenario for leachables occurring during manufacturing or arising from packaging components/systems during shelf life of the drug product (e.g., contact area, temperature, duration). For critical items such as packaging components, assessment should include impact of shelf life."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PDA	314	314	4.3	PDA suggests expanding the statement to add more clarity.	PDA recommends the following addition: "The extractables report describes details on analytical procedures, **treatment of data, and data analysis"**
PDA	321	323	4.3.1	For single-use applications, the statement from lines 321-323, "A semi-quantitative extractables study may be appropriate in scenarios where a leachables study will subsequently be conducted..." seems to imply the expectation that the USP <665> Plastic Components and Systems Used to Manufacture or Biophorum aligned extractables data (i.e., that employ semi-quantitative extractables studies) are not adequate to address the risk and/or must be supported by additional leachables studies. PDA propopes to update the statement to clarify this expectation, keeping the leachable scope focused to the final container.	PDA encourages the following update: "A semi-quantitative extractables study may be appropriate in scenarios where a **primary packaging** leachables study will subsequently be conducted to establish the acceptablity of materials for intended use."
PDA	330	330	4.3.1	In this context "semi-quantitation" is a more accurate description.	PDA recommends the following change: "• **Semi-**quantitation ~~Quanitification~~ of observed extractables against relevant standard compounds."
PDA	340	341	4.3.2	PDA recommends adding clarification regarding the use of authentic or justifiable surrogate standards because these are needed to achieve "identical or similar" responses. The proposed update also aligns the statement with standard industry terminology.	PDA encourages the following edits: "Quantification of the identified extractables above the AET using **authentic or justifiable surrogate standards** ~~standards with identical or similar analytical response~~."
PDA	359	362	4.4	The use of the same lots of components between extractables and leachables may be difficult. Additionally, it has not been common industry practice to include multiple lots in extractables studies; the importance of lot-to-lot matching is unclear if one needs to use multiple lots for leachables studies. PDA proposes to add flexibility to this statement to ensure it is understood by the reader as a recommendation and not taken as a requirement. Proposed update would temper the expectations that the ideal conditions are always feasible.	PDA suggests the following addition: "Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables. However, this may not be possible in some cases due to the time elapsed between extractables and leachables studies and the availability of materials."
PDA	455	457	5	The statement on lines 455-457 does not seem to take into consideration that standardized extractions studies may be generated with a reporting limit, and not in conjunction with an AET. The AET may not be known at the time the extraction study is performed, but that does not invalidate the study; proposed update will clarify this for the reader.	PDA proposes the following addition: "An extraction study should include the establishment and application of an AET (or reporting limits) to indicate extractable chemical entities to be detected, identified and reported as potential leachables for the drug product."
PDA	481	482	5.1	It would be beneficial to expand the statement and clarify the circumstances in which it would be acceptable to use an uncertainty factor (UF) no greater than 0.5. Additionally, PDA proposes to expand the statement to state that a UF of 0.5 is appropriate when there are subsequent studies that are executed to reduce risk.	PDA recommends expanding the statement to: "Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5. An uncertainty factor (UF) of 0.5 is acceptable for use in semi-quantitative analytical methods when a subsequent quantitative method or leachable evaluation is utilized."
PDA	526	528	6.2	Materials that use bisphenol A (BPA) as precursors (such as polycarbonate (PC), polysulfone (PSU), and epoxies) have been heavily used in bioprocess equipment (e.g., connectors, fittings, etc) for decades. This language, which uses the words "may leach", could be interpreted to imply that one should avoid/replace these materials versus taking a more risk-based approach to how these materials are used. PDA recommends modifying the language to reduce potential misunderstanding.	PDA proposes the following edits: "For such Class 1 leachables, it is considered most practical to avoid the use of materials which may leach such compounds (see Section 5).Materials known to contain Class 1 leachables should be included in the risk assessment considering the process risk and propensity for leaching."

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PDA	540	541	6.3	The safety assessment is a toxicology assessment and as written it seems redundant and could be confusing. PDA recommends removing "If toxicologically justified". If not feasible to remove, it would be helpful to give examples as to what would be "toxicologically justified". Many limitations come from analytical (e.g., mass spectral quality due to low response), PDA proposes to make the statement clearer, delineating between analytical and toxicological justifications for partial or tentative identifications.	PDA suggests the following edits: "If toxicologically justified, Partial partial elucidation providing tentative structures may inform a safety assessment in certain cases, such as excluding high-risk compounds (e.g., potentially fully assigned (PFAs) or nitrosamines, potentially not assigned/partially not assigned (PNAs))."
PDA	565	574	6.3	The read-across approach is encouraged but lacks specific criteria for surrogate selection. Additionally, it would be benefical to add additional information when the read-across or NAM-based toxicology is sufficient without further in vivo data. Providing references for the reader on this approach would be helpful, such as the 2023 article from the Regulatory Toxicology and Pharmacology Journal: Harmonisation of read-across methodology for drug substance extractables and leachables (E&Ls).	PDA encourages adding additional guidance regarding this approach such as a checklist or decision tree for how to choose a surrogate.
PDA	595	597	6.4.1	In lines #595-597, the statement "any leachable present" may be overly broad given the capability of analytical methods to detect down to the ppb range. This expectation may be unnecessary, because in certain cases such low concentations would not be of concern. It is recommended to direct the reader to evaulate the risk posed by the specific leachable that is under evaluation.	PDA encourages providing additional guidance regarding this statement to make the intent more clear. Proposed updates provided below: "A qualitative safety assessment may be required, of any leachable present should be provided, since such leachables may be of relevance even when for leachables present at a concentration below 20 ppm, depending on the risk posed by the specific leachable."
PDA	691	693	7	PDA recommends updating the definition of AET to clarify that it is a concentration threshold and to distinguish from exposure (or dose)-based thresholds. This recommendation also aligns with the general comment regarding AET.	PDA suggests the following updates to the AET definition: "The **concentration** threshold **at or above** which an extractable or leachable should be identified, quantified, and reported for safety assessment."
PDA	719	722	7	PDA encourages updating the definition for Lowest-Observed (Adverse) Effect Level (LO(A)EL) to parallel that for No Observed (Adverse) Effect Level (NO(A)EL). In particular, it is recommended that the definition should indicate that it is the lowest dose that causes any statistically or biologically significant adverse effects compared to a control group.	PDA proposes the following updates to the LO(A)EL definition: "The lowest exposure (or dose) of a substance in a study or group of studies that produces at which there is a statistically or biologically significant increase in adverse effect frequency or severity of any (adverse) effects in the exposed humans or animals population compared to a control group."
PDA	735	738	7	In alignment with the comment to lines 719-722, the definition of No Observed (Adverse) Effect Level (NO(A)EL) should parallel that for Lowest-Observed (Adverse) Effect Level (LO(A)EL). In particular, it is recommended that both the LOAEL and the NOAEL are typically defined as a dose, not a concentration.	PDA recommends the following updates to the NO(A)EL definition: "The highest concentration or amount exposure (or dose) of a leachable or extractable that does not cause any substance in a study or group of studies at which there are no statistically or biologically significant increases in (adverse) effect frequency or severity in the exposed population compared to a control group."
PDA	802	805	Appendix 1	PDA proposes another action "diamond" to Figure 4 to allow a decision step regarding if the initial risk ranking warrants the need for extractable/leachables data. This would allow the user to take into account process risk and conditions, such as those listed in USP <1665> and BioPhorum's Leachables Best Practice document, with the output to establish whether only basic safety (compendia tests) or extractables evaluation (or in high risk cases, full leachables testing) is required.	***Attached figure below shows proposed addition.

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PDA	829	829	Appendix 1	In Table A.1.2: Examples For Abbreviated Data Package for Packaging and Delivery Device Components, Example 3 may not be correct considering the changes that will be coming to ISO 10993-1 and the change to how exposure categories will be calculated. Regardless of the type of contact, there will likely still be a need to identify pyrogenic, mutagenic, and genotoxic risks from "short/transient" contact. Also, it is important to note that "short" and "transient" are not terms that will be used in ISO 10993-1:2025 to describe contact durations. PDA proposes updating the verbiage to align with upcoming definitions for device contact durations. Anything that is repeated daily or intermittently used will automatically have a contact category of "prolonged" due to having more than 24 hours of contact.	PDA proposes the following udpates: "Delivery device components with limited very short/transient contact with oral drug products (e.g., oral syringes, oral dosing cubs), due to being used only once and which are compliant with regional food contact regulations."
PDA	905	905	Appendix 3	PDA encourages reevaluating this formula for accuracy. It does not appear that the units match up correctly if using "doses per drug product batch". Using the formula as written results in a unit of ug/day*dose. Correction to formula is proposed for consideration.	PDA suggests the following edits to the formula: "AET (µg/mL drug product) = SCT (µg/day) × UF ÷ Maximum dose in a day (mL**/day**)"
PDA	955	956	Appendix 1	Suggest to amend the title of this table to indicate this is an example list. Many similar compounds to those listed are not included in the table.	PDA proposes the following edit: "**Example** Class 1 Leachables to be avoided"
PDA	957	985	Appendix 4	Suggest to amend the title of this table to indicate this is an example list. Many similar compounds to those listed are not included in the table.	PDA proposes the following edit: **"Example** Class 3 Leachables With Relatively Low Toxic Potential (Chronic Parenteral PDE ≥ 1 mg/day). Monographs In Supporting Documents."
PDA	1132	1136	Appendix 5	There seems to be a general lack of information on this new variable F7 factor. It would be helpful to the reader to provide specific criteria to be considered in establishing similarity and to be applied in selecting the appropriate value for F7. Additionally, in the text it states "based on the criteria described in this guideline"; it would be helpful to provide a specific internal reference for where the reader can find the applicable gudiance to F7.	PDA encourages adding a a short example be provided for F7 similar to what was done for F6. PDA also recommends providing a detailed intext reference directing the reader to where the applicable criteria in the guidance can be found.
Julie Boberg, Novo Nordisk	544	546	0.25138889	Improvement of Fig 1 suggested. See inserted object below (line 84 of commenting template)	See figure
Boehringer Ingelheim	20	22	2.	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	Propose to align with Figure 5 and e.g., lines 822-823 to clarify scope.
Boehringer Ingelheim	35	39	2.	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definiton of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/
Boehringer Ingelheim	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment".	Propose to adapt Figure 1 accordingly
Boehringer Ingelheim	60	61	3.1.	Sentence is somewhat unclear on requirements for products in clinical trainls	Propose to add " for approved products"
Boehringer Ingelheim	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. Especially for small-scale components, the relative surface area in contact with the formulation can be disproportionately high, potentially increasing the leaching propensity. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as “small parts”—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Boehringer Ingelheim	85	85	3.2	Exposure time is deemed a relevant factor to be considered in the risk matrix. Suggest to add exposure time to Figure 2, e.g., for a fluid path of a medical device	e.g. for a fluid path of a medical device; short / long contact time
Boehringer Ingelheim	89	96	3.2	As for oral drug products, the risk for topical other than ophthalmic administration is regarded low both in the EMA Guideline for plastic immediate packaging matierials and the FDA Guidance on Container Closure Systems for Packaging Human Drugs and Biologics. In both guideline requirements for safety are the same as for oral DP.	Propose to add topical other than ophthalmic, not only oral DP
Boehringer Ingelheim	166	172	3.4	This is an example for an abbreviated data package: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
Boehringer Ingelheim	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Prpopse to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA
Boehringer Ingelheim	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of asessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
Boehringer Ingelheim	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focussed on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements
Boehringer Ingelheim	205	207	3.5	If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.
Boehringer Ingelheim	212	216	3.5	Please clarify if a **list** of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated?	It is not clear which documentation shall be submitted. Propose to provide a bullet-point list instead of a narrative focussing on general expectations and to reference ICH M4Q for details.
Boehringer Ingelheim	218	221	3.5	It is unclear how to report prior knowledge on extractables and leachables in the filing submission.	Propose to include guidance on reporting prior knowledge on extractables and leachables in the filing submission.
Boehringer Ingelheim	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5
Boehringer Ingelheim	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, **outside previously tested worst-case conditions,** may cause different leachables or different amounts of leachables from the existing formulation contact material."
Boehringer Ingelheim	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	
Boehringer Ingelheim	285	286	4.2	Non-lyophilized solids are described as an example for dosage forms which exhibit a minimal propensity for leaching. Also lyophilized solids show a low risk for interaction. Drug product is reconstituted and administered within a short time-period and the duration between filling and lyophilization is also short.	It is proposed to give further examples like lyophized or frozen DPs.

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Boehringer Ingelheim	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
Boehringer Ingelheim	326	326	4.3.1	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
Boehringer Ingelheim	342	343	4.3.2	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
Boehringer Ingelheim	344	346	4.3.2	If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted.	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
Boehringer Ingelheim	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.
Boehringer Ingelheim	359	361	4.4	It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. It needs some time to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability have to be demonstrated before starting a leachables sudy. In addition, extractables studies can be performed product independently. So they can be performed long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	Proposal: The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be be used.
Boehringer Ingelheim	406	408	4.5	Clarify the meaning of „qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
Boehringer Ingelheim	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient.
Boehringer Ingelheim	504	506	6.1	Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list

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Boehringer Ingelheim	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addtion of SCT in Table 1 would be helpfull to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity threshholds subcutaneous? --> For clarfication add comment to local toxicity threshholds " Only applicable for certain scenarious - see chapter 6.4"	An addtion of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day
Boehringer Ingelheim	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5.
Boehringer Ingelheim	538	539	6.3	In addition to leachables also potential leachables should be assessed 1.in order to inform on target leachables 2.in case of abbreviated data package (refer to chapter 3.4 and Appendix 1 Table A.1.2	Add potential leachables
Boehringer Ingelheim	544	545	6.3	Figure 3 The starting point is not correct, because the AET based on the SCT is for organic leachables and not for elemental impurities. Only class 1 elemental impurities are considered, while all other elenmental impurities are not considered here.	Recommend to revise the workflow: Starting point "List of identified and quantified potential leachable or leachable", then go to decision point "Is the compound an elemental impurity?" if yes go to "Evaluate in accordance with ICH Q3D", if not go to decision point "Compound exceeding AET based on SCT" go on as described in the current flow chart.
Boehringer Ingelheim	544	545	6.3	Figure 3 In the field „further risk assessment": The duration of use and route of exposure are already considered when selecting the SCT or QT from table 1.	Recommend to remove "duration of use and route of exposure"
Boehringer Ingelheim	560	564	6.3	Sentence not complete/understandable.	Propose to adjust to: "Conversely, if data do not sufficiently support the safety of the leachable, further action is needed, which can include reduction of the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level."
Boehringer Ingelheim	595	597	6.4.1	This statement is interpreted, that a complete assessment for every potential leachable is required without a SCT. Guidance is missing how to calculate the AET. Is the proposed PDE calculation intravitreal applying a factor of 1/500 x parenteral PDE deemed applicable (Lovsin-Barle et al 2019)?	Kindly either provide a threshold for injections into ocular tissue or esp. Intraventrial or use 20ppm for all ophthalmic dps.
Boehringer Ingelheim	676	682	6.5	Chapter 6.5 For ICH S9 products, the TTC would not be applicable and the SCT would be defined by the QT. By this statement, only systemic toxicity is addressed for ICH S9 products.	It is proposed to add verbiage that the SCT is derived from QT or local toxicity threshold, whatever is lower.
Boehringer Ingelheim	690	763	7.	Chapter 7. Glossary Glossar missing abbrevations MDD, NAM, AI	Propose to add definitions
Boehringer Ingelheim	690	763	7.	Chapter 7. Glossary Following definitions are not included: packaging, primary packaging secondary packaging and Container Closure System	Propose to add definitions and ensure the right terms are used throughout the document and not interchangeably

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Boehringer Ingelheim	802	802	Appendix 1	Figure 4 In case of any extractables above the AET, two options are described: Identify extractable(s) above AET and quantify against proper standards as decribed in 4.3.2: "For the quantification of identified extractables ABOVE the AET standards with identical or similar analytical response should be used." or Conduct a leachables study according to 4.4: using "reference standards, if available". However, in case of unavailabilty of reference standards, e.g., for oligomers, one can only apply estimated analytical responses in both types of studies, which always include analytical uncertainty. So one can neither fully quantify these compounds as extractables nor as leachables, only semi-quantitative extractable or semi-quantitative leachable studies are possible.	Proposal: Allow the option to use uncertainty factors for quantitative extractables studies in case of unavailability of reference standards in section 4.3.2. Or allow this option in Appendix 1, figure 4.
Boehringer Ingelheim	815	816	Appendix 1	Figure 5 In several sections of this guideline abbreviated data packages (without leachables studies) also for packaging and delivery device components are described, however these possibilities are not implemented in Figure 5: In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Reasons for low risks of leachables are explained by the risk matrix in figure 2: Also for packaging materials risk factors like leaching propensity of the formulation, dosage form and storage temperature should be considered. For example, an aqueous solution without or with only low amounts of surfactant stored at cold temperature would minimize the risk for leaching which can be demonstrated by extraction studies using a solvent with the same or higher extraction propensity than the drug product and appropriate extraction time and temperature mimicking long term storge at cold temperature. In addition, a low dose and intermittent or acute treatment would lower the risk. If no critical amounts of extractables were determined, i.e. potential leachables or probable leachables obtained under justified worst case drug product conditions, then no target leachables can be defined.	The workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components should be adapted adding a decision point "any individual EXTRACTABLES above the AET?" If yes add the option to assess identified EXTRACTABLES OR perform a leachables study.
Boehringer Ingelheim	815	816	Appendix 1	Figure 5 The impact of leachables on the product quality should already be assessed by information about extractables i.e. potential leachables, e.g., to inform compatibility studies. However , it should be considered that E&L studies are triggered by safety levels. Also levels below safety thresholds can impact the drug product quality. In those cases the workflow is often the other way round, first an impurity or degradation product is detected in a stability study and then leachables are assessed as one potential source.	The product quality assessment should be described in a separate workflow
Boehringer Ingelheim	829	838	Appendix 1	Table A.1.2 Only examples for oral drug products are described , where "Components may be considered qualified without additional extractables or leachables testing." However, according to the footnote further examples can be considered: "*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. " This approach is also supported In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" and section 4.3.2. For a better understanding and more clarity these eamples should be added in the table.	It is proposed to include further examples for non-oral drug products: Container closure system components for small volume parenteral drug products with cold storage or aqueous inhalation solution with low dosage: 1 No packaging or delivery device components extractables above the applicable AET in a semi-quantitative extractable study -> Components may be considered qualified without additional leachables testing. 2 All packaging or delivery device components extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) > Components may be considered qualified without additional leachables testing.

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Boehringer Ingelheim	830	830	Appendix 1	Refer to Table A.1.2, in example 3: "short/ transient contact" is not defined. Furthermore this should also be valid for parenteral DPs, not just oral DPs	Suggest to provide a definition of "short/ transient contact" Propose to add another example of an abbreviated data package for a parenteral drug product e.g., administered using a CSTD
Boehringer Ingelheim	862	866	Appendix 3	Intermittent dosing: Many monoclonal antibodies are administered at a once every three weeks (q3w) schedule. Assuming daily dosing and using the daily QT would also not be adequate in this case.	Please include a suggestion for q3w (or q2w) dosing or allow ≤ 1 month QT as well.
Boehringer Ingelheim	939	942	Appendix 4	"Class 2 is the default leachable classification and includes compounds for which the chronic parenteral administration thresholds for mutagenicity (TTC) and systemic toxicity (QT)." It is not only the default for parenterals.	Remove "parenteral"
Boehringer Ingelheim	955	956	Appendix 4 Class 1 Leachables	Values for Benzo(a)pyrene considered to be too high, Refer also to comment to line 1173ff, Appendix 6: Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	
Boehringer Ingelheim	957	959	Appendix 4 Class 3 Leachables	What is the rationale for selection of these Leachables? Proposed to take up further compounds, e.g. Irganox 1076 (Broschard et al. 2016), Irganox® 1010, Irgafos® 168, Butylated hydroxytoluene (Parris et al. 2020), see also ELSIE database	Consider to include more substances
Boehringer Ingelheim	957	959	Appendix 4	Is the PDE only for parenterals? Is the interpretation correct, that parenteral is worst case and e.g., for inhalative or oral dosage, higher amounts may be tolerated.	Please include explanation how this table should be used.
Boehringer Ingelheim	980	982	Appendix 5	Substances classified as class 3 in ICH Q3C should also be mentioned as examples for class 3 leachables	Include ICH Q3C class 3 compounds as class 3 leachables.
Boehringer Ingelheim	1072	1074	Appendix 5	"...the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose": Why maximum daily dose? Rather route of administration is assumed to be correct reference here.	Please provide further explanation
Boehringer Ingelheim	1107	1107	Appendix 5	The given Range ("≥ 1% and <50% (divide by a modifying factor of 10)") is consideres a wide range….	Propose to allow adjustment of factors depending on the bioavailability.
Boehringer Ingelheim	1125	1127	Appendix 5	"… a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes, respectively": please clarify: 70% for organic, 50% for water-based or dispersed dilutes? 50% for water-based dilutes would be relatively high and not considered "sufficiently conservative" when extrapolating from dermal to parenteral administration (see e.g., https://pmc.ncbi.nlm.nih.gov/articles/PMC7027575/), only if extrapolating from parenteral to dermal.	Please provide further explanation
Boehringer Ingelheim	1173	1215	Appendix 6: Benzo[a]pyrene	Benzo[a]pyrene is correctly described as mutagenic carcinogen, but has no AI calculated in ICH M7. As TD50s are relatively low (e.g., 0.956 mg/kg/day in Rat, Gold TD50 in Lhasa Carc DB), also a PDE/AI for mutagenic endpoints should be calculated. According to risk levels calculated in Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Benzo[a]pyrene (and an own quick AI calculation based on the TD50), the AI would be lower than the calculated PDEs. Therefore the calculated PDEs based on non-mutagenic endpoints would be too high to used as SCT. Or: If the AI was calculated higher than the PDE for non-mutagenic endpoints by the authors, this should be mentioned as well.	Add calculation of PDE/AI for mutagenic endpoints based on carcinogenicity data according to ICH M7.
Boehringer Ingelheim	0	498	6.1	Typo Add verb: is	As such, in addition to amount of exposure, the SCT **is** dependent on both route and duration of exposure

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Boehringer Ingelheim	0	553	6.2	Typo Start new paragraph at "Subsequently…" as this relates to all leachables, and not only to the Class 1 leachables at the beginning of the paragraph.	
Boehringer Ingelheim	0	1079	Appendix 5	Typo ", if justified…": separate with ; or .	; if justified

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