EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/CHMP/SWP/364535/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (EMA/CHMP/ CVMP/ SWP/169430/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Arevipharma GmbH Bayer Pharma AG BASF PharmaChemikalien GmbH & Co. KG Merck KGaA (Chemicals)
2	European Federation of Pharmaceutical Industries and Associations (EFPIA)
3	Association of the European Self-Medication Industry (AESGP)
4	Active Pharmaceutical Ingredients Committee - Cefic
5	Allergy Therapeutics (UK) Ltd
6	Martin Patrick Hughes, Ph.D.
7	The BioPhorum Operations Group (BPOG)
8	Bulk Pharmaceutical Task Force (BPTF) of Society of Chemical Manufacturers and Affiliates (SOCMA)
9	Maarten Prause, CARBOGEN AMCIS AG
10	Vetter Pharma-Fertigung GmbH & Co. KG
11	Cancer Research UK
12	European Allergen Manufacturers Group (EAMG)
13	European Industrial Pharmacists Group (E.I.P.G.)
14	LS, Department in charge of setting ADEs/PDEs, OELs
15	International Society for Pharmaceutical Engineering (ISPE)
16	Gedeon Richter Plc.
17	GlaxoSmithKline

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Stakeholder no.	Name of organisation or individual
18	International Federation for Animal Health (IFAH-Europe)
19	Laboratoire BIODIM
20	Eli Lilly and Company
21	Lofarma S.p.A
22	Merck KGaA (Chemicals)
23	Merck Sharp & Dohme (MSD)
24	PharmaConsult Us, Inc.
25	SciencePharma
26	Stallergenes
27	Recipharm Stockholm AB
28	Xiphora Biopharma Consulting
29	EMA Guideline Consistency Group (GCG)

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	Industry are in agreement that dedicated facilities are not required if a health-based limit can be appropriately established and met. While the overall approach and direction of this draft guideline is positive, a number of revisions are essential to ensure that the agreed upon methodology is feasible and pragmatic for the pharmaceutical industry yet ensures patient safety. Workshop: Many comments have been received from industry members on the draft guidance, and this EFPIA response presents only the key observations. Industry understands that there is a firm commitment from the EMA to conduct a practical workshop between agency and industry to work through the guidance. In view of the complexity of this topic, such a workshop is strongly advocated by industry, timed to take place before guidance is finalised. Assuming there will be opportunity to discuss these during the workshop EFPIA has refrained from submitting all detailed comments received. • Flexibility Industry consider that guidance should allow for flexibility in two key areas: First, the ICH PDE-based approach is an older methodology intended for impurities with sparse datasets. This methodology alone is considered too restrictive for cases where broader datasets are available. Appropriate other methodologies, such as the ISPE Risk-	Accepted Accepted

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	MaPP paradigm for ADEs to address patient safety, should be encompassed by guidance. Second, the guidance would be improved if the methodology recognises that there are a number of reasons why unchanged manufacturing processes of existing products can be adequately risk managed under existing arrangements. Using new methodology for the entire library of existing products would be unmanageable and of no benefit to patients. Allowing some flexibility will focus efforts on the areas of most benefit to patients. • <u>TTC for genotoxicants</u> Industry strongly feels that the approach proposed in the guidance of managing risk at a theoretical 1 x 10^{6} excess lifetime cancer risk corresponding to a limit dose of 0.15 µg/person/day, not appropriate. It is not consistent with the proposals in ICH M7 and there is no logic to distinguish between intrinsic genotoxic impurities arising in the product and genotoxic impurities introduced as a carry-over from a previously manufactured product. Moreover, and in accordance with this notion, ICH M7 also suggests similar TTC levels to be applied in case of leachables and extractables. Thus the 10^{-5} risk level is considered appropriate for all these scenarios. A 10^{-6} requirement would be overly restrictive with no benefit to patients but potentially adverse impacts on manufacturing logistics. • The proposed application of the toxicological methodology is excessively broad in scope as it currently applies to both "old" products having been marketed for many years, and "new" products being either under development or intended to be marketed after implementation of the guideline. The guidance would be improved if the methodology was adjusted such that	Partly accepted; The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified. Accepted Not within the scope of this guideline.

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	the application of the new methodology for toxicological evaluation deriving a PDE or other benchmark is focused on new products and also on existing products undergoing a significant change management process such as a manufacturing site to site transfer. In other circumstances, the guidance should allow existing legacy documentation and procedures to be retained. A diagrammatic flow chart is appended to better explain this point.  Guidance scope (2).pdf	
	• There are a number of reasons why unchanged manufacturing processes of existing products is adequately risk managed under existing arrangements, and the use of a 1/1000 MED which almost always is more conservative than a PDE based approach. In those few circumstances where 1/1000 MED is not appropriate (for example, certain high potency anticancer drugs or DNA reactive compounds, certain hormones and extreme sensitisers), EFPIA member companies already use specific risk management measures. We believe this approach will focus efforts on the areas of most benefit to patients whilst remaining consistent with the spirit of the draft guidance. Using new methodology for the entire library of existing products would be unmanageable and of no benefit to patients.	Not within the scope of this guideline.
	• The guidance should not be used in isolation to determine if dedicated facilities are required - all of the information requested in GMP Chapters 3 and 5 needs to be taken into account.	Accepted
	• **Investigational products**	

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	Industry has considerable concern that in the pre-commercial arena, this guideline is not practicable. Although the IMPs are currently clearly in scope, as currently written it would force industry to change current practices or potentially redesign/ rebuild facilities. The specific problem for investigation facilities stems from the fact that the guideline is based on determining specific limits based on extensive toxicological evaluation of the drug substance, including understanding of reproductive toxicology. In investigational facilities, much of this toxicological data may not be available. In early investigational development, a precautionary approach is typically taken which could be modified later in development as and when additional toxicological data becomes available. For example, this approach can provide a basis for classification of the material into one of a number of handling classes and this can then determine what handling, cleaning and facilities provision are established for manufacture in early development. This can allow for cleaning approaches for example to be set on a fractional (/ 1/1000th of a clinical dose) that is suitably precautionary, given the short duration of the investigational studies undertaken, for all but a small number of cases of concern. Cases of concern, determined on the basis of structural class / indication (e.g. penicillins / beta lactams with known and serious sensitisation properties or human hormones with known class effects) or known toxicology of the drug substance (i.e. Ames positive genotoxic materials used in oncology research) would be handled on a case-by-case basis. If industry comments are adopted into revisions to this guidance, then it may be possible to accommodate IMPs, otherwise the scope of the guideline would need to be modified to exclude IMPs.	Accepted

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	• **Multi-purpose facilities and API manufacture** As written, the guidance does not adequately address circumstances where there are multi-purpose facilities using equipment of variable configuration. If the use of alternative benchmark methodologies was adopted in the guidance, this would allow this concern to be addressed. For example, modern manufacturing technologies frequently make use of containment and/or disposable systems or dedicated parts so as to first manage risk at source. The guidance, as drafted, tends to think on a whole facility level, whereas in fact decisions and management measures need to be first taken at the individual equipment/part level, and the use of a dedicated item of equipment could fundamentally alter the risk assessment as a whole. As a second example, API manufacture tends to use multi-purpose process vessels with variable configurations of equipment for different steps in the synthetic process. Risk of carry-over can be from an intermediate of unknown toxicity into a second intermediate or API. For example, in active substance manufacture a Maximum allowable residue (MAR) calculation can be used based upon the max therapeutic dose (MTD) of the outgoing product, (notwithstanding the use of default values where the MTD is not yet determined). • **Veterinary products** Guidance should not apply in a dedicated veterinary facility. A veterinary product which shares an API with a human product or where the human toxicity is appropriately characterised, can be manufactured in a shared facility with a human product. For the specifics of veterinary products, EFPIA are not commenting in	Accepted Not accepted: Carryover limits will need to be scientifically justified (although see implementation strategy), including in veterinary only facilities.

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	detail; IFAH-Europe should be consulted. **Implementation** EFPIA would like to engage in discussions around an implementation period, as the amount of work resulting from the implementation of the guidance should not be underestimated. Company experts will need time to become familiar with operating and documenting the new methodologies, and presumably, GMP inspectors will also need familiarisation time. The overall implementation time will be critically dependent on the content of the final guidance.	See implementation strategy
3	We understand that this guideline has not been drafted to address cross-contamination issues which would have occurred in practice but rather to recommend a more scientific approach based on the pharmacological and toxicological profile of the substances. We believe that both the approach described in this guideline --which we will call "**PDE approach"** -- and the current widely accepted approach **should co-exist and be considered as equivalent and equally acceptable approaches. Companies should be able to chose the approach they want to follow**. We think it is appropriate to keep the current approach i.e. criterion	Accepted

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	(e.g. 10 ppm) concerning the risk evaluation as part of the cleaning validation process. On that basis it can be decided whether the manufacturing of the respective medicinal product should be executed in dedicated or in shared facilities. Particular APIs and corresponding medicines (penicilins, certain antibiotics, certain hormones, highly sensitizing substances etc.) may benefit from following the PDE- approach but again this decision to choose the current or the PDE approach should be left to the company. The PDE- approach should in any case not be required for *all* medicinal products and *all* active substances but should be an option for companies that chose to follow it e.g. by the producers of certain hazardous contaminants such as highly sensitising materials (such as beta lactams), biological preparations (e.g. from live micro-organisms), certain hormones, cytotoxics, and other highly active materials. Applying the proposed guideline to all APIs and finished products would be excessive and would engender unnecessary high cost with minimum value added. The possibility of a dual approach would not be new as in another field the ICH Q8 guideline already offered the possibility for companies to choose between a so-called “traditional approach” and a more “enhanced approach”.	Not accepted: The approach adopted will need to be adequately and scientifically justified. Partly accepted: While Chapters 3 and 5 in Part I of the GMP Guide are not applicable to Active Pharmaceutical Ingredients (APIs) the general principles outlined in this guideline to derive a threshold value for risk identification could be applied where required.

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	More flexibility with the use of higher PDE values in specific cases should be possible. For example, • when compounds with the same mode of action (e.g. all cytotoxic anticancer drugs, or all ACE inhibitors), or when only veterinary products are produced on the facility; • or in the case that substances subsequently produced in the facility are for single/short term administration (see also comment above) and/or for use in specific subpopulations only (e.g. for early clinical studies in male subjects).	
	We suggest that a transition period of 2 years for implementation of the guideline is inserted for companies deciding to follow the PDE approach. This should allow sufficient lead time for the implementation of the PDE approach to future compounds, products and processes to companies. The setting of PDEs for concerned compounds/products and potential change of the processes will be a complex and resources-intensive exercise.	Partly accepted: see implementation strategy
	Under the PDE- approach, we propose that a public database for PDEs on compendial products should be established to avoid the use of multiple PDEs for the same compounds. This would avoid that companies derive their 'own' PDEs for the same compendial compounds or similar drug products, which may lead to different PDEs in different companies. The current draft guideline suggests that the final acceptability might	Not accepted: At this point in time a public database is not envisaged but may warrant further discussions in time.

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	only be given at cGMP inspections. As decisions regarding specific measures, such as containment or dedication, may be associated with significant investments an earlier agency feedback, e.g. during MAA review or at time of submission, is deemed preferable in the light of potentially required measures and resources that companies choosing to follow the PDE-approach will invest. Introduction. Comment: With reference to our general comments, we consider the general application of this guideline to all APIs and medicines excessive. We strongly suggest that both the current approach and the PDE- approach coexist with companies being free to choose the approach that they want to follow. Proposed change (if any): We propose the following rewording: "*Due to the perceived risk, certain classes of active substances have previously been required to be manufactured in dedicated or segregated self-contained facilities including, "certain antibiotics, certain hormones, certain cytotoxic and certain highly active drugs". **The current approach is as follows**: Pharmaceuticals not considered to be covered under these criteria **can be** addressed by a cleaning validation process involving reduction of the concentration of residual active substance to a level where the maximum carryover from the total equipment train would result in no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured. This criterion **is** applied concurrently with a maximum permitted contamination of 10 ppm of the previous*	Partly accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified. Not accepted: See current wording of the guideline.

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	active substance in the next product manufactured. Whichever of these criteria ***result*** *in the lowest carryover,* ***constitutes*** *the limit applied for cleaning validation.* ***However, a new PDE-approach may be followed that takes into account the available pharmacological and toxicological profile of the substance.*** ***For particular products or particular substances (e.g. certain antibiotics, certain hormones, certain cytotoxics and certain highly active drugs) the current approach may be*** *too restrictive. Hence,* ***for those products and substances*** *a more scientific case by case approach is warranted.* ~~*for all classes of pharmaceutical substances*~~*.* *In order to accommodate a more scientific approach, Chapters 3 and 5 of the GMP guideline have been revised and refer to a "toxicological evaluation" for establishing threshold values for risk identification* ***for particular medicinal products****. The objective of this guideline is to* ***present*** *a* ***new*** *approach* ***(so called PDE approach)*** *to review and evaluate pharmacological and toxicological data of* ***particular*** *active substances and thus enable determination of safe threshold levels as referred to in the GMP guideline.* ***Both current and PDE-approach are equally acceptable.*** *In cases where scientific data does not support threshold values (e.g. allergenic potential from highly sensitizing materials) or where the risk cannot be adequately controlled by operational and/ or technical measures, dedicated facilities are required for manufacturing these high risk medicinal products. "*	

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	Scope Comment: With reference to our general comments, we consider that both current approach and PDE-approach should coexist and companies should be able to chose the approach that they want to follow. Proposed change (if any): The guideline applies to all human and veterinary medicinal products, including investigational medicinal products, and all active substances that are intended for manufacture in premises used for the manufacture of other products or active substances. **Both current and PDE approach have the same aim i.e.** to ensure the safety of human patients and target animals exposed to residual active substances via medicinal products as well as consumers potentially exposed to residual active substances in products derived from treated food producing animals. This document aims to present a **new** approach (so called PDE- approach) for deriving a scientifically based threshold value for individual active substances to be applied for risk identification. This guideline also outlines how the data on which the threshold value is derived should be presented in the risk assessment report in order to achieve a clear and harmonious approach across pharmaceutical **companies choosing to follow the new PDE approach. Both current and PDE-approach are acceptable**".	Partly accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.
4	APIC generally welcomes this guidance on the determination of	Accepted

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	health based exposure limits that can be used to calculate the Acceptance Criteria for cleaning of Pharmaceutical Equipment used for different products and to decide when Dedicated Facilities are required. Further guidance should be considered for Intermediates and other chemicals (like excipients) that can be manufactured in the same equipment as active substances. APIC is aligning its Cleaning Validation Guidance with ISPE Risk Mapp that uses the concept of Acceptable Daily Exposures(ADE) based on No Observed Adverse Effect Levels (NOAEL). We request that the Safety Working Party should clarify that ADE should be regarded as a synonym for PDE s within the scope of this Guidance document. **It is recommended to have a workshop between industry and EMA Inspectors Group and the toxicologists of The Safety Working Party to review the comments and to work through the guidance with specific examples** It is recommended to have a workshop between industry and EMA Inspectors Group and the toxicologists of The Safety Working Party to review the comments and to work through the guidance with specific examples. There should be clear transition time when going from the current methods of defining acceptance criteria for product carry-over to the new proposed calculation.	Accepted
8	Member companies of the BPTF have reviewed the draft guidance and support establishing a clear and scientifically-based standard for	Partly accepted: The general principles outlined in this guideline to derive a threshold value for risk identification

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	cleaning limits in multi-use facilities that manufacture active pharmaceutical substances (APIs). Member companies may contract with various customers to manufacture APIs in all stages from development through commercial, and may also manufacture API intermediates (non-pharmacological chemicals) in the same equipment. Based on our experience, customers' toxicological data sets vary greatly, from quite limited to complete, including human API dose data. This is true for APIs, but is especially true in the case of API intermediates. There are several situations in the guidance that require the use of dedicated facilities in the absence of toxicological data based on the NOEL, leading to significant and unreasonable manufacturing restrictions for APIs and API intermediates. It is suggested that when limited toxicological data exists for a compound, that allowance be given in the guidance for establishing cleaning limits for compounds by using the ADE from NOAEL or other available toxicological data, as discussed in REACH chapter 8 and/or the ISPE Risk MaPP Guidance on limits for different classes of APIs. In addition, and to facilitate the sharing of toxicological data, it would be helpful if the guidance included a requirement for contracting pharmaceutical companies to provide all available data (including bioavailability) to their contract manufacturers to support a proper risk assessment. The use of a compound-specific risk assessment report (Section 4.2)	could be applied where required to APIs. Accepted

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	that provides a harmonized approach for summarizing the data used for the cleaning limit decision is supported by the member companies.	
9	From our experience as a CMO it is extremely difficult to receive the detailed pharmacological and toxicological information from our customers which is necessary to calculate the PDEs. Moreover the PDE calculations performed by different toxicologists often lead to differing results. Therefore we propose the following procedure: EMA should publish the PDE values for the individual active substances on the EMA homepage. The PDEs should be calculated by EMA toxicologists to guarantee a consistent calculation. The procedure for PDE derivation of substances/products in early development phases (non-commercial products) is even more difficult. In this case the CMO depends on the customer who should provide the data for PDE calculation or the calculated PDE. Are the CMOs obliged to verify PDEs calculated by customers?	Not accepted: This guideline should be implemented for all products in line with the implementation strategy outlined. Publishing a list of PDE values is not in the scope of the guideline
11	Cancer Research UK (CR-UK; Registered charity no. 1089464) are the world's leading charity dedicated to cancer research and the largest independent funder of cancer research in Europe. Over half of all cancer research in the UK is carried out by our doctors and scientists and our work is entirely funded by the public. In 2011/12	Accepted

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	we spent 388 million euros on research. The charity's pioneering work has been at the heart of the progress that has already seen survival rates in the UK double in the last forty years. We receive no government funding for our research. **Summary:** Cancer Research UK welcomes the opportunity to respond to this consultation. We are supportive of the proposed scientific approach for establishing permitted daily exposure limits (PDE) outlined in the draft guideline, however, we are concerned that as currently written the guideline presents a 'one size fits all' blanket approach to determining PDEs for all active pharmaceutical ingredients (APIs), investigational medicinal products (IMPs), irrespective of their stage in development, as well as marketed products. We would recommend that additional wording should be added to recognise that for APIs and IMPs early in clinical development, PDEs may be established based on minimal data and a risk assessment. PDEs should then continue to be reviewed and revised in line with new toxicology and clinical data acquired during product development. **Response to consultation:** Cancer Research UK's Drug Development Office (DDO) seeks to develop new treatments for cancer patients. The Office manages and executes drug development programmes from exploratory and preclinical development through to designing, conducting and	

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	monitoring high quality, ethical, early phase (often first-in-human [FIH]) clinical trials. We work closely with the CR-UK Formulation Unit and Biotherapeutics Development Unit, both CR-UK supported manufacturing facilities licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) and specialising in the manufacture and release of small molecule and biological IMPs for testing in early phase trials. These units would be classified as 'shared facilities' in the context of this draft guidance. All trials undertaken by the DDO are sponsored by CR-UK. CR-UK are supportive of the approach outlined in the draft guidance '*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*'. We are, however, concerned that as written the guideline presents a 'one size fits all' approach to cover APIs, IMPs and marketed products and does not take in to account the different levels of toxicological and clinical data available to support determination of a PDE at the different stages of a product's development. Lines 73-75 in the draft guidance state that this guideline 'applies to all human and veterinary medicinal products, including investigational medicinal products, and all active substances that are intended for manufacture in premises used for the manufacture of other products or active substances.' As written this would apply to all IMPs, irrespective of their stage in development. Data availability to support the determination of a PDE will vary considerably for products at each end of the development spectrum with very limited data available prior to GMP manufacture of APIs/IMPs for a FIH clinical trial. From DDO's experience formal GLP toxicology studies to support the clinical study will often be conducted in parallel with GMP	

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	manufacture of the API and IMP for clinical trial use. Only minimal toxicology data to establish a PDE for the API and IMP would therefore be available prior to commencement of GMP work at this stage of development. In addition cleaning validation derived from these assessments may be difficult to perform as analytical methods will also still be in development at this early phase and therefore may not be sufficiently sensitive. In addition, a clearer distinction between product contact surfaces and non-product contact equipment, or facilities, would also be advantageous in the guideline. Line 38 (the executive summary) infers that the guidance applies to surfaces in direct contact with the API/IMP being manufactured; however lines 237 and 269 refers to entire production facilities. The option should be given for the adoption of risk-based approaches to determining the cleaning threshold for non-product contact surfaces. Delaying GMP manufacture until additional toxicology information for the API/IMP is available will significantly impact the development timelines for our early FIH trials, increase development costs and potentially delay these new agents benefiting patients. With only a finite budget for development of new drugs this guidance as drafted will limit the number of new FIH IMPs that CR-UK's DDO will be able to bring to clinical trial in Europe. However, we are supportive of the scientific approach for establishing threshold values for risk identification outlined in lines 63-65 of the draft guidance. We would propose that a PDE should be determined for all APIs, IMPs and marketed products based on available data but there should be a recognition that the data available to support the derivation of the PDE for IMPs (and associated APIs) early in	

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	development will be limited. Therefore at this stage we would suggest that the confidence in the determined PDE value should be recognised and supported by a risk assessment. As toxicological and clinical data is then acquired through continued product development the PDE should be revised to reflect this and the confidence in the PDE limit increased. If this approach for early phase trials was not accepted, then the potential requirement for manufacture of both APIs and IMPs in dedicated facilities would be prohibitively expensive, particularly for an organization such as CR-UK.	
12	This guideline together with the revised version of the chapter 3 of the GMP has introduced the notion of “allergenic potential” besides the one of “highly sensitising materials”. Definition of “highly sensitising materials” may need further clarification – most allergens are natural substances that individuals are naturally exposed to every day, without causing any specific adverse effect related to production of allergens for diagnostics and treatment af allergy. Allergenic potential from “highly sensitising materials” is currently illustrated by the beta lactams.	Accepted
13	1. We recognize that the method proposed is based on that described in Appendix 3 of ICH Q3C (R4) and Appendix 3 of VICH GL 18, which were developed for “residual solvents”. 2. We recognize that the risk assessment approach is introduced, being in agreement with the general view of risk	

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	evaluation instead of determining rigid prescriptions. 3. We appreciate that this approach allows a more rational decision in determining the need for dedicated facilities. 4. We observe that this risk assessment requires specific resources in terms of available toxicological data and toxicological expertise for data evaluation. 5. We would consider it to be useful for officially valuable reference sources of toxicity values and data be reported in an Annex of the Guideline, at least for substances on the market for many years. 6. We observe that in the present Annex of the Guideline, the name and the signature of an “Expert” are required: we think that the minimum profile, the responsibilities and the reporting of this “Expert” must be fully defined. 7. Although this risk assessment is to be performed by an expert, the results of the report would represent a key element for a quality assessment and for batch release whose responsibility is by the QP 8. For this reason a clear understanding of the role and responsibilities of these two functions are required. 9. In our opinion, an industrial pharmacist with appropriate experience is ideal for the position of this expert, taking into account that toxicology is part of the pharmacists academic degree.	Partly accepted: The expert should be suitably qualified or have experience in a relevant discipline/area Not accepted: Quality assessment and criteria for batch release are outside the scope of this guideline

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14	The guideline is warmly welcomed and an excellent piece of work overall. Roche has worked with the principles laid down in this guideline for some time and this has proven practicable and successful in practice. **Equivalent approaches have been proposed or used by companies and professional societies (e.g. ISPE) using slightly differing terminology (e.g. ADE, Acceptable Daily Exposure instead of PDE). Existing hazard assessments should be acceptable to the EMA even if the exact terminology used therein does not correspond in every detail to the one proposed in the present guideline.**	Accepted
15	The Guideline suggests the use of prescriptive adjustment factors. Such an approach is restrictive in that it will not allow industry to take advantage of the existing vast quantity of data and science available on medicinal products This approach may also limit future scientific development. A more open risk based approach that encourages industry to use good science rather than trying to fit the very narrow band of prescriptive factors detailed in the document would be more in line with other regulatory initiatives. Proposed change: Allow companies to take full advantage of the science and data they have at their disposal to more accurately select adjustment/safety factors in determining the threshold values. The company would be expected to justify the selection of these factors with the data/science used to determine the threshold values.	Accepted

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	The term NOEL as defined in the document more closely reflects the term NOAEL (no observed adverse effect). This similarity will give rise to confusion. Proposed change: Replace all instances of NOEL to NOAEL (no-observed-adverse-effect) as this more closely reflects the definition provided in the document. Comment: The guideline does not provide any guidance on handling existing products. Specifically, action to be taken should the calculation of the threshold value change the data for any existing product. This could have a huge impact for a global company that manages numerous products in multi-product facilities. No guidance is provided as to the implementation date and what sites would need to do by way of repeat work eg is there an expectation to re-evaluate all existing Cleaning Validation studies? Proposed change: Provide some indication on what the Agency expects relative to existing products in the market. Comment: As this will become a reference text for those who manufacture in third countries for the EU it is recommended that the	Accepted: See guideline for implementation strategy Accepted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	glossary is comprehensive ie not just acronyms. Proposed Change: Glossary to be made comprehensive	
16	Scientifically justified PDE limits should be determined for hormones and cytotoxic materials already available on the market as is in the case of ICH Q3C for residual solvents or EMA Guideline on the Specification limits for Residual Metal Catalysts or Metal Reagents. PDE calculation should be applicable for material missing from the Annex of this guideline. "Highly active material" or "highly potent material" expressions are used even in GMP chapters, but they are not appropriately defined. It should be defined scientifically, quantified with PDE results which type of materials are considered to be highly active or highly potent. The risk assessments should be done by industrial parties, but the approval of shared facilities should be done by the Authorities. The 3rd country shared facilities should be approved by EU Authorities, customer audits are not sufficient. The companies that are planning to introduce hormone containing products into a non hormone plant should inform the customers and corresponding EU Authorities.	Accepted Not within the scope of this guideline
17	GSK welcomes the opportunity to provide comments and feedback on this important guideline as part of the EMA consultation process. We appreciate the complexity to assure assessments are performed by a standard and consistent approach and that the results of such assessments are acted upon in the appropriate manner. To this end we feel the link to 'Threshold of Toxicological Concern' is a welcome association.	Accepted

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	To enhance understanding by those businesses and institutions affected by the development of this guidance, the following general items are suggested as important consideration when the draft guideline is being finalised: The guideline specifically focuses on residues in relation to cross contamination of active pharmaceutical substances; however, it is not clear what to apply if the cleaning process physically destroys the API. This approach is specifically/typically used within the vaccines and biotech environment where total organic carbon is used to determine the effectiveness of cleaning and determination of any residues. It would be beneficial to clarify the scope in relation to this approach. Specifically the scope of the guideline talks about active pharmaceutical substance which is relatively straightforward when relating to small molecule pharmaceuticals; however, some formulation/product types such as vaccines or biotech products could potentially pose a risk that needs to be assessed for example adjuvants. The guideline would benefit from some clarity on these compounds. Scientific justification for health-based limits provides a good baseline for any guideline, however, consideration/ guidance should be given to the 'health-based limits' specifically in relation to 'low potency' APIs that may scientifically yield a limit significantly higher than currently in place and in some instances a limit that would be above the 'visibly clean' limit/criteria currently applied. While common	Not within the scope of the current guideline

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	sense should prevail the guideline should be explicit in what to apply.	
	In the interest of global harmonisation where approaches are aligned but terminology may differ, we would suggest the guideline contains a 'References' section where appropriate links to other guidance could be documented, for example,2010 publication by ISPE entitled "Risk Based Manufacture of Pharmaceutical Products"	Accepted
	The guideline makes reference to concepts for determining PDEs for residual solvents etc; however, as valid are references to determination of occupational exposure limits (OELs). PDE's can be readily determined from OELs	Not accepted: OEL considered inadequate: data for deriving OEL may be used.
	We appreciate the use of Permitted Daily Exposure (PDE) throughout the document as this aligns with the references made; however, this is interchangeable with Allowable Daily Exposure (ADE). Making some reference to this link for example in the definitions would facilitate global alignment of this guideline.	Accepted
	In addition to the comments on the draft, provided above, GSK would like to propose some areas for clarity and support on interpretation for implementation – This could be in the form of a complementary Q&A.	
	1. Calculation of health-based limits will likely result in higher	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	allowable levels of residual contamination on product contact surfaces of equipment in shared facilities (for many APIs). How does EMA propose to rationalise the future existence of older and more conservative cleaning validation limits with availability of generally higher limit values?	Not within the scope of the guideline
	2. Is it intended that the health-based limit could be applied to equipment or facilities undergoing decommissioning, sale, or transfer of ownership and use? Is there intent that the health-based cleaning limit could also be applied to general facility surfaces (not intended for direct product contact)?	Not within the scope of the guideline
	3. Previous guidance has mandated dedicated facilities for materials such as 'certain antibiotics, hormones or cytotoxics or highly active drugs'. In cases where it is possible to calculate a PDE (ADE) value for such materials, and cleaning procedures can demonstrate reduction of the 'contaminant' below the PDE (ADE) level, can these products be manufactured in a shared facility?	Partly accepted: The determination of the PDE is just one part of the risk-based approach to manufacture of medicinal products using shared manufacturing facilities in accordance with Chapters 3 and 5 of the GMP Guide.
	4. More guidance is required on the application of these adjustment factors F1-F5, and its scoring – Examples of use	Accepted
	5. What is the difference between compounds with "no discernible threshold" versus "no threshold"?	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	6. Currently certain materials, for example beta Lactams are currently restricted to dedicated facilities, if the risk based assessment demonstrates that the compound poses no risk or below the threshold set for manufacture in dedicated facilities would the use of shared facilities be accepted?	Partly accepted: The determination of the PDE is just one part of the risk-based approach to manufacture of medicinal products using shared manufacturing facilities in accordance with Chapters 3 and 5 of the GMP Guide.
	7. How would it be perceived going from a current tight control to a less restrictive one based on a scientific risk assessment?	Partly accepted: The determination of the PDE is just one part of the risk-based approach to manufacture of medicinal products using shared manufacturing facilities in accordance with Chapters 3 and 5 of the GMP Guide.
	8. For changeovers which involve different route of administration, e.g. inhalation to oral, can an example be provided for better clarity? Logically, changeovers from an inhalation to oral API should result in a larger PDE.	The more conservative approach should be considered.
18	IFAH-Europe welcomes the opportunity to comment on this guideline and would like to share the issues of concern for the veterinary industry. A science-based approach to setting exposure limits is the most appropriate from a scientific standpoint to ensure that the limits are sufficiently protective for health, and not unnecessarily stringent. However, its practical implementation in the Animal Health industry raises serious concerns in some situations. The Animal Health industry produces small batch sizes for hundreds of multispecies products: this is a key differentiation from the Human Health industry. The implementation of the current version of the GL for veterinary	Partly accepted – The guideline aims to outline a scientific approach for the determination of appropriate carryover limits and was developed in response to a need identified by GMP inspectors. Fundamental questions relating to the need to move away from the existing approach are not within the scope of the guideline and are considered to be GMP issues. However, it seems that having a harmonised approach for human and veterinary medicinal products will offer advantages in some situations and disadvantages in others. From a scientific point of view it makes sense to have harmonised requirements as many substances are dual use. Having veterinary specific requirements could lead to difficulties for the industry as manufacturers are expected to

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	products to the same level as in human products will be denying this specificity and will negatively impact this industry. The implementation of the GL would necessitate substantial workload and cost in each GMP site to establish the toxicological evaluation and assessment report, to conduct an expert review and maintain the record of the risk assessment. It will not simplify the rules governing manufacturing sites, it will contribute to decreased medicines availability in Europe and decrease the competitivity of EU GMP facilities for exported products. We support the establishment of a harmonised approach with the Human Health sector provided that requirements are proportionate to the size of the Animal Health market, that it is economically viable for the Animal Health companies, that sector specificities are recognized and that it improves Health and medicines availability.	focus on the requirements for the larger human industry. While the new approach does require a toxicological evaluation, if it allows sharing of facilities where dedicated facilities would otherwise have been required, this would presumably be considered as an overall gain. Efforts have been made to address specificities of the veterinary industry. In particular, one of the complications presented in relation to veterinary medicines is the fact that different PDEs could be calculated for each relevant species. However, a pragmatic approach is taken in the guideline, with the human PDE being taken as the starting point from which to calculate carryover limits, regardless of the species for which the product is intended. This is consistent with the approach taken in the VICH residual solvents guideline (VICH GL 18). Furthermore, an extended implementation period has been given for veterinary medicinal products.
	We would also like to highlight the unique Animal Heath MRL Regulation when compared to the Human Health sector that provides a specific toxicological assessment applicable and available for about half of the veterinary compounds (products for food producing animals). The MRL risk assessment process sets an Acceptable Daily Intake (ADI) for active substances and could be cross-referenced in order to avoid repeating an internal risk assessment to set a permitted daily exposure (PDE) in many situations.	Accepted – the guideline does not rule out the use of alternatives to the PDE. If an ADI has been established it would be reasonable to use this.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	This GL mentions both veterinary and human medicinal products, but does not specifically address the manufacture of both in the same facility. It would be appropriate in this document to indicate that a science-based approach (*i.e.* deriving a PDE or using TTC) sufficiently addresses any human safety concerns for manufacture of both veterinary and human medicinal products in the same facility, as long as the risk can be adequately controlled by operational and/or technical measures. Appropriate science-based derivation of a human safety threshold (i.e. PDE, TTC) for any chemical entity ensures safe limits for carryover into a human medicinal product. This scientific concept remains true regardless of the intention for which the medicinal chemical is manufactured. Thus, it is acceptable in terms of objective safety to manufacture veterinary and human medicinal products in the same facility if a science-based human safety threshold has been established for the veterinary substance.	Accepted - the approach described would be applicable in facilities that manufacture both human and veterinary medicines (as well as shared facilities that manufacturing only human or veterinary products)
	Consequently the previously accepted categories for dedicated facilities and campaign manufacturing (including comments in Annex 4) for VMP's should be maintained (see proposal below). Products already established within manufacturing should continue to be justified based upon existing rationale with the amended guidelines being used to control the introduction of new products. **Proposal**: CATEGORY 01: Dedicated and self-contained facilities are mandatory *inter alia* for: • Cytotoxics /Cytostatics.	Not accepted – carryover limits will need to be justified based on scientific principles, as described in the guideline (although see implementation strategy for timelines). However, it is expected that, in many cases, existing carryover limits will be shown to be safe and so can continue to be used.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• Beta-lactam antibiotics*. • Radiopharmaceuticals (see annex 3). • BCG vaccine and for the handling of live organisms used in production of tuberculin products (see annex 2). • Other highly sensitising genotoxic or teratogenic materials. *The requirement for dedicated facilities may be dispensed in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross contamination and any risk to operator safety in accordance with the guide (annex 4). CATEGORY 02: Manufacture on a campaign basis is possible after positive risk-evaluation *inter alia* for: • Antibiotics i.e. of any class other than Beta-lactam antibiotics. • Hormones e.g. peptide and steroid hormones. • Immuno-suppressives. Ectoparasiticides (see annex 4).	
	Although the concept of restricting contaminants to levels safe for all populations is appropriate for Veterinary products which enter the food chain this is not necessarily appropriate for companion animal products (*i.e.* products used in animals with no impact	Not accepted – it is not considered practical to have different approaches for different species.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The guideline should make it clear that the risk assessment report including the PDE/TTC calculation needs to be available to GMP inspectors and should not be an integral part of the registration dossier.).	Accepted – The introduction to the guideline explains that it relates to the "toxicological evaluation" referred to in chapters 3 and 5 of the GMP Guide.
19	Comment: never is written in the text that the cleaning of the production equipment is / should be validated ; its efficiency should be validated whose main purpose is to fight against cross-contamination, whatever the active is "dangerous" or not…it is a basis obligation Proposed change (if any): add 2 case Comment: who is supposed to fill in the annex? Who is responsible ? The manufacturer (often without a regulatory department or no regulatory survey) or the contractor (MAH ? …)	Not accepted. This is not in the scope of the guideline. Please refer to GMP requirements.
20	Eli Lilly supports the EMA in this effort to provide consistency and clarity for the development and communication of exposure limits. Eli Lilly agrees that approaches to establishing acceptable exposure limits should be the result of a scientific evaluation by an expert who considers relevant toxicology and pharmacology data. A guideline with recommendations for how to consistently approach derivation of acceptable exposure limits is valuable, however appropriate, case-by-	Accepted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	case, expert judgment will still be necessary.	
22	Merck generally welcomes this guidance on the determination of health based exposure limits that can be used to calculate the Acceptance Criteria for cleaning of Chemical and/or Pharmaceutical Production Equipment used for different products and to decide when Dedicated Facilities are required. Further guidance should be considered for Intermediates and other chemicals (like excipients) that can be manufactured in the same equipment as active substances.	Partly accepted: Not within the scope of the guideline but the same approach would be supported.
23	MSD strongly supports EMA's efforts to develop clear guidance on conducting toxicological assessments to support quality risk management programs. We also believe that any technical guidance should be consistent with good science and the principles set out in ICH Q9. Decisions regarding cleaning validation, acceptance limits and the need for dedicated facilities should be risk-based, reflecting all available toxicological and pharmacological data and current state-of-the-art exposure limit setting methods, and should be well-documented. We also understand EMA's concern for potential inconsistencies in the way companies derive and apply health-based limits (e.g., acceptable daily exposure values or ADEs). Regardless of the terminology used (e.g., ADE vs. PDE) it will be important for EMA to capture the best science and state-of-the-art with respect to identifying the critical endpoint(s), sources of uncertainty and application of appropriate safety or uncertainty factors. The challenge will be to provide guidance on each factor that is not overly prescriptive, but ensures	Accepted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	consistency (e.g., within a range of values) while allowing for the appropriate use of expert judgment. There are a number of guidance documents that recommend specific factors and methods for applying them. Good science should prevail over prescriptive use of a rigid system of adjustment factors. Examples of current approaches for using data to replace default adjustment factors are 1) the use of chemical-specific adjustment factors (CSAFs), as recommended by IPCS/WHO, and 2) the reliance on the Threshold of Toxicological Concern (TTC) concept for genotoxic substances and compounds with limited data. Application of the TTC concept to the reproductive toxicity endpoint based on published literature is feasible. In cases where the data permit, default uncertainty factors can and should be replaced with data-derived values. If used, these alternative approaches should be clearly described in the documentation. Any system for setting safe levels of exposure must allow for incorporation of expert judgement, supported by sound data and science, and well documented. The specific comments below are intended to make the guidance document as clear as possible and to reflect current risk assessment terminology (e.g., use of NOAEL vs. NOEL). We realize that the proposed terminology and methods were extracted from the guideline on residual solvents, several other more recent guidelines contain terms and methods more closely reflecting the state-of-the-art in risk assessment used in the EU and other parts of the world. We commend EMA for developing guidance to ensure consistent application of science-based approaches to setting health-based limits using the best science and all available data. The toxicologists	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	in pharmaceutical companies have significant experience setting safe levels of exposure to ensure both patient and operator safety. The methods we use reflect current science and risk assessment methods. It would be inappropriate and unnecessary to revise the acceptable daily exposure (ADE) values in our existing exposure limit monographs to align with the prescriptive methods outlined in this guideline. Although the concept of restricting contaminants to levels safe for all populations is appropriate for veterinary products which enter the food chain this is not necessarily appropriate for companion animal products (i.e. products used for animals with no impact on food chain). Consequently the reference to all populations should be modified to indicate 'or target species' as appropriate. Similarly the estimation of standard bodyweight for a veterinary product, where mg/kg is not specified, of 1 kg is needlessly worst case. Provision should be made to estimate the bodyweight for specific target species. We would welcome any opportunity to collaborate with EMA toxicologists working on the guidance document, through teleconferences, focus group meetings and consultations, workshops or other venues, to ensure that the final document is scientifically sound and finalized according to the proposed timeline. Collaboration on the final version of the guidance document will ensure that it incorporates the best science on setting health-based exposure limit, which is in the best interest of both EMA and industry.	
24	The guide should allow for the use of other methods to determine threshold values (such as ISPE's ADE) as long as good science is	Accepted

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	applied. The current use of the F factors from ICH Q3C may negate data obtained from scientific studies used to determine the safety of the compound by the prescriptive nature of the these factors. Comment: ICH Q3C clearly states that "The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs." So by expanding the definition of PDE to include other APIs confusion will arise in expanding the use of the PDE term. Proposed change (if any): Change PDE to Health-Based Exposure Limits or use the Threshold Value (more generic terms) throughout. There is confusion on the term NOEL in the document as the definition within the document more closely reflects the term NOAEL (no observed adverse effect). Proposed change (if any): Replace all instances of NOEL to NOAEL (no-observed-adverse-effect) as this more closely reflects the definition provided in the document.	
25	It is fully agreed that for many substances a thorough evaluation of all clinical and non-clinical data is the only way to derive a reliable threshold. It seems however that for APIs well known not to be connected with neither any significant toxicity nor sensitizing potential, a simplified approach with the use of a generic threshold would be the best option to avoid unnecessary work. If agreed more	See previous comments on APIs

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	data on such an approach would be very helpful. Exemplary assessments for APIs representing a wide selection of risks (i.e. for APIs connected with either significant or very little risk) would be highly helpful. Of particular importance would be examples of assessments where NOEL data are lacking.	
27	From a medical product life cycle perspective the responsibility for the development of PDE:s must be clarified. The production of especially mature products but also of new products is in many cases outsourced to contract manufacturing organizations. The scientific knowledge from clinical pharmacological data is in most cases consequently not in the hands of the companies that manufacture the medical products. It is not a good idea if contract manufacturing organizations develop PDE:s since their access to clinical pharmacological data is limited. Our suggestion is that this Guideline clarifies that “the owner” of each medical product is responsible for developing the PDE:s. Our suggestion is also that PDE:s shall be a part of the Material Safety Data Sheet for each active compound. In api manufacturing there are intermediates and by-products before finally crystallizing the pure api. The toxicological and pharmacological knowledge from this intermediates and by-products are extremely limited. The interpretation from this guideline is that almost all api:s shall be manufactured in dedicated equipment? This is impossible!	Not accepted: The determination of the PDE is just one part of the risk-based approach to manufacture of medicinal products using shared manufacturing facilities in accordance with Chapters 3 and 5 of the GMP Guide.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The really highly hazardous medicinal compounds are today manufactured in dedicated equipment/plant according to the principles in PIC/ S PI006-03. In section 7.6.2 states “Dedicated equipment should be used … for products with a high safety risk….” Furthermore, in Section 7.11.3(d) is the paragraph “For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products. The linking between PDE and the critical cleaning validation principles must be clarified. Especially if highly hazardous medicinal compounds that previously were manufactured in dedicated equipment from now on can be introduced in shared facilities. Equpiment knowledge, api behavior knowledge, excipient behavior knowledge and specific chemistry used for cleaning are critical to avoid cross contamination. If focus is on PDE calculation instead of performing critical cleaning validation activities on a properly manner, the patient protection from highly hazardous contaminants in medicinal products will decrease.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	This Guideline shall be limited to highly hazardous medicinal compounds/products. If “the 1/1000 from the therapeutic dose calculation” for a medicinal compound is “to stringent” in comparison with a developed PDE for this compound the criterion for visually clean will apply anyway. PDE calculation for non- highly hazardous medicinal products will not enhance either the patient protection or the effectiveness for the companies with respect to cleaning between products.	Not accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
5-7	27	Comment: This Guideline is applicable just for highly hazardous medicinal products. Proposed change (if any): Change title to: "Guideline on setting health based exposure limits for use in risk identification in the manufacture of **highly hazardous** medicinal products in shared facilities"	Not accepted: See implantation strategy
5-9 Footer Page	10	Comment: Why a standard body weight of 50 kg should be used? For ADE calculation according to ISPE Risk Mapp a standard body weight of 60 kg is used. Proposed change (if any): A harmonised standard body weight of 60 kg should be used.	Accepted
35	17	Comment: The Executive Summary, as a potentially stand-alone abstract of the more complete text, would benefit from mention that the considerations of this guidance are intimately related to Chapters 3 and 5 of the EU GMP guideline. This is mentioned in lines 63-64	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		as part of the Introduction and again in lines 87-88. Proposed change (if any): Add to the Executive Summary a brief mention that the guidance under discussion relates to EU GMP guidelines in Chapters 3 and 5.	
36, 39, 52, 269,	10	Comment: It is not clear what is meant with the term 'facility '. Proposed change (if any): Please specify the terms 'facility'. Is dedicated facility the same as dedicated equipment? What's about the surrounding area? Do the PDEs apply only to equipment with direct contact to the product?	Outside the scope of the this guideline.
36-39	24	Comment: Cleaning is not the only manner in which cross contamination can occur. Other methods are by mix-up, mechanical and airborne transfer. Proposed change (if any): Hence, residues of an active substance may be available to contaminate other medicinal products produced in the same facility by one or several modes; mix-up, retention, mechanical	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		transfer or airborne transfer.	
42-44	8	Comment: Add the option to use an Acceptable Daily Exposure (ADE) from available toxicological data. Proposed change (if any): The derivation of a threshold value (permitted daily exposure (PDE), acceptable daily exposure (ADE) or threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation … .	Accepted
42-45	15	Comment: A rational for not using other values such as Acceptable Daily Exposure (ADE) or Acceptable Daily Intake (ADI) as a threshold valve is not provided. Proposed change (line 42) : The derivation of a threshold value (permitted daily exposure (PDE), acceptable daily exposure (ADE), acceptable daily intake (ADI)) or threshold of toxicological concern (TTC)) should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data.	Accepted
42-45	20	Comment:	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Nomenclature for the acceptable threshold value could be broadened to include possible synonyms. Proposed change: "The derivation of a threshold value **(synonyms include** "permitted daily exposure" (PDE), **"acceptable daily exposure"** (ADE), **and "acceptable daily intake" (ADI))** or a threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation of ~~all~~ available pharmacological and toxicological data ~~including~~ **that may include** both non-clinical and clinical data."	
42-45	23	Comment: EMA should not expect to see prescriptive terminology such as the permitted daily exposure (PDE) in company exposure limit monographs. For many years, companies have established health-based limits using good science but may refer to them as acceptable daily intake (ADI) values, or more recently acceptable daily exposure (ADE) values as a result of collaboration with the US FDA during the completion of the ISPE Risk-MaPP baseline guide. Companies should not be expected to rewrite documentation solely to change the terminology used if the underlying science and use of NOAELs/LOAELs, uncertainty factors, bioavailability	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		correction, TTC, etc. are consistent with the guideline. Proposed change (if any): The derivation of a health-based exposure limit, such as permitted exposure limit (PDE), acceptable daily exposure (ADE) or that derived using the Threshold of Toxicological Concern (TTC) concept, should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data.	
42-44	4	Comment: Include the option to use Acceptable Daily Exposure (ADE) as a synonym for PDE. Proposed change (if any): The derivation of a threshold value (permitted daily exposure (PDE), acceptable daily exposure (ADE) or threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation. PDE and ADE should be regarded as synonyms.	Accepted
42	18	Please amend the sentence to read: "contaminants should be restricted to a level that can be considered safe **either** for all populations **or the target species as appropriate**."	Not accepted – the existing sentence, shown below, appears in the Executive summary and is considered acceptable as, if there is no exposure (to species other than the target species) there will be no risk. "*Hence, the presence of such contaminants should be managed according to the risk posed which in turn are related to levels that can be considered safe for all*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			populations."
43-44	18	**Comment:** This revised wording reflects fundamental differences between PDE and TTC concepts. New TTC values are not likely to be derived; instead a TTC value would be assigned based on widely-accepted and expertly-derived thresholds. **Proposed change:** We suggest revising to "The derivation of a threshold value (permitted daily exposure, PDE) or **application of a** threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation…"	Partly accepted – it is accepted that there will not be routine derivation of TTC values. While the text in the Executive summary remains unaltered it is considered that in subsequent sections, where reference is made to use of TTC values, it is clear that the values used have to be widely accepted.
46	5	Comment: Definition of "highly sensitising materials" needs further clarification – most allergens are substances that individuals are exposed to every day without causing any adverse effect. Will there be a list of "highly sensitising materials" Proposed change (if any):	Accepted
46	26	Comment: This guideline together with the revised version of the chapter 3 of the GMP has introduced the notion of "allergenic potential" besides the one of "highly	Not accepted. It is not in the scope of the guideline to draw a list of sensitising materials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sensitising materials". There is a need to define "allergenic potential" because the "allergenic potential from highly sensitising materials" is currently illustrated by the beta lactams. Is there an official list? Proposed change (if any):	
48 and 70	17	Comment: The term "high-risk medicinal products" in reference to certain products which could be contaminants is somewhat misleading in the sense that risk is invoked only as a function of exposure, which is to be controlled in this context by use of dedicated facilities. Proposed change (if any): Suggest substituting the term "high-**hazard** medicinal products" to replace "high-risk medicinal products".	Partly Accepted: Reference to high-risk medicinal products removed
48	18	We suggest adding to the end of this paragraph: "In order to recognize the specificity of the veterinary sector (size, fragmentation of products, several species, ADI established database adopted by CVMP from MRL regulation for many actives), the "toxicological	Not accepted. Carryover limits will need to be scientifically justified (although see implementation strategy).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		evaluation" might be conducted in case of specific class of actives where a risk for the animal/human with potentially contaminated drug product is described by the scientific community /in the site and when an ADI has not been established. In other situations, the maximum permitted contamination of 10 ppm of the previous active substance in the next product manufactured can apply".	
51-52	10	Comment: It is not clear what is meant by "certain antibiotics, certain hormones, certain cytotoxic and certain highly active drugs". Proposed change (if any): Please define the terms and specify them.	Not accepted: the definition of the high-risk medicinal products is a challenging one and must taken in consideration with a number of factors which will impact on its classification
51	19	Comment: ….in dedicated or segregated or isolated self-contained facilities Proposed change (if any): "or isolated"	Not accepted. Terms sufficiently defined.
52-62	15	Comment: This section implies a narrow focus i.e. to set cleaning limits whereas the detail in the guideline	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		suggests a broader approach i.e. to set limits for managing the risk of cross contamination as a whole. To reflect this broader approach other modes of transfer could be included in this section e.g. mix up, mechanical transfer and airborne transfer. Proposed change (line 52): Pharmaceuticals not considered to be covered under these criteria were addressed by several processes designed to minimize the risk of cross contamination such as mix-up prevention, gowning, decontamination/wipe down of materials and cleaning validation processes involving reduction of the concentration of residual active substance to a level where the maximum carryover from the total equipment train would result in no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured.	Introduction re-written to take account some of these points raised/
52-62	24	Comment: This section implies the document has a rather narrow focus i.e. to set cleaning limits whereas the detail in the document suggests a broader approach i.e. to set limits for managing the risk of cross contamination as a whole. To reflect this broader approach other modes of transfer could be included in this section e.g. mix up, mechanical transfer and airborne transfer.	As per previous point

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Pharmaceuticals not considered to be covered under these criteria were addressed by several processes designed to minimize the risk of cross contamination such as mix-up prevention, gowning, decontamination/wipe down of materials and cleaning validation processes involving reduction of the concentration of residual active substance to a level where the maximum carryover from the total equipment train would result in no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured.	
55	6	Comment: The term “lowest clinical dose” in line 55 is inadequate in that it fails to define the temporal basis for the dose exposure. There seems to be some misalignment in this area among pharmaceutical stakeholders, including pharmaceutical manufacturers, professional associations, regulatory bodies and pharmacopieal groups. A great deal of effort has been invested in clarifying the appropriate exposure basis for the minimum dose (lowest clinical dose), in the interests of sound science, harmonization, patient safety and pharmaceutical supply. For example Technical Report 29 of the Parenteral Drug Association specifies that the appropriate term is the minimum daily dose (MDD). (“The use of a minimum daily dose has a scientific	Not accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		rationale based on normalizing the dosage frequency for the cleaned product and the next product.") The use of a daily exposure basis for the minimum dose has the added benefit of aligning with the conventional practice accepted for toxicity assesments. In fact the current Guideline itself references the "permitted daily exposure (PDE)" in line 43, so the specification of a "minimum daily dose" rather than "lowest clinical dose" in line 55 should be chosen in the interests of internal consistency alone. As further supporting rationale, consider that the purpose of employing the minimum therapeutic (clinical) dose in setting cleaning limits is to ensure that contamination of a given product by carryover from the previously manufactured product will not adversely impact a patient receiving the maximum dose of the given product. The cleaning limit is therefore expressed in terms of the maximum allowable carryover (MACO), which is set to ensure that such contamination will not exceed the toxicologically insignificant exposure limit (TIEL) or the no observed effect level (NOEL). The minimum therapeutic dose (MTD) multiplied by a safety factor (SF; e.g. 0.001 or 1/1000) is in fact a surrogate for the TIEL or NOEL.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Regardless of whether the MACO calculation incorporates the TIEL or NOEL directly, or the MTD x SF surrogate, it is important that terms be consistently applied in such calculations. Thus, both the dose of the given product and the exposure of the potential contaminant should be expressed on the same timeframe (normalization). By convention, a basis of daily exposure is generally applied for toxicity assessments. Examples include: • organic impurities in drug substances and drug products (maximum daily dose, MDD: ICH Q3A, ICH Q3B); • residual solvents (permitted daily exposure, PDE: USP <467> / ICH Q3C); • leachables (PQRI Leachables & Extractables Working Group); • mutagenic/genotoxic impurities (ICH M7 / FDA Draft Guidance on Genotoxic Impurities); • toxicity thresholds for chemicals (acceptable daily intake, ADI: National Toxicology Program); • excipient biological safety evaluation guidelines (USP <1074>: “Acute: exposure to a test agent within a single, 24-hour period. Doses may be single, multiple or continuous during a 24-hour period.”)	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This harmonization is accepted across related industries as reflected in the similarity in approach evident throughout the literature and various guidance documents. Examples include the IPCS (International Programme on Chemical Safety) report on Assessing Human Health Risks of Chemicals: Derivation of Guidance values for Health-Based Exposure Limits (EHC 170, WHO, 1994), the US EPA (IRIS), the US FDA (Red Book) and the USP, and others (see also *Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data*, Layton, D.W.; Mallon, B.J.; Rosenblatt, D.H.; and Small, M.J. Regulatory Toxicology and Pharmacology, 7, 96-112, 1987). Currently, a number of cleaning guidelines and recognized standards have accepted the daily basis timeframe for both the product dose and the carryover exposure in the calculation of cleaning limits (reference APIC-CEFIC *Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants*, December 2000; PDA Technical Report No. 29, *Points to Consider for Cleaning Validation.* See also: *Establishing Scientifically Justified Acceptance Criteria for Cleaning Validation of Finished Drug Products*, LeBlanc, D.A.; Pharma. Technol. 22(10), 136-148, 1998). Therefore the minimum therapeutic dose for the cleaned product should be calculated in terms of daily exposure.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "...equipment train would result in no greater than 1/1000th of the minimum daily dose of the..."	
55	17	Comment: It might be useful to qualify the 1/1000th of lowest clinical dose concept in cleaning validation as historically important by citing the original publication which popularised this concept. Proposed change (if any): Cite the following publication as a reference when discussing the "1/1000" concept – *Reference: G.L. Fourman and M. V. Mullen, Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations, Pharm. Technol. 17 (4), 54-60 (1993).*	Not accepted – not longer relevant as reference to 1/1000 concept has been removed.
57	17	Comment: The use of an upper limit for adulterant carryover is frequently cited as **visually clean** and no more than 10 ppm carry over where rinsate analysis is used **and / or** 100 mcg/swab (25 cm^2 or 2 x 2 inch area swabbed) if direct access and swabbing is feasible. For	Not accepted: no longer cited

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		completeness, the introductory section of the guidance might use both expressions of maximum allowable carry-over. Proposed change (if any): First insert the *proviso* that visual cleanliness must first be achieved. Then cite the following publication as a reference when discussing the 10 ppm or 100 mcg/swab adulterant limits *Reference: R.J. Forsyth, A, Leblanc and M. Voaden, A Single Adulteration Limit for Cleaning Validation in a Pharmaceutical Pilot-Plant Environment, Pharm. Technol. (2007).*	
56-67	20	Comment: We agree that a scientific evaluation is the best approach for establishing threshold values for risk identification. However, we would like to offer that where current processes exist for establishing a threshold value as the lower of a default (e.g., 10 ppm or 1/1000th of the therapeutic dose) or a toxicological or medical assessment, the resulting threshold value would be the most restrictive and could be considered appropriately protective.	Not accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (Add to line 62): "Hence, a more scientific case by case approach is warranted for all classes of pharmaceutical substances. **While restrictive, limits derived from the lower of a default and a science-based evaluation of toxicology/pharmacology data are considered acceptable**."	
59-62	27	Comment: If the 0,001 limit for a non-hazardous substance is significant lower then the PDE limit, in most cases the visually clean requirement will be the most stringent criteria anyway and the costs for cleaning and cleaning validation will not decrease. Using PDE solely for such products may effect the strength of the next product. Is the visually clean requirement not taken into account in this Guideline? Proposed change (if any): Line 61; Erase "all classes" and replace with "highly hazardous". The sentence will read: Hence, a more scientific case by case approach is warranted for all highly hazardous pharmaceutical substances.	Not accepted: The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
63-64	9	Comment: The draft guideline refers to contaminating an active substance with another active substance only, whereas this is an exception in multi-purpose equipment for chemical synthesis of drug substances, where in most cases a multi-step synthesis leads to an API. Contamination of an intermediate by an active substance or by another intermediate or contamination of an active substance by an intermediate is not addressed in the guideline. For the mentioned types of contamination no toxicological or pharmacological data will be available for establishment of a threshold in the majority of cases. Question: Does the fact that risk of contamination of or by synthetic intermediates respectively, is not addressed, imply that alternative risk identification methods may be used?	Partly accepted: The general principles outlined in this guideline to derive a threshold value for risk identification could be applied where required for APIs.
68-69	5	Comment: Same comment as above Proposed change (if any):	See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
68-69	12	Comment: Same comment as above Proposed change (if any):	See above
68-69	26	Comment: Same comment as above Proposed change (if any):	See above
70	18	Please amend sentence to read:"…dedicated facilities **or equipment** are required for manufacturing…."	Accepted – the following text is now included in the Executive summary: *"Due to the perceived risk, certain classes of medicinal product have previously been required to be manufactured in dedicated or segregated self-contained facilities…"*
71	18	We suggest adding to the end of the paragraph: "In order to recognize the specificity of the veterinary sector (size, fragmentation of products, several species, ADI established database adopted by CVMP from MRL regulation for many actives), the "toxicological evaluation" might be conducted in case of specific class of actives where a risk for the animal/human with	Not accepted: Carryover limits will need to be scientifically justified (although see implementation strategy)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		potentially contaminated drug product is described by scientific community /in the site and when an ADI has not been established. In other situation, the maximum permitted contamination of 10 ppm of the previous active substance in the next product manufactured can apply."	
72-82	27	Comment: The scope of this Guideline shall be limited to highly hazardous medicinal compounds/products. Proposed change (if any): Line 74: include Highly Hazardous into the sentence Line 74 will read: medicinal products, and all highly hazardous active substances that are intended for manufacture in premises used for.	Not accepted: see implementation strategy.
73-74	14	For investigational medicinal products, a science based flexible approach should be acceptable, taking into account, for example short duration of intake of a product carrying a contaminant. A PDE according to the definition of being safe for long term exposures can still be set, but in an individual specific risk assessment, exceeding this PDE should be acceptable if this does not entrain a health risk to the clinical study participant.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
73-75	17	Comment: It is not clear if the scope also extends API and finished product intermediates. Proposed change (if any): More clarity is required	Accepted
73-75	1	Comment: Inclusion of investigational medicinal products without any differentiation regarding availability of tox-data and the variety regarding pre-products in the development plants (e.g. Excipients, Cosmetics, fine chemicals). Proposed change (if any): Define explicit rules for investigational medicinal products with consideration of the intrinsic differences to standard API production. e.g. LD_{50} values with safety factors must acceptable because the rational that a long time exposure with a defined pre-product impurity is contradicted to the situation in a development plant	Accepted. Scope has been rewritten.
73-74	18	**Comment 1:** Investigational medicinal products are per definition for human products only (annex 13 GMP Clinical trials):"*Any investigation in human subjects intended to discover or verify the clinical…. "* **Comment 2:** It is difficult to apply the same standard to finished product, active substance and investigational	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product (IVP). A stepwise approach for risk calculation during development process is needed, meaning that for an investigational medicinal product only a "preliminary" PDE or TTC can be calculated, whereas for API in finished products a final classification similar to ADI calculation can be centrally published. **Proposed change:** We propose following changes on lines 73-74: "This guideline applies to all human **(including investigational medicinal products)** and veterinary medicinal products **for which a clear proof of risk for the animal or the human has been demonstrated and all GMP** active substances that are intended for manufacture in premises **and in product contact equipment** used for the manufacture of…"	See guideline for proposed wording
77-78	18	**Comment 1**: Safety for consumer is addressed in the MRL regulation an appropriate measure of control (Reg. 882/2004). **Comment 2:** Although the concept of restricting contaminants to levels safe for all populations is appropriate for Veterinary products which enter the food chain this is not necessarily appropriate for companion animal products (i.e. products used for animals with no impact on food chain). **Proposed change:** We suggest deleting "~~as well as consumers potentially exposed to residual active~~	Not accepted. Consumer safety needs to be considered - if residues of a companion animal or human product are carried over into a food animal product, the level of contamination must be safe. Not accepted: Carryover limits will need to be scientifically justified (although see implementation strategy)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~substances in products derived from treated food producing animals "~~	
79 - 82	14	Comment: The Guideline should explicitly allow or even recommend the use of different approaches if scientifically equally or even more appropriate, based on the data – and not give the impression of insisting on the default approach recommended in the guideline. Proposed change (if any): The presence of active substance or contaminants should be managed to a threshold level that can be considered safe for all populations. Threshold values should be derived from critical scientific evaluations of all available pharmacological and toxicological data, including both non-clinical and clinical data, to establish permitted daily exposures.	Accepted
80-82	15	Comment: Exactly why the risk assessment report has been given this title is not clear. The information provided in this risk assessment report more closely resembles risk identification i.e. only one of the risk	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessment processes identified in ICH Q9. Proposed change (line 80): The guideline also outlines how the data on which the threshold value is derived should be presented in the risk identification report…..	
80-82	20	We support the effort to harmonise communication for how the threshold values were derived, but we believe that recommending an “executive summary” signed by an expert (e.g., toxicologist or clinician) could be sufficient. A more detailed report could be made available to EMA by the marketing authorisation holder on request. Proposed change: Therefore, we recommend changing Lines 80-82 as follows: “~~This guideline also outlines how the data on which the threshold value is derived should be presented in the risk assessment report in order to achieve a clear and harmonious approach across pharmaceutical industry.~~ **This guideline recommends that the rationale for derivation of the threshold value be documented in a concise executive summary provided by an**	Not accepted: Reporting of the PDE determination strategy is required as per section 6 of the guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		expert (e.g., toxicologist or clinician). A risk assessment report should be made available to EMA by the marketing authorization holder upon request"	
80-82	24	Comment: While Risk Identification is one of the three steps in Risk Assessment per ICH Q9, suggest that the report be identified as a Risk Identification report as that more closely resembles the information provided in the report. Proposed change (if any): The guideline also outlines how the data on which the threshold value is derived should be presented in the risk identification report…..	Accepted
80	20	Since this recommendation is focused on the approach for developing an acceptable carry-over limit, please clarify that in instances when processing equipment is not shared, the overall risk of cross contamination is significantly reduced and carry-over limits do not need to be applied. Proposed change: **Addition** of the following sentence at line 80: "**This recommendation is focused on the approach for developing acceptable carry-over limits, which may not be applicable in scenarios when**	Not accepted: Not within the scope of this guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		processing equipment is not shared since the overall risk of cross contamination is significantly reduced."	
83-98	23	Comment: Several other guidelines (e.g., IPCS/WHO, ISPE Risk-MaPP, Guideline on Pharmacological ADIs, guideline on user safety for pharmaceutical veterinary medicinal products, and regulations on setting residue limits for veterinary products) are also relevant and should be considered within the context of the other guidelines listed. Proposed change (if any): Add the following references: - IPCS/WHO (2005). Chemical-specific adjustment factors for interspecies differences and human variability. - ISPE Risk-MaPP (2010) – Risk-Based Manufacture of Pharmaceutical Products. Volume 7, First Ed. - Guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006) - Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) 15-March 2010. - Regulation (EC) No 470/2009 (Article 6) for establishing residue limits of pharmacologically active	Accepted <

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substances in foodstuffs of animal origin.	
83-98	27	Comment: Quality risk management unfortunately is missing in chapter 3 “Legal basis”. Proposed change (if any): Line: between 98 and 99: Also add reference to Eudralex Volume 4; GMP-Guideline Part III Q9 Risk Management (EMA/INS/GMP/79766/2011)	Not accepted: Not within the scope of this guideline
83-98	27	Comment: Quality risk management unfortunately is missing in chapter 3 “Legal basis”. Proposed change (if any): Line: between 98 and 99: Also add reference to Eudralex Volume 4; GMP-Guideline Part III Q9 Risk Management (EMA/INS/GMP/79766/2011)	Accepted
83-98	18	**Comment:** Several other guidelines (*e.g.* IPCS/WHO, ISPE Risk-MaPP, Guideline on Pharmacological ADIs, guideline on user safety for pharmaceutical veterinary medicinal products, and regulations on setting residue limits for veterinary products) are also relevant and should be considered within the context of the other	Not Accepted: Reference has not been made to these guidelines. However, the use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		guidelines listed. **Proposed change:** Please add the following references: IPCS/WHO (2005): Chemical-specific adjustment factors for interspecies differences and human variability. ISPE Risk-MaPP (2010): Risk-Based Manufacture of Pharmaceutical Products. Volume 7, First Ed. Guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006). Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) 15-March 2010. Regulation (EC) No 470/2009 (Article 6) for establishing residue limits of pharmacologically active substances in foodstuffs of animal origin.	
84-98	19	Comment: add the reference to ICH Q9 “Quality Risk Management” Proposed change (if any): ICH Q9	Not accepted: Outside the scope of this guideline.
87-88	25	Comment: Reference to the document mentioned here is not necessary as the paper only informs about planned	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		revision of chapters 3 and 5 of the GMP Guide.	
99 - 178	2	**Methodology** • There are multiple, internationally recognised health-based hazard characterization paradigms, including the ICH Q3C paradigm for PDEs and the ISPE Risk-MaPP paradigm for ADEs to address patient safety (as well as our OEL paradigm for worker safety). The ADE methodology rewards the more robust datasets for developed APIs, allowing the toxicology professional more leeway to make appropriate extrapolations from the data. The ICH paradigm is more conservative, perhaps overly conservative, as an older methodology intended for impurities with sparse datasets. The current draft only presents the ICH Q3C methodology not taking sufficiently into account all available data. Therefore, this methodology alone is considered too restrictive for cases where broader datasets are available. Endorsement of appropriate other methodologies could be a suitable topic for ICH and beyond due to the international nature of the manufacturing industry, and the divergent regulatory expectations that currently exist. • Even within a certain methodology, for	Accepted

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		pharmaceuticals there is more opportunity to derive compound-specific adjustment factors than is typically done for solvents. There are distinct differences in the datasets for solvents (as specified in ICH Q3C) and the safety data for pharmaceuticals. The approval of modern pharmaceuticals requires the development of a robust collection of animal and human data. These data may support the use of substance-specific adjustment factors that may be lower or higher than contemporary defaults and the guideline should reflect this. We recommend more flexibility in adjustment factors, which reflects international guidance on best practices in risk assessment (e.g. WHO), and the large, high-quality, nonclinical and clinical datasets coincident with pharmaceuticals. • **NOEL** (lines 148 – 154): throughout this draft guideline, emphasis is placed on using the NOEL for risk assessment. However, in modern pharmaceutical drug development, it is rare to have a NOEL even at the lowest dose tested in animal studies, and it is extremely rare to have a NOEL for pharmacological effects in animal or human studies for large molecules. In typical GLP toxicology studies for pharmaceuticals, the objective is to identify a NOAEL and not a NOEL. In addition, according to the draft guideline, for therapeutic macromolecules and peptides ("large molecules"), the use of a LOEL for	

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		pharmacodynamic effects is "not considered acceptable". However, pharmacodynamic studies are used to derive an effect level and are rarely dosed to a NOEL. Moreover, it is unnecessary in order to derive technically sound PDE limits. Thus, the NOAEL is more appropriate (or MABEL for Biologics). **Less than lifetime exposure**: the establishment of a control standard (the PDE) based on exposure of a dose "every day for a lifetime" is an unreasonable perspective on such cross-contamination risk, including in the case of investigational products. It would not be expected that such lifetime exposure would result from manufacture of products in a multi-use facility as it would not be likely that every product lot would be preceded by the same cross-contamination risk. The guideline should allow the calculation of PDEs around less than lifetime exposure scenarios if indicated. In fact, only in rare circumstances is any patient taking **a single batch** of product for more than 12 months and the usage and manufacturing data for the product may be factored into the calculation.	
100 - 102	14	Comment: Generally, there are a lot more safety data for residual active substances available than for residual solvents. It might be useful to add in this place a comment that science-based PDE setting for active substances has to take into account all available data and that this may require different or additional	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approaches than for solvents. This should prevent that anybody without sufficient expertise may feel enabled to calculate a PDE by just applying the formula to the results of any toxicity study while ignoring other data. Proposed change (if any):	
100-106	20	We suggest broadening the nomenclature for threshold values by adding the following sentence: Proposed change: "The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. **While PDE is the chosen nomenclature for this document, this recommendation is not intended to be prescriptive, and synonyms are appropriate (e.g., "acceptable daily exposure" (ADE), "acceptable daily intake" (ADI), "acceptable threshold value").**	Accepted
101-106	23	Comment: The guideline should refer to health-based	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		limits generically throughout the document and terms such as PDE or ADE should only be used as examples. The PDE methodology from ICH Q3C should not be the only one allowed. This method embraces the general approach used globally by many agencies and expert committees but should not be considered the only method that is acceptable. Any similar method addressing the same sources of uncertainty and using similar adjustment factors should be acceptable as long as they are scientifically justified. Proposed change (if any): Add the following sentence on Line 104 after the first sentence: "***Other well-accepted exposure limit setting methods that use these procedures and essentially similar adjustment factors are acceptable as long as they are scientifically valid, supported by the peer-reviewed literature and regulatory precedent, and the justification for identification of the critical effect and specific adjustment factors is well documented.***"	
102	3	Comment: Other synonyms for PDE are used by other authorities and in the public literature, such as "acceptable daily exposure" (ADE) and "acceptable daily intake" (ADI) …	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Include these synonyms for a better understanding. The use of other synonyms should be allowed, e.g. in already existing documents/risk assessment reports.	
102-103, 110	1	Comment: The reference to the guideline on residual solvents may indicate that the level of safety data is comparable between solvents and medicinal products. However, medicinal products are pharmacologically active and are usually associated with clinical data. It is recommended to point out, that all relevant data (e.g. clinical data vs. animal studies) have to be taken into account.	Accepted
105-106	18	Please include allowances for safety assessment based on less-than-lifetime exposures, as long as the potentially contaminated product is intended for less-than-lifetime use. The majority of veterinary drugs are administrated for one to several days, one to 2 months at maximum (very few exceptions given on a daily basis and lifespan). Therefore, the risk assessment should be proportionate to the actual treatment schedule of the potential contaminated drug. In this general situation, the relevant study should be single dose toxicity or short duration toxicity studies without an additional safety factor. Please include the use of modifying factors or PK factors	Accepted. Product specific assumptions relating to exposure and modifying factors should be suitably justified in the evaluation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for calculating a PDE when appropriately justified.	
105 and 142 - 146	14	Comment: The users of the Guideline may have different understandings of the meaning of “safe” and “adverse effects”. We understand from lines 142-146 that even beneficial effects of an impurity (e.g. lowering of the blood cholesterol level) would not be acceptable. Also, lines 143-146 do not emphasize sufficiently that clinical data have a key role in determining the critical effect. Proposed change (if any): A definition of “adverse effect” should be given in the context of this Guideline. Roche uses the term “undesirable physiological effect”.	Not accepted. “Adverse effects” is a commonly used term. Importance of clinical data is explicitly mentioned.
105	8	Comment: NOEL is defined as the “no observed effect level”, and is separate and distinct from NOAEL, “no observed adverse effect level”. Because this line is related to the NOEL, not the NOAEL, the statement should not include the word “adverse”.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): … unlikely to cause an observed effect …	
105	15	Comment: There is a lack of clarity on setting some threshold values e.g. dosing “every day for a lifetime” is a scenario that isn't applicable to development products or products such as antibiotics; Proposed change (line 105): Clarity should be provided on setting threshold values for different situations.	Accepted
107-112	1	Comment: It is recommended that NOAEL values are also allowed for the calculation of PDEs (with a respective adaptation of the adjustment / safety factors) in case a NOEL cannot be derived from safety information generated in animal or human studies. Proposed change: Use of the term NOAEL in addition to the NOEL throughout the document such as... *"Determination of a PDE involves (i) hazard*	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		identification by reviewing all relevant data, (ii) identification of "critical effects", (iii) determination of the no-observed-effect level (NOEL) of the findings that are considered to be critical effects, or the no-observed-adverse-effect level (NOAEL) and (iv) use of several adjustment factors to account for various uncertainties."	
108	15	Comment: The term NOEL as defined in the guideline more closely reflects the term NOAEL (no observed adverse effect). This will give rise to confusion. Proposed change (line 108): (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects	Accepted
108	24	Comment: (iii) determination of the no-observed-effect level (NOEL) of the findings that are considered to be critical effects more closely resembles the definition of the no-observed-adverse-effect level (NOAEL). Proposed change (if any): (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects	Accepted
108-111, 129, 148-154, etc.	23	Comment: NOAEL should replace NOEL here and throughout the document. The same applies to the use of LOAEL an LOEL.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
108, 146, 183	1	The terms 'critical effect' and 'adverse' need clarification in the context of the avoidance of unintended pharmacodynamic effects (cf. line 183)	Accepted
113, 124-127	1	If the PDE is expressed on a mg/kg body weight basis, the 'weight adjustment' in the equation is not considered useful	Not accepted.
113 and 125 - 127	14	Comment: The point of departure (NOEL) has the dimension of a dose (mg/kg) and results after weight adjustment (kg) and application of adjustment factors F1 – F5 (without dimensions) in a PDE of the dimension mg. It appears not logical to request the back-calculation of the PDE into a value expressed as mg/kg. Proposed change (if any): PDE value on a per person basis	Not accepted.
113	15	Comment: The adjustment factors are in line with those recommended in ICH Q3C (R4). They are however different from those recommended in REACH (European Chemicals' Regulation), which may result in 2 different	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		limits for the same population under the different regulations. As the document will apply to sites in third countries manufacturing for the EU these assessment factors may also not be the same as those used in different parts of the world. A prescriptive non flexible approach will be difficult for companies to manage. Proposed change (line 113): Either do not state the exact assessment factors in the document or give them as examples which are not mandatory.	
113-114, 162-173	1	The 'uncertainty factors' or 'extrapolation' factors F1-F5 were taken from the ICH Q3C. However, these factors do not comply with current scientific standards and need to be revised and harmonised with other regulatory documents/approaches (FDA, ECHA). In addition, the use of these factors should allow flexibility to account for substance-specific properties. It is considered important that these factors are set according to the individual compound's properties and that their setting is transparently explained in the documentation. The setting of appropriate uncertainty factors shall be restricted to persons with sufficient expertise.	Accepted
116-127	18	**Comment:** Similarly the estimation of standard	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		bodyweight for a veterinary product, where mg/kg is not specified, of 1kg is needlessly worst case. Provision should be made to estimate the bodyweight for specific target species. **Proposed change:** The reference to all populations should be modified to indicate "or target species as appropriate." It is agreed that use of a human PDE is most pragmatic, however, this GL should clarify that it is acceptable to derive a limit specific to a target species when the company/manufacturer deems appropriate to do so.	Partly accepted: Although the text still provides the default value of 1kg, the use of other approaches may be accepted if adequately and scientifically justified.
116-123	1	The guidance may allow for the derivation of an animal-specific PDE in case the manufacturer considers the human PDE not appropriate due to inter-species differences	Accepted provided the product is a veterinary product
116	15	Comment: Replace "carryover limits" with "acceptance limits" to more accurately reflect the management of cross contamination rather than only cleaning validation. Proposed change (line 116): In relation to the establishment of acceptance limits…	Accepted
116	24	Comment: Replace "carryover limits" with "acceptance limits" to more accurately reflect the management of	Partly accepted. Guideline reworded to reflect management of cross contamination rather than cleaning

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		cross contamination rather than only cleaning validation. Proposed change (if any): In relation to the establishment of acceptable limits…	validation only.
118-123	14	This section is a not clear. In Section 2 (Scope), it states that this guideline is for both human and veterinary medicinal products. Although the VICH guidelines may be applicable for residual solvents across species, there are inter-species differences for animal pharmaceuticals. Therefore, it seems reasonable that an ADE separate from that for humans might be necessary for animals (e.g. manufacturing line solely for animal health products) and that the default human PDE would not be appropriate.	Accepted
120-121	18	The pragmatic approach to calculate the level of contamination on the basis of human PDE is appreciated. However, if there is evidence that humans are not the most sensitive species, the most sensitive target species should be used.	The guideline continues to make reference to the human PDE, but deviation from the guideline can be accepted where adequately justified.
120-123	25	Comment: Although the approach proposed by EMA seems to be pragmatic, there are APIs which exert significantly higher pharmacodynamic effects or higher toxicity in animals than in humans, e.g. paracetamol. Limits for such APIs set based on human PDE may not be restrictive enough for particularly sensitive species. It would be recommended to state here that sensitivity of	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relevant animal species should be taken for calculations where it is known to be significantly lower than human sensitivity.	
121-123	18	PDEs are used to calculate residual solvent limits applied for veterinary medicinal products. To avoid creating a new document in case of veterinary facilities, a reference to the established ADI (and its summary of opinion) and/or existing User Risk assessment of the formulated product (part of the existing document for Marketing Authorisation) is considered appropriate documentation to avoid duplication of work by the establishment of a PDE, the writing of a risk assessment report and the expert review.	Accepted. Where ADIs have been established the use of these is considered appropriate.
126	3	Comment: For a high percentage of substances the PDEs are expected to be in the µg/day range. Proposed change: The general convention of setting the PDEs on a µg/kg bw (or µg/day) basis should be considered	Accepted
127, footnote 1	18	We request the last sentence of the foot note is deleted because it is not representative of the variability in bodyweight across the animal sector; it would lead to a gross overestimation of risk in some cases: "For medicinal products for veterinary use doses are	Partly accepted. Although the text still provides the default value of 1kg, the use of other approaches may be accepted if adequately and scientifically justified.

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		generally expressed on a mg/kg bw basis. ~~In those instances where this is not the case, a standard body weight of 1 kg should be assumed as this would represent the lower end of animal body weights. "~~	
127 and footnote on page 5/9	14	Comment: The majority of oral drugs are dosed on a mg/person basis. The present text proposes a body weight of 50 kg to be used for the calculation of mg/kg dose for such products. However, 70 kg would be more conservative for transforming a clinical mg/person dose into a mg/kg dose. On the other hand, 50 kg would be more conservative when used for weight adjustment in the PDE formula. This means, for conservative approaches two different body weight values would have to be applied. This would harmonise the document with the FDA approach which also uses 60 kg as the default body weight. Proposed change (if any): A default body weight of 60 kg to be applied to clinical and preclinical data.	Not accepted. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation.
129	1	Other scientific approaches not limiting to Benchmark dose for the calculation of the NOEL should be taken into account.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
129	8	Comment: Provide alternatives for compounds that do not have a NOEL developed. Allow for the use of a NOAEL, LOAEL, or acute dose toxicity data, with additional safety factors, to calculate an ADE. Proposed change: Alternative approaches to the NOEL, such as the Benchmark dose (BMD), NOAEL, LOAEL or the acute dose toxicity data may be used. ADE calculations using this alternative toxicological data are the same as the PDE calculation, with the use of appropriate safety factors specific for the type of toxicological data that is available. The development of an ADE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.	Accepted
129	9	Comment: Drug substance manufacturers like CMO's and others that are not the originator of an active substance in development will not always have access to the complete proprietary data set consisting of pharmacological and toxicological information, which is required to derive a reliable health based exposure limit. In these cases alternative methods of deriving carryover	Partly accepted. The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		limits, not necessarily based on toxicological data only, have to be applied. Proposed change (if any):	
129	18	**Proposed changes:** The use of Acceptable Daily Intakes (ADIs) established for food-producing animals by the CVMP should be possible as an alternative to PDEs. We recommend replacing the acronym “NOEL” with “NO(A)EL” to indicate that a NOEL or NOAEL may be used for threshold calculations.	Accepted. Where ADIs have been established the use of these is considered appropriate.
129	24	Comment: See comment for line 108 Proposed change (if any): Change NOEL to NOAEL	Accepted
129	25	Comment: It would be highly advisable to describe in details alternative approaches to the NOEL (in particular Benchmark dose). It would be helpful to provide exemplary thresholds (or, ideally, reference thresholds) and relevant literature references.	Accepted
131-140	3	Comment: Of major importance for the risk assessment is also the pharmacokinetic/ADME data of the	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substance, including the comparison of human and animal PK/ADME data, when a PDE calculation is based on animal data. Proposed change: Please include a respective statement.	
131-140 137	14	Comment: use all relevant information for holistic assessment Proposed change (if any): Other data e.g in silico data, information from transgenic models and class effects can also add value.	Accepted
131-140	18	The request for data related to companion animal products should not exceed the already established data requirements for these species (to avoid a negative impact on medicines availability and animal welfare).	Partly accepted. The PDE approach does not require a particularly rich dataset but introduces safety factors to account for limited data. Consequently, it is not expected that would be a need to generate new data in order to comply with this guideline.
132-140	15	Comment: This guideline would apply to Investigational medicinal products: for early R&D stages, there is too little information available to set limit values. There is insufficient guidance on when to initiate an assessment (i.e. how early in development) and then how frequently this should be reassessed/updated. The guidance given does not provide for full use of the TTC concept where	Accepted

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		there is a staged approach to the value depending on the likely characteristics of the compound. This may have a significant impact during early development where safety data is continually evolving. By comparison to OEL, this would not normally set this before the siting decision when reprotox, ADME, genotox, 6 month rodent data, and some Phase I and II data are available. If limits are set too early, the lack of data needs to be compensated with an extra assessment factor, and the resulting threshold value is likely to be very low. Proposed change (131): Provide additional discussion within the guidance document on the use of the TTC concept for early stage products.	
134-137	3	Comment: Further data of relevance for hazard identification may exist, e.g. safety pharmacology data, or data on local tolerance or sensitization. Proposed change: Either “Data for hazard identification would include for example …” or mention safety pharmacology data, and data on local tolerance or sensitization in particular.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
138-140	8	Comment: The ideal case is to have a complete toxicological data set available for evaluation. Contract manufacturers are not likely the company that will be developing the toxicology data, and would see an advantage to a guideline requirement for an innovator company to provide a complete data set. In addition, at early stages in development, or for API intermediates, there is not a complete toxicology database. The wording on data completeness should allow for the use of a safety factor approach, e.g., using the ADE calculation. Proposed change (if any): If data sets are incomplete, the identified gap(s) may be accounted for in the calculation of the ADE with a safety factor.	Accepted
138-140	15	Comment: The following statement while apparently reasonable is very difficult to interpret practically: “If data sets are incomplete, the identified gaps need to be critically assessed with regard to the uncertainty impact this might have on deriving a reliable health based' exposure limit.” Clarity is required as to EMA’s expectations.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (line 138): Add clarity as to EMA's expectations in this situation. Possibly by adding an example.	
140	4	Comment: **Data Requirements for Hazard identification.** Information on Occupational Exposure Limits (OEL) for active substances and intermediates should be included as potential source of data. Proposed Change: Add the following sentence. Available Occupational Exposure Limits (OEL), may also be considered as relevant data for establishing PDE or ADE for active substances and intermediates. It should be taken into account that OELs are derived to the healthy adult worker population.	Not accepted: OEL considered inadequate: data for deriving OEL may be used.
142	17	Comment: Concerning selection of critical effects – the guidance document should point out that critical effects properly include anticipated pharmacodynamic effects when these could be construed as adverse for exposed individuals. As written the emphasis appears to be on toxicological effects and "clinical therapeutic and adverse effect(s)" (line 146).	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Refine text to clarify that anticipated pharmacodynamic effects often will be the most sensitive indicator of a critical effect when considering the issues of carry-over.	
146	15	Comment: Reproductive and developmental toxicity should always be evaluated against other data and points of departure to ensure that the male, female, and unborn are all protected by the threshold value. Proposed change (line 146): Add at the end of the paragraph "It is important to always compare reproductive and developmental toxicity to other sensitive endpoints to ensure protection of the male, female, and unborn."	Accepted
149	8	Comment: For incomplete data sets, a NOEL may not be able to be determined. Proposed change (if any): For all critical effects identified, and given an adequate set of toxicological data, the NOEL should be established	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and used.	
148-54	15	Comment: The text describes the NOAEL rather than the NOEL Proposed change (line 148): For all critical effects identified, a NOAEL should be established. The NOAEL is the highest tested dose at which no “critical” effect is observed. If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value. If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used. A NOAEL based on clinical pharmacodynamic effects should correspond to the highest dose level tested which is considered therapeutically inefficacious.	Accepted
148-160	28	Comment: The NOAEL is considered much more relevant. At the time of writing the ICH Q3C guideline, NOEL and NOAEL were often used interchangeably. But now most toxicologists distinguish between the two and there is a consensus that the NOAEL is the most relevant metric since this excludes consideration of non-relevant effects. (See publication by Dorato and	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Engelhardt, Regul Tox Pharmacol, 2005) Proposed change (if any): Use of NOAEL rather than NOEL is required.	
148-154	1	Proposed Change: Use of the term NOAEL in addition to the NOEL.	Accepted
148 - 154	24	Comment: The text describes the NOAEL rather than the NOEL Proposed change (if any): For all critical effects identified, a NOAEL should be established. The NOAEL is the highest tested dose at which no “critical” effect is observed. If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value. If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used. A NOAEL based on clinical pharmacodynamic effects should correspond to the highest dose level tested which is considered therapeutically inefficacious.	Accepted
148-154	25	Comment: According to the guideline, to determine the PDA value	Not accepted. This is not envisaged at this time.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the NOEL value should be established. NOEL values are often not available, especially for 'old' active substances like paracetamol or ibuprofen. It would be helpful to publish the list of NOEL values for such substances.	
150-151	1	Comment: Instead of generally using the lowest NOEL, the NOEL from the most relevant / predictive species should be selected. Proposed Change: If the critical effect is observed in several animal studies, the lowest NOEL from the most predictive species should be used for calculation of the PDE value.	Accepted. The chosen NOEL should be justified.
150-151	4	Comment: **Establishing NOEL(s)** No Observed Adverse Effect Level (NOAEL) should be accepted as alternative to NOEL and justified in the Risk Assessment. Refer to ISPE Risk MaPP Guidance for more details. Consider further explanation of the NOEL for all critical effects identified. Proposed change (if any): If the critical effect is observed in several animal studies, the NOEL occurring at the lowest dose should	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be used for calculation of the PDE (ADE)value. This dose is also named as the NOAEL. The rationale should be included in the Risk Assessment. If no NOEL is obtained, the lowest-observed-effect-level (LOEL) may be used.	
150-151	14	Comment: It is not always the NOEL of the most sensitive species that should be applied but if one species is clearly more representative in a specific case, then the NOEL from a study in this particularly representative species should be used, even if its NOEL is not the lowest. Proposed change (if any): "…the NOEL from the study in the species most representative for humans should be used. If this species cannot be determined with certainty, the NOEL occurring at the lowest dose should be used …."	Accepted. The chosen NOEL should be justified.
150-151	15	Comment: If several animal studies are used the lowest NOEL may not give lowest PDE. Is the use of the lowest (NOEL/F1) not just lowest dose NOEL more applicable here ? Proposed change (150): If the critical effect is observed in several animal studies, the critical effect producing	Accepted. The chosen NOEL should be justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the lowest threshold value should be used.	
152–154	25	Comment: A drug product dose may be therapeutically inefficacious, yet still causing some PD effects, or even worse, adverse reactions. The aim of this guideline is to establish limits, which would ensure that no effects of eventual API contamination occur. Proposed change (if any): *"(…) the highest dose level tested, which is considered ~~therapeutically inefficacious~~ not to cause any clinical effect*".	Not accepted.
156-173	1	The calculation of adjustment or safety factors should also consider the already implemented "staged Threshold of Toxicological Concern (TTC)" approach that is valid for genotoxic impurities in pharmaceuticals. Since the acceptable limits for daily intake of even genotoxic impurities contained in drug products can vary depending on the duration of treatment / exposure in patients, it is proposed that the use of adjustment factors for limit calculation should also consider the maximum therapeutic dosing period of the subsequently manufactured compound.	Accepted
157	24	Comment: Use no-observed-adverse-effect-level rather	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		than NOEL. Proposed change (if any): The PDE is derived by dividing the NOAEL for the critical effect	
157-160 162-168	23	Comment: Replace PDE with health-based value. Indicate the adjustment factors given should be considered as default values that can be replaced with data-derived or chemical-specific adjustment factors (CSAFs) when scientifically justified. Proposed change (if any): Line 157: "The ~~PDE~~***health-based value*** is derived by dividing the NOAEL for the critical effect…" Line 160: ***Adjustment factors*** F1 to F5 ~~are~~ address***ing*** the following sources of uncertainty: Below line 168: ***"These should be considered default values that can be replaced with data-derived or chemical-***	Not accepted: The current guideline describes the PDE as the procedure for determining a health based limit - use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified *Partly accepted:* The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		specific adjustment factors (CSAFs) when scientifically justified. These adjustment factors are often referred to by other terms but are considered equivalent. For example F1=UF_A, F2=UF_H, F3=UF_S, F4=MF, F5=UF_L. Another term (UF_D) that is not reflected in the guideline is often used to address issues with database quality and completeness. It is important not to double count in certain areas of uncertainty (e.g., severity of effect is mentioned in both F4 and F5).”	
160	20	We believe the key message is: “The use and choice of adjustment factors should be justified.” Proposed change: We suggest adding this sentence to Line 160 as follows: “The use and choice of adjustment factors should be justified, **and considerations for uncertainty relative to the evaluated data should be outlined. For instance, the adjustment factor approach outlined in ICH Q3C addresses the following sources of uncertainty**:”	Accepted
160-171	25	Comment: Data on the choice of adjustment factors are not complete in relation to the data presented in the guideline ICH Q3C (R4). E.g., for F3 only value “10” is	Accepted - reference is made to ICHQ3C (R4)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		given (to account for repeat-dose toxicity studies of duration less than 4-weeks), while according to ICH Q3C values “1”, “2” and “5” are also possible. Proposed change: Adding complete description of all adjustment factors according to the guideline ICH Q3C (R4).	
162	1	Please harmonise the factors with other regulatory documents (e.g. FDA) according to current scientific standards, i.e. factors lower than 2 are applied for certain species (dog, mini-pig)	Not accepted. Reference is made to ICH Q3C. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.
162	14	Comment: Harmonise with customary adjustment factors as much as possible. The FDA proposes and the community has used factors <2 occasionally, e.g. dog to man = 1.8 (FDA recommendation) or mini-pig to man (1.1, also FDA) Proposed change (if any): “F1 (Values between 1.1 and 12)”	Not accepted. Reference is made to ICH Q3C Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.
163	1	A standard factor of 10 for variability between individuals is usually considered appropriate to protect also sensitive subpopulations. But in case good quality clinical data from large populations is available, a factor	Partly accepted. Deviations from the default values for the adjustment factors presented above can be accepted if

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of 10 is often too high. In such cases, this factor should be set based on the available data (i.e. F2 <10).	adequately and scientifically justified.
163	3	Comment on "F2": A factor of 10 to account for variability between individuals": For details on this factor Line 170 relates to ICH Q3C (R4), which says "A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this guideline." As this draft guideline is on pharmaceutical ingredients - with generally a lot of human/clinical data available, including on variability between individuals - and not on organic solvents with usually no human data, it should be possible to deviate from the default factor based on the actual data, if adequate. Some substances show a relatively small variability between individuals, while others show high variability particularly related to pharmacokinetic effects (e.g. due to genetic polymorphism in cytochrome P450 enzyme activity, or in case of renal or hepatic impairment) and adverse effects (idiosyncratic reactions etc.). This should be taken into account in the calculation of the PDE. See also the comment to Line 167. Proposed change: Allow for a data-driven setting of F2.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
163	4	Comment: F2: A standard factor of 10 for variability between individuals is usually considered appropriate to protect also sensitive sub-populations. But in case good quality clinical data from large populations is available, a factor of 10 is often too high. In such cases, this factor should be set based on the available data (i.e. F2 <10).	Partly accepted: see above points
163	14	Comment: Despite high coverage of the total population by a factor of 10, this default may not be adequate for certain circumstances or minority subgroups of the population, e.g. sensitive subpopulations with severe disease or paediatric subpopulations if indicated by the results of toxicity studies in juvenile animals. Therefore, F2 shall be modified (smaller or larger) based on scientific data (e.g. if human variability is known to be small or if clinical data from a large population base are used to set the PDE, F2 can be set below 10) Proposed change: The default adjustment factor of 10 generally also covers age-related variability including children. The default adjustment factor of 10 generally also covers age-related variability including children. F2 may be modified (smaller or larger) based on scientific	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		data (e.g. if human variability is known to be small or if clinical data from a large population base are used to set the PDE, F2 can be set below 10).	
164	1	This factor should reflect the duration of the experimental study, i.e. the longer the study duration, the smaller the factor should be. Thus, this factor may range from 10 for short-term studies to 1 for chronic studies (i.e. ≥26 weeks)	Accepted
164	3	Comment on "F3": A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks". For details on this factor Line 170 relates to ICH Q3C (R4). However the factors in ICH Q3C (R4) are questionable. Several guidelines use different factors, and nowadays, no 7 year studies in non-rodents are performed any more. According to ICH S4 much shorter studies are sufficient for testing for chronic administration of medicinal products: "…the following studies are considered acceptable for submission in the 3 Regions: … Non-rodents: a study of nine months duration." The typical safety/assessment factors for sub-acute (usually referring to a 28-day study) to chronic is 6 and sub-chronic (usually referring to a 90 day study) to chronic 2-3, see e.g. ECHA. Guidance on information requirements and chemical safety assessment Chapter	Partly accepted. See above points

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		R.8; German TRGS 901; ECETOC Technical Report No. 86; Naumann BD and Weidmann PA. Human and Ecol. Risk Assessment 1(5): 590-613 (1995) and literature cited therein; Batke et al. Toxicol Lett. (2011) 28;205(2):122-9. Proposed change: Please reconsider the F3 factors.	
164	4	Comment: F3: This factor should reflect the duration of the experimental study, i.e. the longer the study duration, the smaller the factor should be. Thus, this factor may range from 10 for short-term studies to 1 for chronic studies (i.e. ≥26 weeks)	Partly accepted. See above points
164	14	Comment: F3 should reflect study duration; other examples would be appreciated (e.g. 13 week study) Proposed change (if any): A factor between 1 and 10 to account for repeat-dose toxicity study duration (1 for studies ≥26 weeks, 3 for 13 week studies, 5 for 2-4 week studies, 10 for <2 week studies)	Partly accepted. See above points

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
164	15	Comment: Uncertainty factors are based on ICH Q3C residual solvents. There is much more toxicology data available for biopharmaceuticals than solvents which may allow for uncertainty factors less than 10. Proposed change (line 164): F3: A factor of 1-10 to account for repeated dose toxicity studies of short duration	Partly accepted. See above points
164	17	Comment: The draft guidance appears to encourage strict application of an uncertainty factor of 10 to both F2 and F3 which limits the scope of professional judgement which could be applied to interpretation of available information. Given that the guidance document encourages creation of a 'Summary Risk Assessment Report' by an expert (supported by expert's CV etc), it appears that some room for variability in application of F2 and F3 could be allowed and this is consistent with general practice in human risk assessment. Proposed change (if any): F2: A default factor of 10 to account for variability between individuals. A variable factor may be applied (1 to 10) when supported by data and documented in	Partly accepted. See above points

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the summary risk assessment report F3: A default factor of 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks. A variable factor may be applied (1 to 10) when supported by data and documented in the summary risk assessment report	
164-172	18	**Comment**: For F3, a factor of 10 to account for repeat-dose toxicity studies of short duration has been proposed. At line 170, the proposed text refers to Appendices 3 of the ICH Q3C (R4) and VICH GL18 on the possibility to adjust factors F1 and F4, but no reference to a possible adjustment of F3 is made. **Proposed change**: Please add reference to ICH Q3C (R4) and VICH GL18 to allow adjustment of factor F3 as well, by using a factor less than 10, if appropriate, in the case of less-than-lifetime exposure.	Partly accepted. The guideline continues to refer to ICH Q3C (R4) and VICH GL18. However, deviation from the values given in these guidelines could be accepted if appropriately justified.
167	1	F5: Variable factor when only LOEL is available: In the Draft Guideline, it is proposed that a factor up to 10 could be used depending on the severity of the toxicity. It is rather suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/ exceptional cases. This takes more into account the dose spacing in recent regulatory study	Partly accepted. See above points

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		designs (mostly between 2-4).	
167-168	3	Comment on “F5”: “When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.” For details on this factor Line 170 relates to ICH Q3C (R4). This approach from ICH Q3C (R4) is adequate for chemicals with generally no human data available. However, a more specific and more detailed approach for pharmaceutical substances would make sense, for which in many cases the pharmacodynamic effects are the critical effects in the calculation of the PDE. In many cases NOELs for the pharmacological effects are not available. Data from clinical studies (at effect levels) and dosing recommendations from prescribing information have to be used for the calculation of the PDE. When using the lowest clinical dose (with known effects) from this data as the LOEL, and the proposed factor of 10, this would clearly differ from the current approach or using 1/1000th of the lowest clinical dose. Both factors are arbitrary defaults that may be too high or too low for many compounds. However the adjustment factor to estimate the NOEL from the lowest clinical dose is the most critical in the calculation of the PDE. It is therefore suggested to give a more detailed guide on the adjustment factor to be used. This adjustment factor should be depending on the mode of action/therapeutic class, the desired pharmacological effects as well as	Not accepted. Definition of PDE is well-established. Further definition to include adjustment factors is not considered to be necessary.

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		undesired pharmacological effects, and the adverse effects typically observed in humans including their dose response and severity. When using the “lowest clinical dose” as starting dose for the calculation of the PDE, a few aspects have also to be considered, e.g.: • Is a single dose or a daily dose used for the calculation? • Is the lowest usual clinical dose used (and e.g. an adjustment factor of 10 for variability between individuals) or should the lowest dose recommended for specific subpopulation (e.g. with renal or hepatic impairment, specific genotypes etc.) be used and therefore allow for the use of a lower adjustment factor for variability between individuals? • Which adjustment factors are adequate based on which effects? E.g. for a newer anti-hyperglycemic substance without the risk of hypoglycaemia at higher doses, a low adjustment factor is adequate (far below the currently used 1/1000th of the clinical dose), while e.g. for a hormonal acting compound or classical DNA-reactive anticancer drug much higher adjustment factors are needed. Proposed change: Please include a more detailed	

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		approach taking into account the pharmacological activity of the compounds and allow for a compound-specific, data-driven deviation of the default adjustment factors.	
187 – 211	8	Comment: When allowing for use of an ADE, the ISPE Risk MaPP calculation for ADE already includes a Pharmacokinetic Adjustment factor, as needed, for route-to-route extrapolation. Proposed change (if any): Note that in some cases, (i.e., when the ISPE Risk MaPP calculation for ADE is used,) no further extrapolation to address other routes of administration may be necessary.	Accepted
170	1	ICH Q3C is R5 now Proposed change (if any): Please refer to Appendices 3 of the ICH Q3C (R5)	Not accepted: ICH Q3C (R4) is still in operation. The R5 is an updated to the Appendices
170- 173	10	Comment: There is no clear guidance or reference how	Not accepted. Reference is made to the ICH documents.

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		to use the adjustment factors F2, F3, and F5. Proposed change (if any): There should be a reference or a clear guidance how to set the adjustment factors F2, F3, and F5 included in the Guideline.	
170-173	23	Comment: Other adjustment factors besides F2 and F5 are used with human data. F3 and F4 equivalents, as well as UF_D, are often used. Proposed change (if any): "~~F2 and potentially F5 would need to be applied when deriving a PDE on the bases of human end points.~~***F2, F3, F4 and F5 are often applied when deriving health-based limits exposure on the basis of human data."***	Partly accepted. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.
172-173	14	Comment: Not clear. Does the agency mean that if a PDE is derived from human end points *only* F2 and F5 should be applied? In our view, F3 and F4 may be equally applicable to a clinical data base, depending on the situation. Also F2 and F5 would also need to be taken into consideration when deriving a PDE from preclinical endpoints. Proposed change (if any): delete the sentence: "F2 and	Partly accepted. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.

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		potentially F5 ….. end points".	
172-173	20	Comment: In order to facilitate global harmonisation, application of chemical-specific adjustment factors as described by the World Health Organization (WHO)* should be considered appropriate. Proposed change: "**For instance, a threshold value derived from human endpoints may only apply** F2 and potentially F5 ~~need to be applied~~ ~~when deriving a PDE on the basis of human end points~~. **In addition, it may also be appropriate to apply chemical-specific adjustment factors as described by the World Health Organization (WHO)* instead of these defaults**." * World Health Organization (2005). Harmonization Project Document No. 2. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment. http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf	Partly accepted. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.
173 - 174	8	Comment:	Partly accepted. Deviations from the default values for the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		To support use of ADE calculations, please provide references to acceptable standards for selection of ADE safety factors. The ISPE Risk MaPP guidance, Volume 7, Sept. 2010 and REACH regulations, chapter 8 are suggested. Proposed change (if any): For calculation of an ADE, the safety factors provided in accepted external references (e.g., ISPE Risk MaPP; REACH Chapter 8) may be used. The calculation and selection of safety factors must be presented and discussed in the Risk Assessment Report.	adjustment factors presented above can be accepted if adequately and scientifically justified.
175-178	18	**Comment:** It would be unusual to calculate more than one PDE for a chemical. From line 151, "the NOEL occurring at the lowest dose should be used for calculation of the PDE value". Thus, only one PDE should be calculated, based on the lowest NOEL for the most critical effect. **Proposed Change:** We recommend removing this section.	Not accepted. A PDE should be calculated for all critical effects. The decision as to the most appropriate PDE should be made with appropriate justification
175-178	20	Comment: Additional examples for when the lowest PDE may not be the most relevant would be welcome.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: “Usually, by default the lowest PDE value will be used. **However, factors such as dosing regimen, pharmacokinetics, and patient population may be considered in the justification of a higher PDE.”**	
175 – 178	8	Comment: To allow for use of either PDE or ADE, both options should be acknowledged. Proposed change (if any): Throughout the paragraph, use the phrase, “PDE or ADE”.	Accepted
		•	
180-269	2	• MED The fraction of Minimum Efficacious Dose (MED) approach has the benefit of managing risk to patients based on pharmacology in patients. This direct measure of risk has advantages over using animal toxicity data which may not be representative of risk to patients.	Not accepted: see implementation strategy

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		Indeed, a case can be made for older products with many years of patient experience, that a human pharmacology based threshold is likely to be more reliable than using decades old toxicology information.	
182 - 186	14	Comment: Given that clinical data are often more relevant than data from animal models, the importance of their use may not be appropriately reflected by the few sentences on this topic in the guideline. Proposed change (if any): We recommend to add at least the following aspects: a) Where possible, a clinical inefficacious dose level should be estimated based on clinical dose-response data or experience. This dose may be used a starting point for a PDE setting or used as a benchmark for comparison with the PDE values derived from preclinical data. b) Where possible, clinical exposure data (plasma) should be analysed for major differences between human and animal species which may be relevant to be taken into account for the translation of animal data to humans (e.g. rationale for adjustment factor F1). c) Where available, the metabolism profile should be analysed for major differences between human and animal species which may be relevant for the selection	Partially accepted. Paragraph has been slightly expanded

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		the most relevant animal species.	
183	23	Comment: More information should be provided to clarify the use of clinical data over preclinical data. For example, when extensive clinical data are available (e.g., marketed product) these data are more relevant than preclinical data and the various factors that have to be applied due to extrapolation. Line 183 Replace “highly relevant” with “preferred” Proposed change (if any): “…quality human clinical data is ~~highly relevant~~***preferred***.”	Not accepted. It is up to the manufacturer to decide what they considered relevant with adequate justification
192	18	Please provide a supporting reference for 40% as a “clear difference”. Otherwise, we recommend removing the “40%” example to avoid unintentionally suggesting that anything <40% is not a clear difference.	Not accepted. 40% is given as an example of a value that might be considered to represent a clear difference. However, specific assumptions should be justified in the evaluation.
192	23	Comment: Bioavailability correction factors should be used whenever appropriate data are available to permit their derivation. These should be used to replace the default assumption of 100% unless the correction will be negligible. Use of 40% as an example is too prescriptive. Upward adjustment of the health-based exposure limit should be allowed, within limits (e.g., 2-5 fold), when	See above

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		scientifically justified. Proposed change (if any): Line 192 – delete (e.g., >40%)	
192	25	Comment: In order to avoid possible misunderstandings, it is recommended not to provide the exemplary value "e.g. > 40%" (as it is not clear whether it may be used as any reference value).	See above
204	14	Comment: The formula needs some explanations: Proposed change (if any): It might be useful to add the following comments: a) Absorption may not equal bioavailability (e.g. a peptide might be highly absorbed by the GI tract but loses biological activity completely; or cases of significant first pass effect in the liver) b) Bioavailability should preferably be assessed based on comparison of dose with plasma exposure data or alternatively, by comparing dose with level of efficacy. c) Parenteral bioavailability is 100% by definition	Principle correct. However no change made as it is explained in the text above that this is a conservative approach assuming 100% bioavailability.

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212-234	1	It does not follow a scientific approach that a contamination from a previous product in a shared facility shall be less acceptable compared to a contamination resulting from the synthesis process itself. The manufacture of an API in a shared-facility and the resulting carry-over is considered as non-avoidable as impurities resulting from the synthesis process. The risk as well as the benefit for the patient is the same. Therefore, the TTC of 1.5 µg/day should be applied also for residual APIs. Moreover, even higher limits than this TTC value should be allowed for genotoxic residuals for example in anticancer agents or drugs at short-term exposure, which would be in line with the recommendations given in respective guidelines. Whenever possible, the derivation of substance-specific PDE values also for genotoxic compounds using a risk-based approach should be encouraged. Generally, alignment with new ICH M7 draft guidance is recommended. Proposed change/addition to the text: *"A limit of 1.5 µg/day is allowed for genotoxic residual active substances which is consistent with the genotoxic*	Accepted in principle ICH M7 should be considered. M7 was not into force at the time of finalisation of this document.

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		impurities guideline. Even higher values may be acceptable under certain conditions, e.g. short-term exposure, for treatment of a life-threatening condition, or when life expectancy is less than 5 years."	
213	28	Comment: Section 4.1.3. The concepts of ICH M7 should be included here; eg *mutagenic* impurity; LTL correction, etc. Proposed change (if any): Amend to align with ICH M7 provisions	See above
212-227	2	While we agree that guidance on how to address active substances with genotoxic potential is important, industry do not agree with approach outlined in the draft guidance. There is no logic to distinguish between intrinsic genotoxic impurities arising in the product and genotoxic impurities introduced as a carry-over from a previously manufactured product. The 10^{-5} risk level is appropriate in both scenarios. A 10^{-6} requirement would be overly restrictive with little benefit to patients. This is also consistent with the approach being proposed in ICH M7. In addition, for genotoxic residual actives in compounds used as anticancer agents the limits for genotoxic	See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		residual actives should be allowed to be higher according to approaches referenced in ICH S9	
212-227	4	**4.1.3 Active substances with a genotoxic potential** Comment: In terms of health risk, there is no logic to distinguish between intrinsic genotoxic impurities arising in the product related to the synthetic process and genotoxic 'impurities' introduced as a carry-over from the previous product. The $1x10^5$ risk level is appropriate in both cases. Effective and reproducible cleaning processes subject to validation should ensure there is low risk of exceeding the TTC limits for compounds with no discernible threshold values. Therefore , additional safety factors should not be necessary. Proposed change:	Accepted
212-227	18	Please add the option to use staged-TTC for threshold calculations.	Accepted
212-227	20	While we agree that guidance on how to address active substances with genotoxic potential is important, we support an alternative approach to the one outlined in 4.1.3. This section states that residual is avoidable, and therefore adopts a higher bar for excess cancer risk (1	Accepted. Consideration of duration of exposure is used to justify a TTC value that would otherwise be considered unacceptable for carryover substances that enter the human food chain.

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		in 1 million) versus the 1 in 100,000 acceptable excess cancer risk that has already been adopted by EMA and is highlighted by ICH (includes EMA and FDA acceptance via Q3C Solvents as well as step 2 M7 Genotoxic Impurities guidelines). On the basis of previously-accepted drinking water, food, and pharmaceuticals applications, a 1 in 100,000 excess cancer risk is appropriate. Further, this document could include a sentence to emphasise those parameters such as patient population, duration of exposure, or indication, that can influence the overall assessment as outlined in the current ICH M7 step 2 document.	
218-223	4	Delete lines 218-223 starting with-In contrast to impurities, residual active substances principally are avoidable...for residual active substances.	Accepted
218-223	8	Comment: Both the EMA and FDA guidance on genotoxic impurities and the draft M7 ICH guidance on DNA reactive impurities in new drug substances have determined that a TTC limit of 1.5 µg/day is an acceptable risk at 10^{-5}. It is only for certain subsets of high-potency carcinogens, i.e., chemicals with structural alerts, that a 10-fold decrease to 0.15 µg/day and a risk of 10^{-6} is considered. The TTC limits adopted in the guidelines for genotoxic impurities were based on an already-	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		conservative analysis of an extensive API database. The same science used for the genotoxic impurities guidelines should be applied to this guidance: TTC limits of 0.15 µg/day might be applied for structurally potent compounds, but not every compound by default when there is no toxicity data. There is no scientific justification that supports a different risk-based limit for impurities from an extrinsic source (carry-over from equipment), as compared to an intrinsic source (arising from the chemical synthesis). Proposed change (if any): Delete lines 218 through 223, starting with the sentence, “In contrast to impurities …”	
218 - 219	24	Comment: While cross contamination should be avoided where ever feasibly possible, it should be noted that manufacturing products in shared facilities does have benefits to patients – such as – lower cost of medicines and availability of medicines. If the cost to manufacture products is too high a company may choose to not produce the medicine which will either cause a rise in cost as competition is not holding the price down or if there are no other options on the market the product	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		will not be available to patients. Proposed change (if any):Delete " thus a more conservative approach is appropriate when setting threshold values for residual active substances."	
218-223	14	Comment: it is not easy to understand why 1.5 mcgr of a genotoxic contaminant should be acceptable if it derives from the API synthesis process of the contaminated DS itself but the degree of contamination can only be 0.15 mcgr if the contamination derives from trace contamination due to a product made earlier on the same equipment. The drug containing the contaminant would be the same, the benefit to the patient the same – so why this difference of a factor of 10? The argument that "residual active substances principally are avoidable and are not associated with related benefit to the patient" may cause confusion. Genotoxic impurities coming from the manufacturing process itself might also be avoidable by the use of highly sophisticated (and more expensive) methods or alternative (economically less attractive) synthetic pathways. Furthermore, the use of active ingredients (e.g. antibiotics, methotrexate) might be indispensable in biological production processes. A scientific case-by-	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		case assessment rather than a default approach should be requested. Proposal: apply the same “genotoxic impurity” 1.5 mcgr/d TTC also for trace cross contaminants.	
218-223	25	The limit for residual genotoxic active substances as stringent as 10-fold lower than the TTC for genotoxic impurities is not well justified in the draft guideline. It should be underlined that TTC of 1.5 µg/person/day is considered to be associated with a very low risk already.	Accepted
219	9	Comment: The TTC (of 1.5 µg/d) already is a very conservative approach to minimise the theoretical excess life time risk of cancer. ICH draft guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (Step 3 document – Feb 2013), which is addressing the same excess life time cancer risk, states that ‘The methods upon which the TTC is based are generally considered very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumour incidence (TD50) to a 1 in 10^{-6} incidence, using TD50 data for the most sensitive species and most sensitive site of tumour induction (several “worst case” assumptions)’. Furthermore it mentions that ‘Some structural groups were identified to be of such high potency that intakes even below the TTC	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens ("cohort of concern") comprises aflatoxin-like-, N-nitroso-, and azoxy compounds.' This group of highly potent carcinogens for which lowering the TTC is proposed, are highly unlikely to be handled in a pharmaceutical manufacturing facility. Therefore further reducing the TTC for residual active substances by a factor of 10 is an unnecessary and over-conservative measure which will not contribute to an increase in patient safety.	
220 – 223	24	Comment: This section states that "in the case of residual active substances without a threshold, a limit dose corresponding to a theoretical 1 x 106 excess lifetime cancer risk should be applied, i.e., 0.15 µg/person/day, or 0.0025 µg/kg bw." The scientific rationale for this approach needs to be referenced. Proposed change (if any): Delete the statement.	Accepted
221-223	3	Comment: In case of mutagenic active substances with sufficient carcinogenicity data available to calculate a	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substance specific cancer risk, it should be possible, not to use the generic TTC of 0.15 µg/person/day (or 1.5 µg/kg/day), but to calculate a compound-specific exposure limit dose with a 10^{-6} (or 10^{-5}) excess life time cancer risk. See ICH M7 Current Step 2 version dated 6 February 2013: "Compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist. For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency and linear extrapolation as a default approach. Alternatively, other established risk assessment practices such as those used by international regulatory bodies may be applied either to calculate acceptable intakes or to use already existing values published by regulatory bodies". Proposed change: Include the possibility of calculating a compound-specific exposure limit dose.	
221-222	10	Comment: Why the TTC for residual active substances without a threshold is set on 0.15 µg/person/day?	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): From our point of view this is very conservative. The TTC for residual active substances without a threshold should also be set on 1.5 µg/person/day.	
221-223	22	Comment: Effective and reproducible cleaning processes should ensure there is low risk of exceeding the TTC limits for compounds with no discernible threshold values. Therefore, **additional safety factors should not be necessary.** Proposed change: Delete lines 218-223 starting with-In contrast to impurities, residual active substances principally are avoidable...for residual active substances.	Accepted
222	18	The conversion of mg/person/day to mg/kg/day is based on 60 kg bw, which is inconsistent with the recommendation to use 50 kg bw in the footnote referenced in line 127.	Accepted. For the sake of consistency 50kg should be used. (Conversion has been deleted)
226	8	Comment: For compounds with evidence of a threshold related mechanism, allow the use of an ADE as well as the PDE. Proposed change: … safe exposure levels without appreciable risk of	Accepted

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>genotoxicity can be established by using the PDE or ADE approach.</td><td></td></tr>
<tr><td>227</td><td>8</td><td>Comment:

For compounds with limited data available, it is recommended to reference the ISPE Risk MaPP Guidance and include guidance on limits for different classes of active substances, as defined in the ISPE Guidance.

Proposed Change:

For compounds with limited data available, the following limits should be considered:

<table><tr><th>For compounds that are …</th><th>ADE</th></tr><tr><td>… likely to be carcinogenic</td><td>1 µg/day</td></tr><tr><td>… likely to be potent or highly toxic</td><td>10 µg/day</td></tr><tr><td>… <u>not</u> likely to be potent, highly toxic or genotoxic</td><td>100 µg/day</td></tr></table></td><td>Accepted</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
228-238	2	The chapter on active substances with sensitising potential is not very specific. Nearly all active substances have a low percentage of patients showing drug-induced immune-mediated hypersensitivity reactions. It should be clarified, under which circumstances a compound is considered as highly sensitising (severity of reactions, percentage of individuals affected). For compounds with a low sensitising potential (e.g. when hypersensitivity reactions are rare / non-severe) it should be possible to define a practical threshold, e.g. by use of a higher safety factor to the doses where hypersensitivity reactions were observed. While highly sensitizing compounds are a concern, as written this could be applied to other compounds that may have the potential to provoke immune reactions. For example, biologic proteins innately have a risk for an immune response. If this is applied to all compounds with the potential for an immune reaction, this could have a significant detrimental impact to patients as dedicated facilities would be required for a significant portion of the production process. We would recommend it be changed back to the GMP language of “highly sensitizing material.”	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: change language throughout section and document from “sensitizing potential” to “**highly** sensitizing **materials**.” Biological products such as monoclonal antibodies and therapeutic proteins rapidly degrade and denature when exposed to pH extremes and/or heat, and thereby become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment must be performed under conditions that ensure degradation and inactivation of protein-based products. After cleaning, only breakdown products such as smaller peptide fragments or amino acid derivatives which are formed due to protein hydrolysis may be present. These breakdown products do not exhibit the pharmacological activity of the actual product. Once the efficacy of the applied cleaning conditions to degrade and denature the product is demonstrated, then the determination of health based exposure limits using Permitted Daily Exposure (PDE) limits of the active and intact product is no longer justified and would not be required. Alternatively, the acceptable level of potential residual soil present on the inner surface of the manufacturing equipment should be expressed in relation to the cleaning capability of the cleaning process itself and the removal of all process residuals If a biologic is determined to be in scope guidance should also reference MABEL (minimum anticipated	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biological effect level) as a potential approach.	
228 – 238	8	Comment:s Deletion of this section and the section on reproductive and development toxicity is recommended. If use of an ADE is allowed, as calculated per the ISPE Risk MaPP Guidance, calculation of the ADE includes determining / choosing the worst case adverse effect based on structural similarity, regardless of whether that effect is sensitising, reproductive toxicity, or another adverse effect. Therefore, these sections would not need to be separately highlighted. It is neither helpful, nor business-possible from a cost-perspective, to default to dedicated facilities due to lack of compound-specific data. Especially in the case of development compounds, for which information is often limited, dedicated facilities would be required for these compounds that may only be manufactured a very limited number of times. It is acknowledged that, unlike the situation for genotoxic impurities, there is no extensive database for sensitizing compounds, nor an extensive database with animal data for reproductive/ developmental toxicity. However, in lieu of information in a database, guidance	Not accepted. Reworded section on reproduction has been included which deal also with situations where data is lacking.

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		can be derived from structural similarity. Use of an ADE allows for expert judgements, based on structural similarity to be employed. Proposed change (if any): Delete this section. – OR – The use of ADE or PDE values for all but the most highly sensitising compounds is acceptable. Compounds such as beta lactam antibiotics would still require dedicated facilities.	
229 - 238	17	Comment: Regarding the section on active substances with sensitising potential -- it is unclear as to how to apply this guidance. Is the guidance on exclusion of sensitisers aimed solely at those that act via heightened levels of specificity (i.e., Type I sensitisers)?	Accepted: Wording included for products with a highly sensitisting potential.

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		There are numerous drugs that are contact sensitisers and given safely via, for example, the oral route (many Type IV sensitisers). This section could benefit from additional clarity	
236 - 238	5	Comment: Allergen manufacturers specialise in production of allergens e.g. pollens and house dust mites for the treatment and diagnosis of allergy. We do not know, how it would be possible to generate a safe threshold value for risk identification for these allergens. In a non sensitised human population the threshold value could not be determined. There are also different parts of the manufacturing process to consider – although theoretically there is the possibility of residuals and cross contamination whilst the allergen is in the powdered extract, good cleaning validation ensures this is low risk and there is no mixing for example at this stage of pollens and mites – once in aqueous form the risk of residuals is minimal. Separate facilities should be available for live source materials, like mites but once used as allergen source material this	Not accepted: Too specific and thus not within the scope of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		becomes unnecessary. Even if there were separate facilities required for different allergens they would need to come together in a shared facility at some point in order fulfil orders that require a mix of allergens . For very high risk allergens like peanut best practice should be always be for the manufacturer to have separate facilities as it is impossible to remove all residuals through cleaning Proposed change: *An exemption clause should be added for the manufacture of all allergens for treatment and diagnosis of allergy (except the very high risk allergens (to be specificaly defined) with the proviso that all manufactureres have full validated cleaning procedures in place that are in compliance with Annex 15 EU Good Manufacturing Guideline and Quality Risk Management (ICH Q9)*	
236 - 238	12	Comment: Allergen manufacturers are specialized in the production of allergen products for diagnostics of allergy and therapeutic use (allergen immunotherapy). Manufacturing of allergen extracts of different types (species) is performed in specialised dedicated facilities. Allergen extracts are produced using the same process and the same dedicated equipment for different species	Not accepted: Too specific and thus not within the scope of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of allergens. This processing implies full compliance with strict rules and full compliance with the principles of Quality Risk Management (ICH Q9). Proposed change: For other routes of administration, a safe level of exposure is more difficult to establish. As outlined in 237 point 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances 238 and medicinal products for which scientific data does not support a threshold value. *Allergen manufacturing is a highly specialized production of allergen products intended for diagnostics of allergy and therapeutic purpose (allergen immunotherapy). The manufacturing process uses the same facilities and/or equipment to manufacture different allergen substances and allergen medicinal products issued from various allergenic source materials. This implies implemented Batch-Change-Over procedure and validated cleaning procedures that are in compliance with Annex 15 EU Good Manufacturing Guideline and Quality Risk Management (ICH Q9)*	
236 - 238	21	Comment:	

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		A plant where allergens (extracts, therapies, diagnostics, etc.) are manufactured must necessarily use the same facility/equipment for manufacturing both different allergen drug substances and products derived from various allergenic source materials. Operational and technical measures to mitigate risks of cross-contamination are already implemented as well as the cleaning validation. Proposed change: For other routes of administration, a safe level of exposure is more difficult to establish. As outlined in 237 point 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances 238 and medicinal products for which scientific data does not support a threshold value. *However it is allowed that allergen manufacturers use the same facilities and/or equipment to manufacture allergen substances and medicinal products from several allergenic source materials provided that they implement adequate Batch-Change-Over procedure.*	Not accepted: Too specific and thus not within the scope of the guideline.
236 - 238	26	Comment: In general, allergen manufacturers are specialized in the production of allergen products intended for diagnostic or for therapeutic purpose.	Not accepted: Too specific and thus not within the scope of the guideline.

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		They manufacture different types of allergen extracts using the same process and the same equipments, in the same premises. This requires a compliance with strict rules and application of the principles of Quality Risk Management (ICH Q9). This corresponds to the “adequate control” that is refers to on line 69. <u>Proposed change</u>: For other routes of administration, a safe level of exposure is more difficult to establish. As outlined in 237 point 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances 238 and medicinal products for which scientific data does not support a threshold value. *However it is admitted that allergen manufacturers use the same facilities and/or equipment to manufacture different allergen substances and allergen medicinal products issued from various allergenic source materials provided that they implement adequate Batch-Change-Over procedure.*	
239-254	23	Comment: The approach for setting health-based limits for therapeutic macromolecules and peptides should be	Not accepted – new wording proposed for this section

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		no different than for small molecules. Both pharmacological and off-target, adverse effects from clinical and relevant non-clinical studies should be considered. No distinction needs to be made between large molecules (e.g., monoclonal antibodies) and conjugates of therapeutic proteins or monoclonals with toxic payloads. The points of departure and adjustment factors may differ depending on the underlying database. Additional clarity regarding the compensation for potential species differences should be provided. This difference could include not only target affinity but also pharmacokinetic differences. Proposed change (if any): Line 247-248 Delete the word "not" on Line 247 or change to "- ***it is not considered acceptable to derive a*** ~~PDE value based on the LOEL for~~ ***health-based exposure limit based solely on the*** pharmacodynamic effects***; toxicity must also be considered***."	
239-254	4	**4.1.5 Therapeutic macromolecules and peptides** Comment / question:	Not relevant – wording amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"For therapeutic macromolecules and peptides, it is not considered acceptable to derive a PDE value based on the LOEL for pharmacodynamic effects. If no clinical pharmacodynamic data are available, the NOEL should be based on non-clinical studies." Why is LOEL not acceptable for peptides?	
240	20	Comment: It may potentially be confusing to introduce alternative descriptors for biotechnology-derived therapeutics or "biopharmaceuticals" as defined by ICH S6(R1) and we therefore recommend consistency with that guidance. Proposed change: Therefore, we recommend replacing "therapeutic macromolecules and peptides" with "**biotechnology-derived therapeutics (biopharmaceuticals)***", and adding the footnote "***As defined by ICH S6(R1)".**	Not accepted. Macromolecule and peptides class is broader than biotechnology products.
240-254	7	Comment: Section 4.1.5 "Therapeutic macromolecules and peptides" should reflect the destructive cleaning that leads to degradation and inactivation of the protein products. Proposed change (if any): Proposed text to be added to	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		section 4.1.5: Biological products such as monoclonal antibodies and therapeutic proteins rapidly degrade and denature when exposed to pH extremes and/or heat, and thereby become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment must be performed under conditions that ensure degradation and inactivation of protein-based products. After cleaning, only breakdown products such as smaller peptide fragments or amino acid derivatives which are formed due to protein hydrolysis may be present. These breakdown products do not exhibit the pharmacological activity of the actual product. Once the efficacy of the applied cleaning conditions to degrade and denature the product is demonstrated, then the determination of health based exposure limits using Permitted Daily Exposure (PDE) limits of the active and intact product is no longer justified and would not be required. Alternatively, the acceptable level of potential residual soil present on the inner surface of the manufacturing equipment should be expressed in relation to the cleaning capability of the cleaning process itself and the removal of all process residuals.	
241-249	14	Comment: We do not believe that it is true that for macromolecules and peptides, adverse events are restricted to exaggerated pharmacodynamics effects. Examples are reactions due to the sensitising effects of some of the molecules, e.g. streptokinase and	Not accepted - Not relevant, wording amended

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		analogues. It may be more meaningful to derive a pharmacologically inefficacious dose in man from a LOEL in man than from a NO(A)EL in an animal (e.g. monkey) study. The man-to-monkey difference may bear more uncertainty than the LOEL-to-NOEL extrapolation in man. Proposal: Re-write paragraph 4.1.5 to express that there is no substantial qualitative difference in the way PDEs are to be derived for macromolecules/peptides versus other APIs.	
243-245	20	Comment: For the sake of clarification, this sentence could be moved to a separate paragraph. Proposed change: Moving “This would not apply to a therapeutic protein conjugated to a small molecule as pharmacophore (e.g. a cytostatic agent), where the toxicity of the conjugate needs to be considered.” to a separate paragraph.	Partly accepted. All risk of potential contamination needs to be considered on a case-by-case basis.
245, 250	24	Comment: See comments on line 108	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Change NOEL to NOAEL	
245-254	20	Comment: For therapeutic macromolecules, especially antibody constructs, it is often not feasible to demonstrate a NOEL for pharmacological effects in animals (e.g., because only a surrogate molecule binds target in the animal efficacy model, or a pharmacodynamic marker is not available for the animal species selected for toxicology testing) or in human studies (e.g., because clinical dosing starts at the MABEL, or a pharmacodynamic marker is not available for initial studies). As such, a pharmacodynamic NOEL must be derived from the MABEL or LOEL by extrapolation or using uncertainty factors. A scientific judgment should be used in determining which approach is most suitable for the given molecule based on the available pharmacology, safety and pharmacokinetic data in humans and/or animals. In addition, please clarify that in addition to evaluation of pharmacodynamic effects, evaluation of pharmacokinetic parameters can be used to provide science-based rationale for specific acceptable limits.	Not accepted – not relevant as wording has been amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed changes: Replace existing lines 245-254 with “A NOEL based on ~~clinical~~ pharmacodynamic effects **in humans (preferable) or non-clinical studies** should correspond to the highest dose level tested which is considered therapeutically inefficacious **or pharmacodynamically ineffective**. **If a NOEL has not been demonstrated, a PDE value should be derived from the LOEL for therapeutic or pharmacodynamic effect by extrapolation of the available clinical or non-clinical data or by applying appropriate uncertainty factors. Non-clinical data used for establishing a PDE value should be from pharmacologically relevant species and/or in vitro models; potential species differences in target affinity or systemic exposure should be taken into account. In addition to evaluation of pharmacodynamic effects, evaluation of pharmacokinetic parameters can be used to provide science-based rationale for specific acceptable limits (e.g., when the dosing regimen for the residual API is different from the dosing regimen for the API containing the residual).”**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
247 - 248	17	Comment: The concept that use of a LOEL as a point of departure in PDE determination for therapeutic macromolecules / peptides is not well supported and appears non-aligned with the allowable use of LOEL in determination of PDE for small molecule pharmaceutical actives. The use of clinical dose-ranging and other results can give a good approximation of NOEL when this parameter is not directly determined. Proposed change (if any): Consider amending the draft text to omit the sentence beginning on line 247 and continuing to line 248. Replace this sentence with new text indicating that when available dose-response and other information is available along with a LOEL for therapeutic macromolecules that an extrapolated NOEL may be used with caution in conjunction with the appropriate F5 value as for small molecules.	Not accepted – not relevant as wording has been amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
248-254	1	For peptides, the species differences with regard to the immunogenic properties have to be taken into account. Therefore, human LOEL may be more significant for the derivation of a PDE than a NOEL from animal data.	Not accepted – not relevant as wording has been amended.
249	20	If the previous comment is not implemented, please change line 249 as follows: "~~All~~ Available **and relevant** non-clinical *in vitro* and *in vivo* pharmacodynamic data…"	Not accepted – not relevant as wording has been amended.
255-269	2	Section 4.1.6 would lead to the conclusion that when insufficient data are available to establish a threshold value, the active substance should be manufactured in a dedicated facility. If this is the intent, nearly all investigational compounds would have to be manufactured in a dedicated facility since developmental and reproductive data are not typically available. Issues may also arise for significant numbers of commercial products where reproductive safety studies have not been conducted. Furthermore the feasibility/value of a generic threshold for repro- and developmental effects as suggested in lines 260-266 is questioned. One concern is the endpoints and NOAELs to be considered in a reproductive toxicology study are much more complex/difficult to define as compared to the TTC for mutagenic compounds (which is based on a rather	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"simple" endpoint, i.e. absence or presence of mutagenic effects in an AMES test). Moreover, we would like to stress that Industry has been dealing with this issue (i.e. indicated data gaps) up to this point in time by applying uncertainty factors or by classification. We are not aware of problems that have arisen from this approach, and see no reason why this should now be considered inappropriate. More importantly the ICH Q3C principles to derive PDEs, advocated in this draft guidance, would allow for addressing this data gap as well by applying an additional uncertainty factor.	
255-269	3	Comment: This paragraph suggests the need for dedicated facilities for all compounds "when insufficient data are available to establish a threshold value", which would mean that facility dedication would have to be implemented in all situations where there are no reprotoxicity studies, e.g. all compounds in early development stages. This is not practicable. Although currently TTCs for reproductive and developmental toxicities have not yet been published for APIs in particular, several other concepts for estimating a threshold may be applied, e.g. by comparison to similar compounds or by using published TTC values that generally do include reprotoxicity endpoints. Proposed change: Please change paragraph accordingly.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
255 - 269	24	Comment: This guidance in this section is not clear. Lines 256-266 seem to imply the use of the threshold of toxicological concern concept when insufficient data is available yet lines 267-269 seem to indicate that if insufficient data is available the substance should be manufactured in a dedicated facility. Proposed change (if any): Delete line 267-269.	Accepted.
255-269	27	Comment: The toxicological and pharmacological knowledge from the early stage development products are limited. The threshold values are very seldom official in public literature, but part of the Intellectual Property of the development organisation. The requirement for official publication will make it impossible for any Pharmaceutical company to conduct manufacturing of Clinical Trial Materials for Phase 1 up to Phase 2A studies since everything is required to be manufactured in dedicated facilities. Proposed change (if any): Line 265-266: Delete sentence: In order to be acceptable, such threshold value would need to be available in public literature.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
261-269	14	Comment: We are not aware, at this stage, of a scientific basis for the level where a generic threshold for potential reprotoxic effects of an API should/could be set. Industry is currently working at gathering data across companies to propose a reprotoxic TTC that might be usable in the future. However, there is evidence that applying a conservative adjustment factor (e.g. 10) to the NOEL of a subchronic or chronic general tox study (i.e. substance-specific dose-response data) will protect from reprotoxic effects in almost all cases. Currently, the call for a generic TTC-type threshold may lead to the automatic application of a 0.15 mcgr or 1.5 mcgr limit (same as for genotoxics) for which there is no scientific basis and which will have no defined benefit to the patient. Scientifically, if the proposed “additional safety factor approach” (cf above) is not accepted, the call for dedicated facilities “when insufficient data are available to establish a threshold value” means that facility dedication would have to be implemented in all situations where there are no reprotox studies. This is the case for certain categories of commercialised drugs (e.g. oncolytics where no reprotox studies are required and such studies will not be conducted) and in a transition phase for almost all drugs (i.e. during the manufacture of early phase clinical material where reprotox studies are planned but not yet conducted).	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposal 1: If no reprotox data are available and there no evidence (e.g. MOA) that would make such effects appear unlikely, propose a generic additional safety factor to the NOEL of a subchronic/chronic general toxicity study instead of proposing a generic threshold such as for genotoxic contaminants. Proposal 2: Last sentence of chapter 4.1.6: "In case the level of residual active substance cannot be reduced to the established or derived threshold value, the active substance should be manufactured in a dedicated facility."	
261-265	25	Comment: More details on a generic threshold concept for fertility and embryo-fetal effects would be very helpful. It would be advisable to provide exemplary thresholds (or, ideally, reference thresholds) and relevant literature references.	Not relevant – wording amended for this section
261-262	1	This sentence may be interpreted in a way that the same TTC as for genotoxic impurities may be applicable also for reproductive and developmental toxicants. In order to avoid such misinterpretation, rephrasing is recommended. Currently research is ongoing regarding the development of a potential TTC for reproductive	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endpoints.	
261 – 269	8	Comment: See comments above for Lines 228 – 238, (Active substances with a sensitising potential)	As above
261 – 269	20	This section on lack of Developmental and Reproductive Toxicology data (Section 4.1.6) suggests that when insufficient data are available to establish a threshold value, the active substance should be manufactured in a dedicated facility. If this is the intent, the majority of investigational compounds would likely have to be manufactured in a dedicated facility since developmental and reproductive data would not typically be available. This could result in a potentially unfeasible situation. Clarification would be appreciated that the described generic threshold approach would need to be data-driven and justified, but would not need to be available in the public literature. In addition to the generic threshold approach, we suggest that lines 261-266 be clarified to provide the option of using comparator data as follows: Proposed change: "In these cases, the use of a generic threshold value ~~as is applied for genotoxic substances~~ may be considered. Such a threshold value could be conservatively derived from a database of NOAELs obtained in animal studies of	Not relevant – wording amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		fertility and embryo-fetal development conducted for active substances representing a wide selection of pharmacodynamic effects. **Additional science-driven approaches such as using comparator data may be appropriate.** ~~In order to be acceptable, such a threshold value would need to be available in public literature.~~"	
263	24	Comment: NOAEL used here but not elsewhere in the document. Proposed change (if any): make sure terms are consistent throughout the text.	Accepted
263	28	Comment: The use of the NOAEL is noted. Proposed change (if any): NOAELs should be used instead of NOELs in earlier sections.	Accepted
267-269	20	This guidance does not provide alternative recommendations for investigational compounds early in the development lifecycle when clinical dose and toxicological data are not available. Acceptable limits	Not relevant – wording amended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		change as data evolve and intended dosages are refined, and generally regarded default carryover acceptance criteria in conjunction with multiple layers of cleaning verification should be acceptable as data are gathered. Proposed change: We recommend **deleting** lines 267-269 and **replacing** with: "**For early phase investigational compounds, alternative means (e.g., adopting a default carryover limit in absence of data, or allowing for use of disposable equipment for product contact surfaces) may be appropriate**."	
269	4	Comment: **In chemical production of APIs** and their precursors we have sometimes **previous products**, which have to be cleaned out **with limited data available** (e.g. in the production of compounds for clinical trials and the production of intermediates and precursors). For such compounds consider to give guidance on limits for different classes of substances. Refer to ISPE Risk MaPP Guidance.	Partly accepted: the general principles outlined in this guideline to derive a threshold value for risk identification could be applied where required for APIs. However, Deviation from the main approach highlighted in this guideline to derive safe threshold levels could be accepted if adequately justified.
269	4	Proposed Change:- Add new sub-section.	Partly accepted. New wording has been included for IMPs and in particular for situations where data is lack for these

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		4.1.7 Compounds with limited data available Add the following sentence:- For compounds with limited data available (e.g. in chemical production of APIs and their precursors and in the production of compounds for clinical trials), the following limits should be considered:- 1) compounds that are likely to be carcinogenic. (PDE, ADE = 1 µg/day) 2) compounds that are likely to be potent or highly toxic. (PDE, ADE = 10 µg/day) 3) compounds that are not likely to be potent, highly toxic, or genotoxic. (PDE, ADE = 100 ug/day).	types of products.
270-281	2	• Many companies already provide documentation of the acceptable threshold values to manufacturing areas to support cleaning validation and cross-contamination control strategies. The risk assessments are science-based, consider relevant toxicological and pharmacological data, and are written by an expert. Therefore, it would be unnecessary and an undue administrative burden on companies who are already making and adequately documenting these science-based decisions to align with the precise format of the Risk Assessment	< Partly accepted. This section had been amended to allow fir the reporting of the PDE determination strategy. The annex remains to provide an overview for GMP inspectors.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Report prescribed in this section and the associated annex. • The summary elements section of the proposed Risk assessment report approach appears to be subjective (no defined criteria for selection of "Yes", "No" etc) and appears to be a level of constraining detail which is not necessary in a guideline such as this. The form requires binary responses which are typically not feasible for pharmaceuticals nor does it facilitate the "structured scientific evaluation of all available pharmacological and toxicological data" to support an overall assessment of risk. In this regard, it is inconsistent with the general approach of scientific risk assessment. The use of literature needs to be pragmatic and informed as there will be circumstances where internal information is unlikely to be supplemented with any information of value in the external literature.	
270-281	20	Companies already provide documentation of the acceptable threshold values to manufacturing areas to support cleaning validation and cross-contamination control strategies. The risk assessments are science-based, consider relevant toxicological and pharmacological data, and are written by an expert. Therefore, it may be unnecessary and an administrative	See previous comment above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		burden on companies who are adequately documenting these science-based decisions to align with the Risk Assessment Report prescribed in this section and the associated annex. In most instances, the published literature may not be as helpful as the internally-generated dataset, and a literature search may not provide any additional value. Proposed change: We suggest changing this section to read: "The risk assessment report should be based on a comprehensive, scientific evaluation by an expert (e.g., toxicologist, clinician). The rationale should be documented in an executive summary that identifies the critical endpoints and justifies the chosen adjustment factors. A more detailed report should be made available to the EMA by the marketing authorization holder upon request."	
270 - 281	24	Comment: The principles of ICH Q9 are being adopted in the EU GMP Guide and the document is referenced in part 3 of the Guide. A consistent approach to terminology is expected as such the report really discusses the Risk Identification phase of the ICH Q9 process which is the first step of the Risk Assessment	Accepted: wording amended to PDE determination strategy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		phase. The Risk Assessment report should encompass not only Risk Identification but Risk Analysis and Risk Evaluation which would use the information developed based on this guideline to analyze and evaluate the risk. Proposed change (if any): Change “risk assessment report” to “risk identification report”. …the initial page of any prepared risk identification report should be in the form of a summary of the process….	
276	14	Comment: Sourcing to original reference may not always be needed or feasible. When quality controlled high-level reports are available (e.g. Investigator Brochure) this can also be used Proposed change (if any): as above	Partly accepted provided the information is of high quality to allow the establishment of a PDE
281	18	We suggest adding: “therefore the ADI established (and the summary of opinion) and/or existing User Risk assessment of the formulated product (part of the existing document for Marketing Authorisation) are appropriate documents to avoid generating a specific risk assessment report and expert review when applicable.”	Not accepted: Report of the derivation of the health based strategy is required.
282 – 301	8	Comment: Add ADE and LOAEL to the definitions list (in alphabetical order).	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): ADE Acceptable Daily Exposure LOAEL Lowest Observed Adverse Effect Level	
282-300	25	Comment: According to the heading, full definitions should be presented in that section. Proposed change: Presentation of full definitions of the terms.	Accepted
282	17	Comment: In common use, the term ADE (Allowable Daily Exposure) and PDE (Permitted Daily Exposure) are used interchangeably – ADE has been adopted by many regulatory and industry bodies. Proposed change (if any): To avoid confusion, the guidance document could add ADE to the list of definitions under PDE with a note that these 2 terms are effectively synonymous.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
302	3	Comment: The summary of the risk assessment report should list all relevant/critical data. The use of purely qualitative descriptors ("hazards identified") without an indication at what doses these effect were observed may however be misleading. Proposed change: A list/description of the most relevant effects instead of the checkboxes should be included. Also comparable other formats, e.g. from already existing risk assessment documents should be acceptable.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.
302 - 328	24	Comment: This summary sheet is confusing as the title relates to Risk Assessment (which include Risk Analysis and Risk Evaluation that are not addressed) but the content relates to Risk Identification. The purpose of the check boxes is not stated. Will they for example flag a special review?, etc. Proposed change (if any): Change title to Summary of Risk Identification Report. Provide an explanation on how this summary is to be used.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
302 (Annex)	18	**Comment:** As said before (see lines 73-74), for an investigational medicinal product, limited data are available; for hazard identification we would recommend the test system used is added. **Proposed Change**: Please amend the table for including a description of the test system used.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.
302-317	20	We are concerned that if the "unknown" check-boxes are ticked in the hazard identification section, the lack of data could routinely be interpreted by an inspector to mean that particular dedication is warranted The format should be presented as an example. Proposed change: Line 303 could be changed to "**Example** Summary of Risk Assessment Report". In addition, please consider replacing Lines 315-317 of the template with "**Executive Summary**".	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.
303	17	Comment: A number of additions to the proposed template for the Summary Risk Assessment Report (Annex beginning page 9) are suggested to enhance the utility of the report – see below. Proposed change (if any): 1. add the intended therapeutic activity and/or	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		mechanism of action to the face page of the report, 2. under the heading “Hazards Identified” consider adding additional tick boxes to highlight active agents that cause target organ toxicity (aligned with GHS TOST classification) especially when such toxicity is considered off-target or exaggerated, 3. reorganise the categorical response tick boxes from “YES / NO / UNKNOWN” to “ YES / NO / SUSPECTED / UNKNOWN” and alter the listing of hazards to read “Genotoxicant / Reproductive or Developmental toxicant / Carcinogen / Sensitiser” thus allowing expression of a more complete range of knowledge, 4. in addition to the summary tick boxes add a blank space to contain any regulatory classification for toxicological endpoints under DSD / CLP (GHS) regulations,	
302 – 328	8	Comment: The BPTF finds that a template for a risk assessment report is a positive aspect as it will facilitate a harmonized approach.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The BPTF fully supports the concept of preparing this risk assessment report based on all the data available, including the consideration of various methods of calculating contamination cleaning limits. Proposed change (if any): The template should be revised to allow for documenting various methods of calculating contamination cleaning limits.	
315-316	14	Comment: All relevant / critical data have to be listed (e.g in silico data, information from transgenic models, class effects). The use of purely qualitative descriptors ("hazards identified") without an indication at what doses these effect might appear may be misleading. Proposed change (if any): add boxes for 'Other data' field. Add a "comments" box to each of the descriptors in 316.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
315-317	23	Comment: The section should be used to guide the inspector to the most hazardous drugs substances to focus on the derivation of the health-based limit and the margin of safety demonstrated in the risk assessment. It should not be used to automatically determine if dedicated facilities are required. The check boxes should be deleted from the annex example. Proposed change (if any): Delete the check boxes. Delete Reproductive developmental toxicant as this is a threshold effect and can typically be controlled to a proper ADE without requiring dedication. If left here with these other non-threshold effects, some inspector will confuse it with a hazardous substance requiring dedication. Most reproductive hazards and hormones can have a proper ADE established that can be met and not require dedication.	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.
317	19	Comment: add in the hazards identified “therapeutic macromolecules or peptides “ and “other” in case of specific risk for an unknown molecule Proposed change (if any): add 2 case (see above)	Not accepted. The annex is a simplified version of the PDE determination strategy and is to assist GMO inspectors. Where further detail is required it can be sought in the report itself.

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147 (11/9/14 draft)	29	In some cases it may be valuable to also consider class effects; especially if the concern is about AEs that would become apparent only after extended exposure, we may often not have these long-term data available.	Not accepted. The use of class effects is considered more applicable to chronic exposures. Chronic exposure posed by cross contaminants is not envisaged – only one batch will likely be affected. Additionally, the current guideline has some solutions for where data is lacking (genotoxicity, reprotox, IMP) and is thought to be sufficient.
238-41 (11/9/14 draft)	29	The sentences could be re-worded as they do not seem entirely comprehensible. Is it assumed that 1 x 106 should be 1/1000000? Please clarify.	Not accepted. The 1x106 value is the calculated upper bound lifetime risk of cancer, so called “virtually safe dose” calculated for most carcinogens (Munro et al. 1999). The TTC value 1.5 μg/day derived for genotoxic impurities in drug substances was given a value of 1.5 μg/day, corresponding to a 10-5 lifetime risk of cancer and was justifiable for pharmaceuticals as a benefit exists. The wording is considered in line with previous guideline (ref GUIDELINE ON THE LIMITS OF GENOTOXIC IMPURITIES (EMEA/CHMP/QWP/251344/2006)
255 (11/9/14 draft)	29	Is what is meant “high” sensitising potential or “highly” sensitising potential? Please check and clarify.	Accepted. The word “highly sensitising potential” has been changed to “high sensitising potential”