14 June 2018
EMA/411141/2018

Overview of comments received on Questions and answers on implementation of risk based prevention of cross contamination in production and '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)

Comments from:

No.	Name of organisation or individual
1.	Science Pharma, Poland
2.	Shire
3.	ERT
4.	ISPE Japan Affiliate Containment COP
5.	PharmaConsult Us, Inc.
6.	EFPIA
7.	Sandip Vitthal, Pharmaceutical Quality Professional, India
8.	Azierta, Spain and Maas & Peither GMP Verlag (GMP Publishing), Germany
9.	Excella, GmbH, Germany
10.	Michel Crevoisier, Consultant
11.	Synthon BV, The Netherlands
12.	Gilead Sciences International Ltd
13.	ChemSafe srl
14.	Azierta
15.	SICOS Biochimie (French Syndicat de l'Industrie Chimique Organique de Synthèse et de la Biochimie)
16.	A3P Cleaning Validation Workgroup
17.	IFAH-Europe
18.	E.I.P.G. – European Industrial Pharmacists Group

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

No.	Name of organisation or individual
19.	AstraZeneca Pharmaceuticals
20.	"Point Forty Five" - France
21.	F. Hoffmann-La Roche Ltd, Switzerland
22.	BioPharmaChem Ireland
23.	Cleaning Validation Technologies, USA
24.	International Society for Pharmaceutical Engineering (ISPE)
25.	Servier Group, FRANCE
26.	Sopharma AD, Bulgaria
27.	REGenableMED consortium, UK
28.	ASTM Team for WK15778 Science-based and Risk-based Cleaning Process Development and Validation Standard Guide
29.	Intertek
30.	AESGP
31.*	Health-Med, Poland
32.*	APIC

* Received after consultation deadline.

1. General comments

Stakeholder number	General comment (if any)
3.	As a toxicologist I routinely prepare Health Based Exposure Limits based on the 2012 guideline. In this current guideline 2016, it does not present the situation for when the PDE is higher than 1/1000th the minimum therapeutic dose for a non-hazardous substance. I assume the PDE should only be applied to calculate the cleaning limit if it is lower than 1/1000th the minimum therapeutic dose? If the PDE is calculated to be higher, then default to 1/1000th minimum therapeutic dose? Some clarification on this would be helpful, as the document seems assume that a PDE will always be lower than 1/1000th the minimum therapeutic dose.
4.	ISPE Japan Containment COP welcomes the opportunity to comment on this document. Some statements in this document would confuse GMP requirements with IH (Industrial Hygiene) ones. It is concerned that those confusions would incur the same ones in Risk Assessment for cross-contamination to be carried into execution.
5.	Thank you for the opportunity to comment on this document. Overall the document appears to be relieving some of the regulatory requirements set out in the 2014 updates to Chapters 3 and 5 which is unfortunate as the original requirements ensured that the all compounds where assessed and understood. The new direction will allow companies that tend to be on the low end of compliance to cut corners and not do the proper assessments. In addition compounds that do not fall into the highly hazardous category but have low HBELs and are used daily such as CNS and anti-psychotic products may not have the proper controls or assessment if allowed to use the 1/1000th rule of thumb rather than a full HBEL. In our experience working with many companies that manufacture these products we find that these products tend to have the highest risks due to the manner in which they are handled and produced. We also have found that many of the generic companies we work with that do not have toxicologists on staff have purchases the PDE/ADE monographs from reputable sources for their full portfolio.
6.	EFPIA welcomes the opportunity to comment on this draft Q&A document.

Stakeholder number	General comment (if any)
	EFPIA companies support a risk-based approach regarding cleaning validation, acceptance limits and the need for dedicated facilities, reflecting all available toxicological and pharmacological data in order to ensure patient safety. As is also reflected in the guideline where this draft Q&A document refers to. However, EFPIA companies have a number of concerns with the provided draft Q&A document: 1. Regarding Question and Answer documents in general we understand that "these are intended to briefly communicate, in easily comprehensible language, requirements, practices or interpretations responding to the most frequent questions in a specific area" (EMA: Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework, 2009). The current draft Q&A document which tries to address issues around 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' does not seem to meet above goals, moreover, it introduces concepts not described in the original guideline and which in part are contradictory. Especially the introduction of the 'highly hazardous' classification, which in our view is not scientifically sound, is highly problematic. EFPIA considers this is a major issue and proposes to delete the classification as such and adjust any other Q&As relating to this (see also detailed comments). 2. Furthermore, to our knowledge, Industry, as an important stakeholder, has not been consulted at the conception of the various Questions stated in this document and therefore, in our view, a number of Questions regarding issues considered important for the manufacturers are missing. The next line is a summary of suggestions made by Industry for Questions for which the addition could add value to the Q&A document.
6.	EFPIA companies provided the following questions not discussed in current draft Q&A document or instigated by the provided draft Q&As: 1. PDE calculations require data from the core data sheet and the Common Technical Document (modules 2.4 and 2.5). However, some of these data are only available in the DP marketing authorization holder dossier which may not be with either or both the Active Substance or Drug Product manufacturer. The Role and Responsibilities of the manufacturer and Marketing Authorization Holder should be clarified in the Q&A. 2. A statement would be welcomed on how to treat atypical API's or other substances with known low toxicological potential like e.g. CaCO3, dexpanthenol, glucose, NaCl, KCl (when applied orally).

Stakeholder number	General comment (if any)
	3. There are different hazard limits expressed in various regulations and guidances based on different terminology. There are PDE limits as defined in ICH Q3C/Q3D and the shared facilities guideline. On the other hand there are OEL limits from OSHA etc. Could it be clarified what the differences are between these especially within the context of current document? 4. What is the definition/threshold of “high sensitizing potential”. 5. There is no effective guidance regarding how to address intermediates used within the manufacture of an active. This is a key area for many and therefore it would be useful to understand what the expectations would be (to be addressed either as part of the Q&A or separately if this would mean introducing new concepts).
7.	Q1 is saying YES we have to establish health based exposure limit for ALL products, while by sub-sequent question is saying to establish it for highly hazardous product and for others the traditional approach(10 ppm, 1/1000th STD) will work.
7.	In earlier published 2014 guidance it was mentioned to comply with this guidance by 2015/16. Now as per this Q and A, It is mentioned to use 1/1000th minimum therapeutic dose approach for non-highly hazardous category based product. Personally I’ve seen that many SMEs (very well recognised regulatory agency) are now not considering this 10 ppm and 1/1000th minimum STD approach, as per their literature the only science based approach shall be followed which is ADE/PDE based limit. Group of industries also believe this and they’ve invested to comply this guidance. Now seeing this Q and A, why we want to consider safety factor approach? However, My personal opinion is to calculate the value by both the way (PDE and 1/1000th STD) and to select the one which is lowest.
8.	In order to assist the pharmaceutical industry in implementing the new GMP regulations, in January 2015, Azierta, as an external service provider, started a new project to calculate the PDE values for active pharmaceutical ingredients (APIs). Azierta compiled full PDE reports as foreseen by the EMA guide (EMA/CHMP/CVMP/ SWP/169430/2012). Azierta has calculated PDE values for more than 1200 substances. This is a huge and unique data base that allows a well-grounded revision, a closer analysis of the results obtained. We do believe, that nobody else in Europe overviews such a huge amount of PDE data. The analysis especially focussed on the questions: Which active pharmaceutical ingredients turned out to have the lowest PDE values,

Stakeholder number	General comment (if any)
	in other words, are highly hazardous? Can they be related to certain groups, certain therapeutic classes? The analysis of 1200 APIs revealed that it is not possible to estimate the danger or toxicity of APIs only by their therapeutic group. Not all substances with a high or very high toxicity level correspond to expected groups such as hormones and cytotoxic agents and, not all APIs in these therapeutic groups are highly hazardous. Therefore it is necessary to perform a toxicological and pharmacological evaluation for every single API, irrespective of the “group” it belongs to. Please find attached the full report for further details.
10.	While the 2015 Guidance and the Concept Paper formed a coherent package and sent a clear message to the industry to adopt science and risk based procedures and to determine Health Based Exposure Limits (HBEL), this Q&A document appears like a step back. Why would the EMA again want to differentiate between highly hazardous and non highly hazardous API, particularly when one of the objectives of the Guidance was to avoid and overcome hitherto fuzzy terms like “cytotoxic products” or “highly active compounds”? In practice, one has to determine HBELs “for all products” (Q/A1) to justify the classification anyway. Once the PDE is known, I can see no significant advantage for companies in a black and white discrimination of API where we better deal with a continuum of hazard. I am afraid the Q&A document, as it questions statements made in the original guideline, sheds a light of contradiction and insecureness on EMA. It leaves the impression of a catechism where some of the questions have been formulated to fit reactionary amendments to the original text presented as answers.
11.	We consider it contains inconsistencies with the original PDE guidance (the document EMA/CHMP/ CVMP/ SWP/169430/2012). One example is the remark in the Q&A document that PDE values cannot be higher than these derived from traditional approaches. This answer in the Q&A results in skewing towards worst case. After all, one would only use the PDE approach here to set a lower limit for compounds of higher potency in line with health based arguments. For less potent compounds on the other hand this would not be

Stakeholder number	General comment (if any)
	applied…It seems strange and undesired…
12.	We understand the intent of the “high hazard assessment” described in the Q&A is to triage which compounds should undergo a PDE approach or other default approaches to define an HBEL. However, the “high hazard assessment” was not originally mentioned in the prior guidance and the EMA should consider adding it to the guideline versus developing new guidelines in a Q&A. In practice many pharmaceutical companies have been deriving PDEs for all compounds regardless of the hazard of the compound. The Q&A seems to require the separation of compounds based on hazard which we believe is not the intent of the original guidelines. The PDE is a science-based, safe HBEL derived from the known hazards of a compound. While our intention is not to remove the triage option, we recommend that flexibility be made for those companies that provide PDEs for all compounds and such a separation of compounds based on hazard is not required.
13.	We assume that 1/1000th of the minimum therapeutic dose, disregarding the administration route, can be considered as sufficiently conservative (as stated in Q4). Moreover, assuming that the body weight of a prematurely born newborn is 0.5 Kg (as stated in Q11), the ratio beetween the standard adult body weight of 50 Kg and 0.5 Kg is 100. If 1/1000th of the minimum therapeutic dose approach is considered as sufficiently conservative also when a drug with exclusively adult population designated target contaminates a drug with prematurely born newborns as designated target population, the safety margin becomes 10.
16.	Is there an international consensus (health authorities) on the different subjects? Should we consider disinfection (use of Biocide) as part of cleaning validation process?
17.	IFAH-Europe welcomes the opportunity to provide comments on this Concept paper. It is appreciated that this Concept Paper is set up to create clarity, however please find a few comments and suggestions. We are welcoming that the 1/1000th dose criterion is now allowed as an alternative to a pure HBEL (Health Based Exposure Limits) approach, if justified. The practice has shown, that very often, the classical residue limits are much stricter than the residues calculated with an HBEL like a PDE value.

Stakeholder number	General comment (if any)
	We are also welcoming that the derivation of a PDE from an OEL or OEB is now allowed, as both HBELs are derived based on toxicological and human health effects characteristics for a substance with the main difference to be the exposure time. OEL are more frequently determined even by API manufacturers for the sake of operational safety. Finally, we are welcoming that the Q&A document opens the possibility to use the human PDE value in case no specific data for the target animal species exist. This facilitates the calculation of residues in case of products with various target species. Industry would welcome a statement how to treat API or other substances with known low toxicological potential like e.g. CaCO3, dexpanthenol, glucose, NaCl, KCl (when applied orally). However IFAH-Europe has serious concerns related to the practical use of this document for the veterinary sector. Regarding Veterinary Medicinal Products we have the following remarks: It seems to be very clear that this Q&A document has been designed from a Human health centric standpoint. This paper remains focussed on the single approach of PDE and TTC described in the Guideline when animal health specificities have not been considered such as for instance: - species consideration for limit calculation - already existing specific toxicological consideration - absence of veterinary Genotoxic level IFAH-Europe would like to remind that guideline EMA/CHMP/CVMP/SWP/169430/2012 has recognised the existence of specificities regarding veterinary industry: - manufacturing facilities dealing only with veterinary products - “interpretations” or “derived safe (threshold) level” are accepted with adequate scientific justification. This document should include more specificity for the veterinary industry especially in regards to species and veterinary products specificities.
18.	This Q&A document is appreciated by our members as it is considered useful for clarifying a number of points on the implementation of the corresponding guideline.

Stakeholder number	General comment (if any)
	In particular, our appreciation refers to the clarification on the following points: - Definition of highly hazardous products/active substances (Q2) - The circumstances where HBEL based on the 1/1000th minimum therapeutic dose approach can be applied (Q4) - The recommendations about the choice of the cleaning limits (Q6) - The adjustments of HBELs for paediatric population (Q11)
19.	There is no clear definition within the Q&A document as to its intended scope. The guideline itself relates specifically to the drug product; however the Q&A document seems to indicate a change in scope to also incorporate drug substance. Further to this point, there is no effective guidance regarding how to address intermediates used within the manufacture of an active. This is a key area for many and therefore it would be useful for the Q&A document to address this.
21.	We appreciate the opportunity of providing comments to the SWP, however we feel it is regrettable that no separate call for questions to be included in the Q&A was made. The types of questions that are addressed have a big impact on the scope and tone of the document. Industry at large had no possibility to ask some of the questions they were really interested in, and other (potentially biased) questions occupy much of the document.
23.	Thank you for this Q&A document. It is a breath of fresh air.
24.	ISPE continues to support the EMA SWP and GMDP IWG efforts to develop clear guidance on setting health-based exposure limits (HBELs) that are consistent with good science and the principles set out in ICH Q9. We also understand the concern for potential inconsistencies in the way companies derive and apply HBELs (e.g., acceptable daily exposure (ADE) or permitted daily exposure (PDE) values). The toxicologists in pharmaceutical companies have significant experience setting safe levels of exposure to ensure both patient and operator safety. The methods they use reflect current science and risk assessment methods. It would be inappropriate and unnecessary to de-emphasize the importance of acceptable daily exposure (ADE) values in favour of old traditional methods such as 1/1000th of the minimum therapeutic dose that do not provide the same underlying scientific support for robust quality risk management programs. In our view, the proposed responses to a number of the questions represent a step backwards and undermine the industry trend to be more scientific in their approach to managing product cross-contamination risks. The Q&A document does not fully embrace the principles laid out in the original guidance document, and may actually contradict some of the most important premises and

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	recommendations. Many companies have already put in place programs to be compliant with the GMP changes within the expected timeframes. We understand the intent of the “highly hazardous” assessment described in the Q&A is to determine which compounds should undergo a PDE approach or other default approaches to define an HBEL. However, the “highly hazardous” assessment was not originally mentioned in the prior guidance. In practice, many pharmaceutical companies have been deriving PDEs for all compounds regardless of the hazard of the compound. The Q&A seems to require the separation of compounds based on hazard which we believe is not the intent of the original guideline. The PDE is a science-based, safe HBEL derived from the known hazards of a compound. Our intention is not to discourage the identification of highly hazardous substances, especially if used to prioritize the establishment of HBELs to support risk assessments. We recommend that flexibility be made for those companies that provide PDEs for all compounds and such a separation of compounds based on hazard is not required. This approach also may miss out on the compounds that do not quite fall into the highly hazardous category but are used daily such as medicines for CNS and anti-psychotic products and due to the way they are produced may in fact represent more risk to the patient than those labelled as highly hazardous.
25.	We appreciate that a Q&A on this guideline was made.
27.	All the partners of the REGenableMED project are aware of the existence of this draft Guidance. We welcome the opportunity to review these questions and answers and guideline on setting health based exposure limits.
27.	This questions and answers document is globally clear. It provides a useful tool for stakeholders. To maximise understanding of this document, it would be useful to add a list of abbreviations at the end of the document. Particular attention should be paid to advanced therapy medicinal products given that different regenerative- medicine based products are more and more developed in cell and gene therapy platform as shared facilities for several products. It may be relevant to mention these particular products and to link this document to the risk- based approach (EMA/CAT/CPWP/686637/2011) that has been promoted for these products given the uncertainties of their risks. Finally, this questions and answers document should also be linked to specific guidelines on gene therapy medicinal products containing genetically modified organisms such as Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs).
28.	The ASTM WK15778 Standard Guide Team is a global team (US, EU, Japan and Asia) of cleaning and cleaning validation SMEs

Stakeholder number	General comment (if any)
	representing API, Pharmaceutical, Biopharmaceutical, and Clinical manufacturing that has been developing a "Science-based and Risk-based" Standard Guide to cleaning process development and cleaning validation based in ICH Q9 principles for the past several years. This ASTM Standard Guide is now in the final stages of approval for publication at ASTM. These authors are: Thomas Altmann — Ecolab — Germany Jim Bergum, Ph.D. — BMS — US Alfredo Canhoto, Ph.D. — Alnylam — US Michel Crevoisier, Ph.D. — Novartis (retired) — Switzerland Igor Gorsky — Valsource — US Michael Hrytzak, Ph. D. — BMS — US Robert Kowal — J&J (retired) — US Marianne Neverovitch — BMS — US Mohammed Ovais, M.Pharm. — Xepa-Soul — Malaysia Daniela Petrova — Actavis — Bulgaria Osamu Shirokizawa — Life Scientia — Japan Andy Walsh, M.S. LSSBB — Clean6Sigma — US Joel Young — BMS — US In this Standard, we intend to provide guidance on how to determine "the level of effort, formality and documentation" that is needed for cleaning validation based on the level of risk. As an implementation of ICH Q9, this guide is specifically designed to use "Science-based" HBELs (ADE/PDE) as the starting point for the Risk Assessment of cleaning processes. The guide uses the HBEL (the Hazard), along with collected residue data (the Exposure), to evaluate the level of risk for a cleaning process. In accordance with ICH Q9, the "level of effort, formality and documentation of the cleaning validation process should be commensurate with the level of risk". By comparing the residue levels found after cleaning to the HBEL the level of risk can be demonstrated.

Stakeholder number	General comment (if any)
	Consequently, HBELs are absolutely critical to this process and must be "Science-based" to ensure that the measurement of risk is correct. Without HBELs, this risk-based evaluation is not only impossible but the whole risk-based approach becomes meaningless. Many of the answers to the hypothetical questions in the Q&A are antithetical and detrimental to the direction and intention of the ASTM Standard Guide and are also in direct conflict with the intentions of ICH Q9. It is clear from the answers that the intention is to allow the continuation of the traditional (0.001 therapeutic dose and 10ppm) approaches that are not health-based, are arbitrary [1-4], and which have been shown to be unsafe in about 15% of cases, putting patients at risk, and overly conservative in over 85% of cases, causing operational difficulties and unnecessary expenses for years for the lowest risk products and situations [4]. These approaches have actually been most restrictive for low hazard products and lax with high hazard products (see Attachment I for a comparison of MAC values for the PDE vs. the 1/1,000th). This is a situation that should not be allowed to continue and these older approaches should be deprecated. 1. Walsh A (2011). Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I. Pharmaceutical Engineering, July/August 2011, Vol. 31 (No. 4). 2. Walsh A (2011). Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part II. Pharmaceutical Engineering, September/October 2011, Vol. 31 (No. 5). 3. Crevosier M, Lovsin-Barle E, Flueckiger A, Dolan DG, Ader A, Walsh A (2016). Cleaning Limits—Why the 10-ppm Criterion should be Abandoned. Pharmaceutical Technology, 40 (1). 4. Walsh A, Crevoisier M, Lovsin Barle E, Flueckiger A, Dolan DG, Ovais M (2016). Cleaning Limits—Why the 10-ppm and 0.001-Dose Criteria Should be Abandoned: Part II. Pharmaceutical Technology, 40 (8).
32.	It would be advantageous in the future to have Q&A documents available either before or during the implementation of guidelines. Specifically in this case where there was no definition / differentiation stated in the guideline around the hazardous classification of the API. This has resulted in many companies progressing all of their current API's to be assessed by an external toxicologist at great cost.

Stakeholder number	General comment (if any)
	Companies have recognised that the PDE values being returned through the guideline are no more stringent (in the majority of cases) than the Maximum Acceptable Residue (MAR) calculated using LD50. Reference should be given in the Q &A to acceptable toxicity studies as alternative to LD50. The overall majority of Residue Acceptance Limits (RALs) are still being driven by calculating the MAR based on 1/1000th of the therapeutic daily dose or a general GMP limit. These factors are not necessarily risk based and can lead to overly-restrictive limits for cleaning. Further discussion is required with industry associations on using the combination of Health Based Exposure Limits- usually the Permitted Daily Exposure (PDE) or The Accepted Daily Exposure (ADE)- both of which have safety factors incorporated and calculations based on therapeutic daily doses for active substances or medicinal products and general cleaning limits set as part of company cleaning policy.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
Q1, “See Q2 for products/active substances considered to be highly hazardous. Products that do not fall into the highly hazardous category may be addressed as per Q4.”	4.	Comment: "Highly hazardous products" should not be defined. Once the definition of "Highly hazardous products" are defined, it would be highly likely that almost manufacturers could misunderstand that the other products could be manufactured in the conventional shared facilities. According to ICH Q9, the risk for cross-contamination should be assessed based on the combination of hazard (the severity of that harm) and exposure (the probability of occurrence of harm). That is, "Highly hazardous products" to be defined contradicts the definition of the risk in ICH Q9. Proposed change (if any): Those statements should be deleted.
Q1 Do companies have to establish Health Based Exposure Limits (HBELs) for all products	6.	Comment: EFPIA agrees to the answer with the restriction that reference to a highly hazardous category is taken out (see also response to Question 2). Proposed: A1: Yes, HBELs should be established for products as per the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) or equivalent. Identification of the most hazardous substances based on OELs /OEBs is useful for prioritizing the establishment of HBELs since these substances, under certain exposure scenarios, may carry the highest risks (see also Q&A 3).
Q1. Do companies have to establish Health Based Exposure Limits	8.	Comment: Our toxicological and pharmacological analysis of 1200 APIs revealed that it is not possible to estimate the danger or toxicity of APIs only by their therapeutic group (s. attached report). Not all substances with a high or very high toxicity level correspond to expected groups such as hormones and cytotoxic agents and, not all APIs in these

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
(HBELs) for all products?		therapeutic groups are highly hazardous. Therefore it is necessary to perform a toxicological and pharmacological evaluation for every single API, irrespective of the “group” it belongs to. Proposed change: The answer to question 1 should consequently be shortened to: Yes, HBELs should be established for all products.
Q1 (page 1)	11.	Comment: HBEL: Health Based Exposure limits :The abbreviation is not part of the EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012). Proposed change : Perhaps it is good, for clarity, to indicate that HBEL = PDE?
Q1.-A (page 1)	11.	Comment: “Highly hazardous”: Terms such as highly hazardous, highly active, and high potent may result in unclarity and unjust classification. The term highly hazardous is not used in EMA guideline. Is it intended to refer to the term “highly active” as mentioned in chapter 1 of the guidance document? Proposed change : - Use one terminology or clarify that they are the same or, if not, indicate what the differences are. - Also consider mentioning that “highly hazardous” does not necessarily mean that dedicated/segregated are required? Rather this should be risk based. This might help in avoiding lengthy discussions.
Guideline 169430/2012 §1	15.	Comment: what is the applicability of both guidelines to API manufacturers 1-chapters 3 and 5 of the GMP guideline part 1 have been revised for the manufacture of drug products but no

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
introduction lines 30-32 “While APIs are not discussed in chapters 3 and 5 ...could be applied when required” and Q&A Q1 “do companies have to establish HBELs for all products”		change has been introduced in the part 2 for API production to promote this science and risk based approach 2- technical concepts and rules introduced in guideline 169430/2012 and in the subsequent Q&A are not adapted to cover the needs of API manufacturers . The common practices of API manufacturers to define cleaning residues are those described in APIC/CEFIC document . These practices allow manufacturers to cover all the range of substances produced in their facilities including APIs, intermediates and industrial chemicals Proposed change (if any):
Q1	19.	Comment: ... Products that do not fall into the highly hazardous category may be addressed as per Q4. The Q&A document introduces an entirely new concept, that of a highly hazardous compound. This has the result of introducing a parallel process to the one defined in the original guideline. It is suggested that the highly hazardous category be incorporated into the guideline itself and not through the Q&A process. Further to this, for compounds deemed to not be highly hazardous, cross reference is made to Q4 and the potential to base limits on either HBELs or classical approach (e.g., 10 ppm, 1/1000th). It is currently not clear as the preferred approach or indeed if there is a preference. Proposed change (if any): The Q&A document should look to define clearer relationship perhaps in the form of a decision tree.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
Q1	21.	Comment: The fundamental principle of the introduction of HBELs is to give every substance its place on the continuum between very toxic and not very active. It goes against this fundamental principle to suddenly put compounds into two boxes: black and white, highly hazardous and not highly hazardous. It is false to suggest that there are groups of compounds where the data assessment would be allowed to be incomplete ("completion in full only for highly hazardous compounds"). Nothing would be gained for industry even if this was introduced because by the time one would show that a compound is not highly hazardous because it does not fulfil any of the criteria in answer to Q2, this information would already constitute a very good HBEL document. Proposed change: Stop after sentence 1 and delete the rest of the text.
Q&A 1	24.	Comment: ISPE welcomes EMA's confirmation that establishing Health Based Exposure Limit (HBEL) for all products is mandatory. However, a distinction should not be made between substances that are, or are not, considered highly hazardous. The introduction to the guideline on setting health-based exposure limits clearly promoted "a more scientific and case by base approach" in lieu of identifying specific classes of substances. In our view suggesting this distinction is a step backwards, and potentially introduces risks based on the answer to Q4. Proposed change (if any): delete the last two sentences and replace with the following: "Identification of highly hazardous substances is useful for prioritizing the establishment of HBELs since these substances, under certain exposure scenarios, may carry the highest risks and require more stringent controls."
Q1	25.	Comment: We welcome EMA's confirmation that establishing Health Based Exposure Limit (HBEL) for all products is mandatory. It is however dangerous to distinguish substances in two groups: "highly hazardous", for which a full hazard assessment should be performed and "not highly hazardous" for which it would be allowed not to perform hazard assessment. The aim of the original guideline was to set compound-specific safe limits (HBEL) for every compound, so that they were assessed following the same methodology. Proposed change (if any): Keep only the following part of the answer: "Yes, HBELs should be established for all products as per EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) or

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		equivalent.”
Q&A 1	28.	Comment: The initial sentence reflects the long-held understanding of both the industry and the regulators that the adequate collection of toxicological and clinical data determines the safety of drug substances for use in humans. It is hard for us to conceive that with all this information available today that industry and regulators would not want to use this information for setting Health based Exposure Limits that ensure risks are adequately identified. The PDE/ADE clearly provides the best available information for risk identification purposes. This answer specifically provides for the continued use of “certain classes” type of approach to setting limits that have been shown to be unreflective of patient safety and will result in setting of biased, subjective and unreliable HBELs. Proposed change: A: Yes, HBELs should be established for all products. HBELs for all products are expected to be completed in full as per the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) or equivalent.
Q1. Do companies have to establish Health Based Exposure Limits (HBELs) for all products.	32.	Comment: While it is helpful to have clarification on types of compounds that should be considered highly hazardous, it is confusing that therapeutic daily dose calculations and general cleaning limits can be used for non-highly hazardous compounds with no clarification on types of toxicity studies that should also be considered. Further review with industry is recommended. Proposed change (if any):
Q2, point 4	1.	Comment: there should be clarified if it means standard dose or maximal dose. Proposed change (if any):

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
Q2, point 5	1.	Comment: this definition is very wide, there should be presented limit as in the previous points in Q2. Proposed change (if any):
Q2. What products/active substances are considered to be highly hazardous?	2.	Comment: Within this Q&A a product is determined to be "highly hazardous" based not only on the negative effects it may cause (i.e. mutagenic, reproductive harm, target organ toxicity), but additionally compounds are also classified as highly hazardous when they exhibit "high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg)" The term "highly hazardous" is defined in the first sentence of the answer to Q2 as: "…those that can cause serious adverse effects at low doses…." The use of this term to describe compounds that can cause actual harm is appropriate and consistent with the above definition. Of the five conditions listed in the response to Q2 for defining highly hazardous compounds: • Mutagenic • Reproductive and developmental effects • Target organ toxicity (or other adverse effects at low doses) • High potency • Sensitizing All of these conditions are actual forms of harm with the exception of potency. A potent compound in and of itself is not inherently hazardous. Highly potent compounds exhibit the inherent concern for detection during cleaning validation when using non-specific methods such as TOC. This concern is addressed in the establishment of testing methods, following EudraLex Vol 4, Annex 15 section 9.1 which states: All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit,…" For a highly potent product with an established PDE, no matter the range of that PDE, firms are already required to ensure analytical testing methods used have appropriate detection limits. Establishing a product as highly hazardous based on this criteria (if none of the others exist) forces a more rigid approach to establishing

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		appropriate limits where it may not be warranted. Proposed change (if any): Therefore, to be consistent with the initial definition of “highly hazardous” and to avoid establishing expectations for compounds that exhibit no known threat to patient safety please consider rewording this document to eliminate condition #4: Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg) as a defined characteristic of “highly hazardous products/active substances”.
Q2, “If in doubt, manufacturers should consider the product potentially highly hazardous and apply the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) in full to derive a safe HBEL.”	4.	Comment: This statement is inconsistent with the statement “Health Based Exposure Limits (HBELs) should be established for all products” in Q1. Essentially, those listed evidences should be considered for setting POD, when PDEs or HBELs to be set. And further, the phraseology of “a high sensitising potential” is cryptic and bring confusion. Proposed change (if any): This statement and those listed evidences 1-5 should be deleted.
Q2 What products/active substances are considered to be highly hazardous?	6.	Comment: The proposal to subdivide all products into two categories – “Highly Hazardous” or “Not Highly Hazardous” should not be adopted. The fundamental principle of the HBELs is to give every substance its place on the continuum between very toxic and /or active and not very toxic and/or active. It goes against this fundamental principle to put compounds into

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		two boxes: highly hazardous and not highly hazardous. The purpose of HBELs values is to inform on required cleaning procedures and, where deemed necessary, make an informed decision on the requirement for dedicated equipment/facilities. Any uncertainty in the toxicological and pharmacological dataset is already captured in the HBEL by applying more conservative uncertainty factors. With the exception highly sensitizing substances (which cannot be predicted on basis of animal data) the introduction of above categories introduces confusion and duplication of effort and therefore is deemed to have no added value. Moreover, this would introduce a concept that was absent in the guideline itself. The purpose of a Q&A document should be to clarify questions on the existing guidance rather than introducing new guidance. Proposed: Delete Q&A2
Q2. What products/active substances are considered to be highly hazardous?	8.	Comment: Question 2 of the Q&A and its answer say that highly hazardous substances can be identified by applying certain, broad categories. This might at least be misleading, as it implies that the hazardousness is predictable from the belonging to a certain group. According to the results of our evaluation of 1200 PDE values, it is not possible to estimate the danger or toxicity of APIs only by their therapeutic group. It is crucial to perform a thorough toxicological risk evaluation for each substance. Proposed change:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Deletion of question 2.
Q2.A.1 (page 1)	11.	Comment: In essence this a clear answer. However threshold carcinogenicity mechanisms are not mentioned. Proposed change: It might be a valuable addition to mention that threshold carcinogens, possibly even threshold mutagens, are not considered to be “highly hazardous”. This will minimize discussions on how to treat threshold carcinogens (mutagens).
Q2.A2. (page 1)	11.	Comment: “Low dosages”. Not properly defined/substantiated. Why is this term used here? With the guidance aiming at health based limits, any PDE set will be sufficiently safe. This answer is aimed at facilitating the voiding of PDE determination. However, this part of the Q&A may result in all reprotoxic compounds having the indicated dose ranges ending up as “highly hazardous” compounds. This may result in lengthy discussions on the requirement for dedicated facilities whereas the focus should be on heath based arguments in combination with analytical capability etcetera. Proposed change : - Remove subgroup/low dosage indication or - Provide scientific rationale for limits provided and/or - Clearly state that regardless of limit these compounds do not require dedicated facilities by default.
Q2.A3 (page 1)	11.	Comment: Dose limit provided: See content/suggestions row above. Basically the same applies here.
Q2	12.	Comment: Many companies provide HBELs using the PDE approach for all compounds, whether or not they are highly hazardous. For those companies, a categorization process for defining highly hazardous is not necessary. The concern based on the question is new processes will be needed to define and document highly hazardous drugs at your company even though a PDE has been already established.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change (if any): Add “If PDE-based HBELs are developed for a compound then there is no need to define whether a compound is highly hazardous.”
Q&A Q2	15.	Comment : for hazardous compounds PDE calculation requires, at least , core data sheet and CTD modules (2.4 and 2.5) that are only available in the drug product marketing authorization dossier belonging to the marketing authorization holder . Role and responsibility should be suggested in the Q&A for establishing some official PDE Proposed change (if any):
Q2	17.	Comment: “Highly hazardous” is a new concept that is not described in the guidance and needs clarification. Proposed change: Please provide a more clear definition of this term.
Q2 §1 to 5	17.	Comment: These points are described from a Human health standpoint and we are not sure whether this approach is taking into account toxicology for animals. For example it is not clear how the extrapolation proposed for the veterinary dose of 0.2 mg/kg/day is calculated. Proposed change: Please provide clarification.
Q2. 3rd paragraph Point 5.	18.	A better definition of compounds with a high sensitizing potential is required. A list of these compounds and examples of how to deal with this category of hazardous materials would be useful.
Q2	19.	Comment: What products/active substances are considered to be highly hazardous... No explanation or justification is provided for the thresholds defined in the document. Moreover these are a mixture of criteria relating to hazard (toxicity) and potency. Without clarification these may be viewed as somewhat arbitrary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change (if any):
Q2	21.	Comment: see above. The grouping of all compounds into two groups, highly hazardous and not highly hazardous is scientifically not justified and will lead to abuse. Also, the potency of the molecules that fit into the subgroups 1-5 is very heterogeneous. It is false to suggest that less than a full toxicological assessment is justified for some compounds. That goes against the principle of ICH Q9 and any good risk assessment practice which calls for the use of all available scientific data. Proposed change: Delete the answer to this question and replace it by: “The distinction of compounds into two categories, “highly hazardous” and “not highly hazardous” goes against the principle of assigning a HBEL to each compound based on all available data. The HBEL is the unique descriptor of the level of hazard that a compound constitutes.
Question 2	23.	Comment: In the answer to Question 2, “Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg” are considered highly hazardous. I recommend that this category of compounds not be listed as a “highly hazardous” compounds unless it also falls into one of the other listed categories (genotoxic, carcinogenic, etc.), or there are other reasons to consider it “highly hazardous”. If the “most sensitive/critical effect” is the therapeutic effect, it would appear that setting an HBEL at 0.001 of the minimum therapeutic daily dose would provide adequate patient safety (as given by the answer in Q4). In other words, a compound dosed at 1 mg/day should be adequately addressed by an HBEL of 1 µg/day (0.001 mg/day). There is no need to consider potent compounds as “highly hazardous” unless there is a critical effect other than the therapeutic effect. I believe part of the reason for including potent compounds in this answer to Q2 is the common confusion within the pharmaceutical industry that uses the term “potent” interchangeably with “highly hazardous”. Proposed change (if any): Delete the following from the answer to Question 2: “4. Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
Q&A 2	24.	Comment: The introduction of the term “highly hazardous products” is a major issue with the EMA Q&A document and it generates a wide range of questions (see e.g., Q4). In this case, it appears that EMA is proposing a regression towards the hazard-based approach in use prior to the adoption of its EMA Guideline on setting HBELs to support the co-manufacturing of different drugs in shared facilities, and away from the risk-based approach it originally endorsed. One of the goals of the EMA guideline was to discard the subjective identification of “certain” groups of APIs (certain antibiotics, certain hormones, certain cytotoxics and certain highly active drugs) and to require the establishment of a compound-specific HBEL for each drug. These HBELs build a continuum of values. To separate drugs again into two groups is artificial and provides no added value for risk identification and risk management. The derivation of the HBEL takes all the hazards into account and reflects all of the inherent variability and uncertainties associated with the compound. As such, the lower the HBEL is the more attention to assessment and control of exposure is required. A full toxicological assessment should be required for all substances, not just the subset that is considered highly hazardous. In order to apply the criteria listed, the reviewing toxicologist would need to have access to all available relevant information and perform a detailed evaluation, the extent of which would very close the level of effort required to apply the guide in full and setting the HBEL. Proposed changes: Amend the first sentence as follows: “Highly hazardous products are those that can cause serious adverse effects at low doses and therefore would benefit from receiving a high priority for a full toxicological assessment in order to derive a safe HBEL. A toxicologist needs to be consulted to determine if a compound is highly hazardous” Delete the last sentence in the third paragraph. Add “If PDE-based HBELs are developed for a compound then there is no need to define whether a compound is highly hazardous. If a PDE is not available, manufacturers should consider the product potentially hazardous and follow the EMA guide in full to derive a safe HBEL.”
Q2	25.	Comment: The introduction of the term “highly hazardous products” is a major issue with the EMA Q&A document and it

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		generates a wide range of questions (see e.g. question 4). In this case, it appears that EMA is proposing a regression towards the hazard-based approach in use prior to the adoption of its Shared Facilities Guideline, and away from the risk-based approach it originally endorsed. One of the goals of the EMA guideline was to discard the subjective identification of “certain” groups of APIs (certain antibiotics, certain hormones, certain cytotoxics and certain highly active drugs) and to require the establishment of a compound-specific HBEL for each drug. These HBELs build a continuum of values. To separate drugs again into two groups is artificial and provides no added value for risk identification and risk management. It may not have been the intent of EMA to divide compounds into two simplistic categories, highly hazardous and non-highly hazardous, but an inspector could interpret it that way and ask for identification of all highly hazardous compounds. Once a toxicologist collects enough data to evaluate whether a drug falls under one of the 5 criteria as indicated in the answer), she/he is already more than half the way to setting a fully data-driven HBEL. The added value of HBELs, when compared to the previously used method of 1/1000 of Minimal therapeutic dose (MinDD), is to identify those substances where MinDD criteria are not stringent enough to be protective of patients, which is the ultimate goal of the shared facilities guideline. Toxicological evaluation can prioritize drug substances which represent the higher risk to patients (Lovsin Barle et al, 2017). Calculating an HBEL is a comprehensive process that delivers information beyond the hazards alone. Communication of a substance as “highly hazardous” based on the answer to Q2 may not cover the spectrum of thought processes and considerations of the experts. This may also lead to misclassification of a drug, as missing data (e.g., based on a narrow or abbreviated data search and assessment only) might give the impression that a compound does not meet the criteria as a highly hazardous drug, and lead to less restrictive data assessment and in rare cases not protective limits Proposed change (if any): Replace the answer by: “EMA does not intend to define highly hazardous products. As stated in A1, HBELs should be established for all

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		products. EMA leaves it to the companies' discretion to define whether it would be useful to define highly hazardous and not highly hazardous products and to use such a classification for internal purposes only, e.g., as a criterion to prioritize the compounds for the calculation of HBELs."
Q&A 2	28.	Comment: We believe that creating two categories of compounds, highly hazardous and not highly hazardous, is simplistic and not scientifically justified. This is also contrary to the principles of ICH Q9 ("The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient") and to the principle of the EMA's (EMA/CHMP/CVMP/SWP/169430/2012) and ISPE's Risk-MaPP guideline that emphasized that risk exists on a continuum and should be identified using all available scientific data (pre-clinical and clinical) and cross-contamination risks should then be managed based on this risk -identification and not on generalized classes of compounds. We strongly believe that the use of categories/classes for defining products should be abandoned, and the Agency's and industry's focus should return to use of science- and risk- based approaches to setting HBELs. Furthermore, these statement "full toxicological assessment in order to derive a safe HBEL" and "apply the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) in full to derive a safe HBEL," in our view, are completely misleading, as they suggest partial toxicological assessment could also be used for deriving HBELs and HBELs could also be unsafe. On the contrary, the derivation of HBELs "should be the result of a STRUCTURED SCIENTIFIC EVALUATION of all available pharmacological and toxicological data" and any HBEL is supposed to be safe irrespective of whether the substance is classified highly hazardous or not. The concept of applying the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) in full or in part is new and not explained in the guide. Proposed change:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		A: Compounds should not be categorized as “highly hazardous” or “not highly hazardous”. All compounds should be subjected to a standard Risk Assessment to determine an appropriate HBEL based on all the available scientific data on that compound.
Q2, point 4	31.	Comment: A general threshold of recommended daily dose <1 mg to distinguish highly hazardous compounds is welcomed. It is however noted that not all compounds dosed below 1 mg should be considered as “highly hazardous”. Most evident examples include certain vitamins or microelements. Full toxicological assessment in order to derive safe HBELs should not be required for such compounds. Proposed change: Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg) unless otherwise justified. Clarification which compounds dosed below 1 mg should not be considered as “highly hazardous” is recommended to be provided.
Q2, point 5	31.	Comment: More details are recommended to be provided which substances should be considered as those with “high sensitising potential”.
Q2. What products / active substances are considered highly hazardous?	32.	Comment: Classification of types of compounds as highly hazardous does not address the issue - to identify compounds that would require dedicated facilities. In this answer it should be stressed that PDEs or ADEs do take account of toxicological effects as well as minimal clinical effective dose levels. For many highly hazardous products, calculations based on therapeutic daily dose would define lower MAR than calculations based on PDE or ADE. Further review with industry is needed. Proposed change (if any):
Q3, “If the resulting PDE value is 10 µg/day or lower the product	4.	Comment: It is concerned that this statement would confuse GMP requirements with IH (Industrial Hygiene) ones. Why is PDE value of 10 µg/day the class limit for highly hazardous? From the point of view of IH, the class limit for highly hazardous which any physical containment devices to be needed in the manufacturing scale, is OEL value of 10 µg/m3 (PDE value of 100 µg/day) or lower.

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should be considered as highly hazardous."		Proposed change (if any): This statement should be deleted.
Q3	5.	Comment: We have found with the thousands of products we have assessed to date that the 10 to 1 ratio of ADE/PDE to OEL is not accurate for the majority of products. This is likely due to the change in the route of administration where the OEL is typically based on inhalation and very few PDEs are based on this route of administration. Proposed change: Change to: "Only as an interim until formal HBEL's can be determined. The use of the OEL can also assist in prioritizing the establishment of HBELs."
Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to support assessment of products to determine whether they may be highly hazardous?	6.	Comment: OELs and OEBs can be used to prioritize those products most urgently in need of a PDE assessment/HBEL. OEL or OEB monographs can also be used as a basis to determine a PDE when performed by a qualified person. In case the full OEL or OEB document should be available, showing the rationale, i.e. critical effects, and the calculation of the OEL with adjustment factors applied and bioavailability correction factors used. Also referring to the comments on Q&A 1 and 2, there is no need for a highly hazardous category. Proposed: Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to support assessment of products? A3. Yes, but only as a means to prioritize the establishment of formal HBELs. Extrapolation of an OEL or OEB to a PDE can be done by a qualified toxicologist taking into account additional adjustment factors due to potential differences in target population (worker vs patient), route of exposure etc., where required.

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Answer Q3	13.	Comment: The target population of OEL and PDE can be significantly different and requires different toxicological-pharmacological Point of Departure. For example the children are not part of the target population of OEL; same reasoning applies to individuals with pathologies that do not allow work. Proposed change (if any): …route of exposure etc. This relation subsists only if the Point of Departure used for the OEL evaluation is considered adequate also for the target population of the PDE. If the resulting PDE value is 10 µg/day …
Q3. A (Lines 1-3)	14.	Comment: According to Methodology for the derivation of Occupational Exposure Limits (SCOEL, Key Documentation (Version 7), June 2013) there are important differences for setting OEL versus PDE. In our opinion, the main differences are the following: - To the establishment of an OEL, background data (e.g. physical properties) are relevant. This means that maybe these data should be taking into account to the application of UFs. - In general, good quality human data (individual case reports, studies in human volunteers, cross-sectional studies, cohort and case-control studies) are to be preferred to animal data. For PDE calculations, critical effects to be considered include the most sensitive indicator of an adverse effect seen in non-clinical toxicity studies. In animal studies, clearly the species under investigation is not the human. In addition, the group sizes of animal studies are very much smaller than those involved in many human cohort studies. - Studies conducted by the inhalation route are clearly to be preferred. - An OEL value might not be recommended for certain chemicals as p.e sensitizers. - It is often appropriate to apply lower UFs than those which are used for PDE calculation due to the following reasons: o The working population may be more homogeneous than the general population. o The working population is commonly exposed for approx. 8 hours/day, 5 days per week, 240 days per year for a working lifetime (up to 45 years). PDEs are calculated for a full lifetime.

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		o In most EU countries, the health of workers is expected to be controlled by periodic surveillance and monitoring programmes. In addition to the above mentioned considering that OEL is based on inhalation route, differences related to bioavailability should be considered regarding PDE calculations. Finally, there are also differences regarding to body weight for PDE/OEL calculations (50 kg for PDEs to cover a spectrum of patients and OELs 70 kg based on worker weights) Proposed change (if any): Before Extrapolation of an OEL or OEB to a preliminary PDE should be taking into account that could have differences to apply UFs and to identify “critical effects” as well as determination of the no-observed-adverse-effect level (NOAEL).
Question 3	16.	Comment: What is the default approach to use (OEL, TTC) in the absence of data from toxicological studies to provide PDE values? Proposed change (if any): N/A
Q3	19.	Comment: Yes. Extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours). Additional adjustment factors may be needed due to potential differences in target population (worker vs patient), route of exposure etc. If the resulting PDE value is 10 µg/day or lower the product should be considered as highly hazardous. Yes, We agree that an OEL or OEB can be used for deriving a preliminary PDE but it has to be clarified in the text

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		that this can only be done if the OEL or OEB is based on a substance specific health based assessment and also that the PDE and OEL relate to the same route of exposure. Further clarification is needed when making any adjustment / extrapolation between routes e.g. extrapolating inhalation values to oral and parenteral routes of exposure i.e. that is requires assessment of any differences in bioavailability, including use of animal vs. human PK data. This concept should not be used when the OEL or OEB is based on a default substance/ pharmacological class as these OEL/OEB limits may not be protective against health effects in all cases. Q2 lays out definitions of highly hazardous – the 10ug/day limit described in Q3 seems to represent another definition – how are these linked? Proposed change (if any):
Q3	19.	Comment: Extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done…. Proposed change (if any): Remove "simply" from the sentence as it is an unnecessary word in this context.
Q3	21.	Comment: again, without any necessity, the notion of having to group all compounds into one of the two groups “highly hazardous” and “not highly hazardous” is presented. Many believe that one can simply take an OEL or OEB from a safety data sheet, multiply it by 10 and is done with the establishment of a HBEL. These people will feel that their view has been confirmed. Proposed change: delete the last sentence. Add a sentence saying that an OEL or OEB can only be used as a basis if a rationale document explaining the OEL or OEB is available that fulfils the documentation requirements as per

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		the EMA guideline on setting HBELs. A value derived from a “naked” OEL is not acceptable.
Q&A 3	22.	Can the resulting value be used as a HBEL?
Question 3	23.	Comment: Question 3 appears to be written to allow use of an OEL or OEB only to determine whether a compound is highly hazardous. It seems to avoid the obvious additional questions. The main additional question is whether the PDE as determined by an OEL/OEB calculation can be used as the HBEL. There would be two situations. First, for a compound that has a PDE calculated by the OEL/OEB formula of >10 µg/day, is it permitted to utilize that PDE value as the PDE value for compliance purposes? Or is an additional evaluation required? The second situation is for a for a compound that has a PDE calculated by the OEL/OEB formula of ≤10 µg/day, is it permitted to utilize that PDE value as the PDE value for that hazardous compound, or is it required to do further evaluation to set the PDE for it since it is therefore considered “highly hazardous”. The EMA’s answer in each situation may be different. My recommendation is that the EMA should simplify the question so that it does not just address whether something is highly hazardous (or not). If it is adequate to use an OEL/OEB to determine a PDE value, then here are two suggested Questions and Answers. Proposed change (two options are given): “Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to calculate a PDE for use as the HBEL? A: Yes. Extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours). Additional adjustment factors may be needed due to potential differences in target population (worker vs patient), route of exposure etc. The resulting PDE may be used as a HBEL for cleaning validation purposes.” Here is the second option and my preference: “Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to calculate a PDE for use as the HBEL?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		A: For compounds that are not considered highly hazardous (See Question 2), extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours). Additional adjustment factors may be needed due to potential differences in target population (worker vs patient), route of exposure etc. The resulting PDE may be used as a HBEL for cleaning validation purposes. For compound considered highly hazardous (See Question 2), apply the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) in full to derive a safe HBEL."
Q&A 3	24.	Comment: ISPE agrees with EMA acknowledging the use of Occupational Exposure Limits (OELs) and Occupational Exposure Bands (OEBs) to derive an interim HBEL as described by Teasdale et al. (2015). These interim limits can provide a screening and prioritization mechanism to ascertain whether cleaning targets and other controls were appropriately protective during the initial implementation of the EMA Guideline for contemporaneously manufactured API, especially for companies with large manufacturing portfolios. While the proposed answer does mention some of the important considerations, only an expert will know how to interpret them and apply the appropriate adjustments. If unqualified individuals merely use the OEL from SDSs, inappropriate PDEs may be estimated, putting patients at risk. The proposed answer may mislead people to believe that a PDE is protective of all populations and routes of exposure when derived by simply extrapolating from an OEB or OEL for healthy adult workers obtained from a publicly available Safety Data Sheet (SDS), i.e., by multiplying by 10 m^3. This practice is not considered adequate and may actually introduce risks. An extrapolation of the HBEL based on an OEL or OEB is only possible if the full OEL document is available showing the rationale, i.e. critical effects, calculation of the OEL with adjustment factors, and bioavailability correction factors used. The use of the formula PDE (µg/day) = OEL (µg/m^3) x 10 m^3 leads to the PDE for the inhalation route. If the PDE for another route (e.g. parenteral route) is required, the PDE for the inhalation route has to be converted to the PDE for e.g., the oral or parenteral route in consideration of the bioavailability data. If the full OEL document is available, this may easily be used to prepare a PDE rationale as well. This may be the case when internal company OELs and OEBs documents are available, where the company

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		can guarantee that the previously conducted work is of equal quality as the one expected for the HBELs. Proposed change: Amend the first sentence as follows: “Yes, but only as an interim approach and as a means to prioritize the establishment of formal HBELs. The estimation of the HBEL based on an OEL or OEB is only recommended if the full OEL document is available showing the rationale for HBEL derivation i.e. critical effects, calculation of OEL setting with adjustment factors applied and bioavailability correction factors. The factors may have to be adapted to e.g., patients vs. workers or parenteral vs. inhalation administration. A qualified expert (e.g., a toxicologist) should be involved in performing this assessment. If the full OEL document is available, this may easily be used to prepare a PDE rationale as well.” Delete the last sentence.
Q3	25.	Comment: We agree with EMA acknowledging the use of Occupational Exposure Limits (OELs) and Occupational Exposure Bands (OEBs) to derive an interim HBEL as previously described by Teasdale et al. (2015). . These interim limits can provide a screening and prioritization mechanism to ascertain whether cleaning targets were appropriately protective during the initial implementation of the EMA Guideline for contemporaneously manufactured API, especially for companies with large manufacturing portfolios. A supplementary method to derive a prioritization plan for large portfolios can be also done based on the toxicological evaluation of the classes of substances from the portfolio. A recent example of this effort is provided by Lovsin Barle et al. (2017, in press), where the relationship between the 1/100 minimum daily dose (MinDD) and the Permitted Daily Exposure (PDE) values for 140 drug substances (DS) were provided in an attempt to identify the high risk groups of products for patient safety based on their therapeutic use and Mode of Action (MoA). Drugs that were identified to have PDEs lower than 1/1000 MinDD included antineoplastics such as sex hormone modulators used in cancer therapy, immune suppressant drugs used in organ transplantation, while other hormone or hormone modulating substances have not been identified as high risk products if 1/1000 MinDD was previously used to derive cleaning limits. However, the answer may mislead people to believe that a PDE protective of all populations and routes of exposure may be derived by simply extrapolating from an OEB or OEL for healthy adult workers obtained from a publically available Material Safety Data Sheet (MSDS) by multiplying by 10 m^3. This practice is not considered adequate. An extrapolation of the HBEL based on an OEL or OEB is only possible if the full OEL document is available showing the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		rationale, i.e. critical effects, calculation of the OEL with adjustment factors, and bioavailability correction factors used. If the full OEL document is available, this may easily be used to prepare a PDE rationale as well. This may be the case when internal company OELs and OEBs documents are available, where the company can guarantee that the previously conducted work is of equal quality as the one expected for the HBELs Proposed change (if any): Delete the last sentence. Replace the remaining sentences by: "In some cases, when a full documentation specifying the rationale for OEL and OEB calculation is available (including: the choice of the Point of Departure, and of the different safety factors and bioavailability correction factors), an extrapolation from the OEL to the PDE can be done. The factors may need to be adapted due to potential differences in target population (workers vs patients), route of exposure (parenteral vs oral), etc."
Q&A 3	28.	Comment: Since OELs are simply a PDE/ADE divided by 10 to adjust for the volume of air breathed by a worker in 8 hours, it can be a simple back calculation to arrive at the starting PDE/ADE. However, these PDEs/ADEs are specifically calculated with only inhalation as the route of exposure in mind. So their Points of Departure may be based on studies that were specifically targeting inhalation and adjustment factors may be considering inhalation only. These PDEs/ADEs may be reflective of this and may not be appropriate for use when the routes of exposure are injection or dermal. Since OELs are already available for almost all drugs they most certainly should be used as the starting point for PDE/ADE calculations, keeping in mind that some of the Adjustment Factors may need to be changed, or even a different Point of Departure chosen. Proposed change: Extrapolation of an OEL to a Provisional Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours). The Point of Departure and study used for the OEL should be reviewed for applicability and a different study and Point of

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		Departure used if applicable. In addition,adjustment factors may need to be changed due to potential differences in target population (worker vs patient), route of exposure, etc. OEBs may not be used due to their highly variable default values and inconsistent practice from company to company
Q&A 3	29.	Comment: In the answer to Question 3, an OEL is always derived for worker only. Therefore, we think that additional adjustment factors will always be needed. Proposed change (if any): “Yes. Extrapolation of an OEL or OEB (lower end of the range) to a preliminary Permitted Daily Exposure (PDE) can be simply done by using the following formula: PDE (µg/day) = OEL (µg/m3) x 10 m3 (the volume air breathed by a worker in 8 hours). Furthermore, additional adjustment factors will be needed due to potential differences in target population (worker vs patient), route of exposure etc.”
Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be used to support assessment of products to determine whether they may be highly hazardous?	32.	Comment: APIC supports clarification that OELs or OEBs, that are widely available for many established compounds, can be extrapolated towards a PDE or ADE. Clarification is needed if this approach can be used for all classes of compounds- highly hazardous or non–highly hazardous. Proposed change (if any):
Q4	1.	Comment: A: We suggest that for existing products with well-established clinical safety profile the calculation of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		HBELs could be done based on NOAEL value. Proposed change (if any):
Q4, “Under these circumstances, HBEL based on the 1/1000th minimum therapeutic dose approach would be considered as sufficiently conservative and could be utilised for risk assessment and cleaning purposes.”	4.	Comment: It should be stated that basically, POD should be set to be NOAEL, LOAEL or BMDL. The 1/1000th minimum therapeutic dose would be too conservative. Should it be explained why 1/1000 minimum therapeutic dose is the basis of HBEL.
Q4	5.	Comment: The establishment of HBELs brings together different departments within a pharmaceutical company and provides more in-depth understanding of the products and allows for appropriate controls to be put in place. Allowing companies to bypass this critical step by using the 1/1000th rule of thumb, takes away the opportunity for the holistic understanding and control of products. While the HBEL may be based on a point of departure that is the therapeutic dose, it is important that it is assessed properly with the appropriate adjustment factors and not just blindly applying 1/1000th.

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		Proposed change: Delete the last sentence.
Q4. Can calculation of HBELs be based on clinical data only (e.g. to establish the HBEL on 1/1000th of the minimum therapeutic dose)?	6.	Comment: A HBEL should be based all available relevant data, both nonclinical and clinical, using the most relevant and sensitive effect as a Point of Departure. Therefore, Q&A 4 is not correct. Although it could be applied when considered appropriate, in itself, applying the 1/1000th rule is not an HBEL. In general human data may be most relevant, however, to be able to apply the 1/1000th on the minimal therapeutic dose properly; one still has to assess all available (preclinical and clinical) data to determine that this approach is correct. Usually a HBEL based on clinical-data would be higher than applying 1/1000 of the minimal therapeutic dose. The HBEL approach can be applied regardless of therapeutic index (or safety window or therapeutic window) or potency of a compound. Current text on Q&A 2 and 4 seem to mix up both concepts. Potent and non-potent compounds can both have large or small therapeutic windows. This window depends on the steepness of the dose-response curve. Proposed change: The derivation of a HBEL should be the result of an evaluation of all available pharmacological and toxicological data. In many, but not all cases, pharmacological activity (the human therapeutic dose) is the most sensitive/critical effect of an active compound. In these cases the HBEL can be based on a fraction of the therapeutic dose. How small a fraction this needs to be, depends on the steepness of the dose-response curve. Under these circumstances, a toxicologist will need to review the 1/1000th minimum therapeutic dose approach to verify that it is sufficiently conservative for use in cleaning applications.
Q/A4	10.	Excerpts from A4: • clinical safety profiles • a favourable therapeutic index • unwanted or adverse health effects (that may have been identified as toxic effects in animal studies at high doses)

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		• the pharmacological activity would therefore be the most sensitive/critical effect. • therapeutic dose information could be used as the 'Point of Departure' for calculation of an HBEL (e.g. the PDE). The evaluation of all the above information is very close to the "full" determination of a HBEL like a PDE. To do all the expert work to only justify the PDE at 0.1% minimal dose hardly makes sense. Why not opt for the PDE right away in such cases? The PDE may of course end up being equal to 0.1% dose; but no need to give it a special mention.
Q4. (page 2)	11.	Comment: This question seems to be aimed at providing a strategy to void PDE (or HBEL) setting. This should preferably not result in default use of old limits again. The voiding of PDE setting is reasonable in specific cases. However, in Q4 it is basically indicated that for compounds not being regarded as "highly hazardous" upon voiding of PDE setting the old approach (1/1000th TTD or 10 ppm) may be applied. This is a departure of the health based limit propagated in the guidance document. Although this may be fit for purpose it does carry the risk of making the old approach standard again for compounds that are not considered as highly hazardous. The use of a higher PDE limit may be considered unacceptable (and hence the health based approach is lost in the process). Proposed change : Indicate that the old approach may be applied but that PDE (HBELs) limits higher than the old limits are also acceptable. If it is felt that an upper limit is required for mostly harmless compounds it should be provided (e.g. max. 1%, 0.1% or other percentage of product containing carry over).
Q4	13.	Comment: It is not clear if 1/1000th of the minimum therapeutic dose for a specific route has to be considered sufficiently conservative also for other different routes of administration.
Q4	13.	Comment: It is not clear if 1/1000th of the minimum therapeutic dose for a drug with only adult target population

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		has to be considered sufficiently conservative also for the pediatric population.
Q&A Q4 : Can calculation of HBELs be based on clinical data only (e.g. to establish the HBEL on 1/1000 of the minimum therapeutic dose)	15.	Comment: the use of 1/1000 of the minimum therapeutic dose is not a common practice for API manufacturers . Proposed change (if any): change 1/1000th minimum therapeutic dose by Therapeutic dose/Safety Factor
Q4	19.	Comment: Many existing commercial products and new products for which clinical safety profiles are well-established and that do not belong to the highly hazardous category (see response to Q2) have a favourable therapeutic index (also referred to as the therapeutic window or safety window). This means that unwanted or adverse health effects (that may have been identified as toxic effects in animal studies at high doses) may occur - if at all - at dose levels orders of magnitude above the therapeutic dose range and the pharmacological activity would therefore be the most sensitive/critical effect. In this situation, therapeutic dose information could be used as the 'Point of Departure' for calculation of an HBEL (e.g. the PDE). Under these circumstances, HBEL based on the 1/1000th minimum therapeutic dose approach would be considered as sufficiently conservative and could be utilised for risk assessment and cleaning purposes. Yes, We agree that e.g. 1/1000 on the minimum therapeutic dose can be used in some cases for deriving the HBEL. Proposed change (if any): It should be noted that such approach may not be suitable for Oncology therapies as the lowest recommended therapeutic dose is often not on the lower end of the dose-response curve. In these cases, other more sensitive

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		indicators for a pharmacological effect could be used as a starting point for the HBEL estimate.
Page 2 / Q4	20.	Comment: It would be useful for industry to clarify the position of the agency not only for finished products, but also fot APIs.. We understand and agree, that for non highly hazardous finished products with a favourable therapeutic index the HBEL should be 1/1000 of daily therapeutic dose or 10 PPM of Maximum Carry Over (MACO).. Does for non highly hazardous APIs in the same way, the HBEL should be 1/5000 to 1/10.000 of daily therapeutic dose to take in account the lower risk of cross contamination for the patients due to the dilution of the APIs in the finished products? Proposed change: Due to the lower risk for the patients, due to the dilution of the APIs in the finished products, different safety factors may be applied for the HBEL in the manufacture of active ingredients. For non highly hazardous APIs with a favourable therapeutic index, the HBEL should be between 1/5000 to 1/10.000 of therapeutic dose, or a MACO between 50 to 100 ppm.
Q4	21.	Comment: the question is false because 1/1000 therapeutic dose is not an example of an HBEL except for very few compounds where the clinical-data-based HBEL would actually be 1/1000 of the therapeutic dose. Usually the clinical-data-based HBEL would be higher than 1/1000 of the therapeutic dose. Clinical data are the preferred starting point for an HBEL calculation as the limit is generally set for humans. Setting a human limit based on human data is the preferred option. The therapeutic window has nothing to do with potency. Potent and non-potent compounds can both have large or small therapeutic windows. This window depends on the steepness of the dose-response curve. Proposed change: Replace the answer by “Setting an HBEL for humans based on human data, if such data of sufficient quality are available, is preferable over setting a human HBEL extrapolated from animal data. In many cases, esp. where a substance has no CMR effects, is not a sensitiser and has no significant off-target effects, the HBEL is actually a fraction of the therapeutic dose. How small a fraction this needs to be depends on the steepness

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		of the dose-response curve. 1/1000 of the therapeutic dose is (unnecessarily) conservative in most cases, but in some cases it is insufficient. The compound-specific data need to be taken into consideration."
Q&A 4	22.	Is toxicologist input required for this scenario?
Question 4	23.	Comment: This is appropriate, but it is important that the determination that the "most sensitive/critical effect" being the therapeutic effect be done by a qualified toxicologist or pharmacologist. Proposed change (if any): Add this sentence at the end of the answer: "The determination that the most sensitive/critical effect is the therapeutic effect should be done by a qualified toxicologist or pharmacologist."
Q&A 4	24.	Comment: HBELs should be established for all substances (see answer to Q1). Use of traditional limits such as 1/1000th of the minimum therapeutic dose used in the cleaning arena should be discouraged in favour of setting HBELs using all available relevant data. Like using OELs without consulting the supporting documentation, using 1/1000th of the minimum therapeutic dose can lead to inappropriate HBELs if key information is not taken into consideration. If all available relevant information is not available, unintended risks may be imposed on certain subpopulations. For example, a drug may be contraindicated for certain subgroups (e.g., women of child-bearing potential), due to its mechanism of action and, unless this was included in the assessment, an unacceptable risk to the developing foetus may result. Some antineoplastic agents are given at very high doses (e.g., 500 mg/day) to kill cancer cells, but may also adversely affect normal cells. 1/1000th of this dose (500 ug/day) is more than two orders of magnitude above the TTC value of 1.5 ug/day, which is likely to be in the range of an appropriate PDE for such a compound. Drugs that may have PDEs lower than 1/1000 of the minimum therapeutic dose include anti-neoplastics, sex hormone modulators used in cancer therapy, immune suppressant drugs used in organ transplantation, among others. Finally, some of the other adjustments that may be appropriate, such as bioavailability considerations, are not taken into account. The use of the criteria in the answer to Q2 to determine if an alternative approach using limited data (i.e., minimum therapeutic dose) can be used is a significant departure from the recommendations in the original guideline, which was to set substance-specific HBELs using all available relevant data. Adopting this

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		simplified strategy has the potential to put patients at risk because the strategy assumes the reviewer is qualified to interpret the criteria provided to make the distinction. As mentioned earlier, this assessment can only be performed by a qualified expert, and the level of effort to make this determination is close to what would be required to recommend a formal PDE. Proposed change: Replace the proposed answer with the following: ”HBELs are typically derived using human data, since this is preferred approach for most active pharmaceutical ingredients. As recommended in the guideline, an evaluation of all available relevant information, including the animal data, should be performed to identify the critical effect, associated point-of-departure, and appropriate adjustment factors to account for PK/PD, bioavailability, etc. to derive an HBEL. The minimum clinical dose may in fact be used as the point-of-departure but the composite adjustment factor may be less than or greater than 1000.”
Q4	25.	Comment: Most of the time, the pharmacological effect is the most sensitive/critical effect. HBEL calculated from human data are most of the time lower than HBEL calculated from animals. Human data should be used every time they are available with a correct quality. However, it has to be reminded that the therapeutic index has nothing to do with the potency. Some highly active compounds might have wide therapeutic index and vice-versa, as this index depends on the steepness of the dose-response curve. Proposed change (if any): Replace the answer by: “The pharmacological activity is often the most sensitive/critical effect. When available with sufficient quality, human data (therapeutic dose, dose-response curve, pharmacokinetics, safety data) should be used as another scenario to animal data to set a HBEL. In many cases, more particularly when a substance has no CMR effects, is not a sensitizer and had no significant off-target effects, the HBEL is a fraction of the minimal therapeutic dose. How small a fraction this needs to be depends on the steepness of the dose-response curve. A HBEL based on the 1/1000th minimum therapeutic dose approach is in most of the cases (unnecessarily) conservative whereas it might be insufficient in some cases. The compound-specific data need to be taken into consideration.
Q&A 4	28.	Comment:

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		We see the question "Can calculation of HBELs be based on clinical data only (e.g. to establish the HBEL on 1/1000th of the minimum therapeutic dose)?" as simply an attempt to continue the use of the "1/1000th of the minimum therapeutic dose" which has been shown to be NOT health-based, is highly inaccurate when compared to a tox/clinical data evaluation (accurate < 1.5% of the time), is not restrictive enough in 15% of cases with hazardous compounds (10X to 100X too high) and overly restrictive in 85% of cases (10X to 1000X too low) with low hazard compounds (see reference 1-3 below). This will impose excessively low cleaning limits on low hazard compounds and, in many cases, as low as compounds that are high hazard compounds. This is not logical at all and only serves to maintain an enormous burden on industry where it is not needed. The use of the 1/1000th of the minimum therapeutic dose has led to unnecessary and excessive controls (dedication of parts, use of disposables, production scheduling issues, etc.) being put in place for low hazard drugs in low risk situations and resulting in unwarranted cleaning failures compounded by unwarranted investigations and unwarranted CAPAs being implemented. It is also hard to understand how a toxicologist upon “STRUCTURED SCIENTIFIC EVALUATION of all available pharmacological and toxicological data” and selecting the low clinical dose as the Point of Departure (POD) would choose to divide the POD by 1,000 instead of applying the appropriate Uncertainty Factors and Modifying Factors and deriving an HBEL. A Toxicologist using the 1/1000th seems to be saving a very small expenditure of time and effort to derive a highly inaccurate and inappropriate value. The assumption that 1/1000th minimum therapeutic dose approach would result in conservative HBELs is not based on objective scientific evidence. To date, to our knowledge, there are no published scientific data (comparing HBELs of highly hazardous versus not highly hazardous products) that suggest that the 1/1000th minimum therapeutic dose when applied to non-highly hazardous products would always result in conservative estimates of HBELs. We have seen data contrary to this (products (see Attachment I for a comparison of MAC values for the PDE vs. the 1/1,000th that show higher MAC values for 0.001 than for the ADE for higher risk products and much lower MAC values for 0.001 than for the ADE for lower risk products)

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		As stated in the General Comments, one of the expressed goals of the ASTM Standard Guide is to provide the means for analyzing the level of risk in the cleaning of compounds to determine the degree of effort, formality and documentation necessary to demonstrate cleaning processes are valid. By maintaining the use of the 1/1000th of the minimum therapeutic dose, low hazard drugs and low risk situations will continue to have excessive degrees of effort, formality and documentation bringing no benefit to the patient and diverting the efforts of industry and regulators from higher risk drugs and higher risk situations. The continued use of the 1/1000th of the minimum therapeutic dose prevents both an accurate and an appropriate risk assessment. This is clearly contrary to the intentions of ICH Q9. 1 Walsh A (2011). Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I. Pharmaceutical Engineering, July/August 2011, Vol. 31 (No. 4). 2 Walsh A (2011). Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part II. Pharmaceutical Engineering, September/October 2011, Vol. 31 (No. 5). 3 Walsh A, Crevoisier M, Lovsin Barle E, Flueckiger A, Dolan DG, Ovais M (2016). Cleaning Limits—Why the 10-ppm and 0.001-Dose Criteria Should be Abandoned, Part II. Pharmaceutical Technology, 40 (8). Proposed change: A: If justified by scientific rationale, therapeutic dose information could be used as the 'Point of Departure' for calculation of an HBEL (e.g. the PDE). However, the continued use of the 1/1000th of the minimum therapeutic dose prevents an accurate assessment/evaluation of the risk posed by a compound, which is contrary to the intentions of ICH Q9 and the use of these limits should be deprecated.
Q&A 4	29.	Comment: In the answer to Question 4, regarding the establishment of a HBEL based on 1/1000th of the minimum therapeutic dose, clarification is needed regarding how this approach is related to the approach outlined in the main

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		guideline where it is stated that “A restriction to use of F2 and potentially F5 may be acceptable when deriving a PDE on the basis of human end points”. If a restriction to F2 and F5 is used, then the maximum adjustment factor is 100 (i.e., 10 for each of F2 and F5), which is 10-fold less than applying a factor of 1,000 to the minimum therapeutic dose. Accordingly, the HBEL (PDE) would be 10-fold higher. Please clarify this apparent discrepancy and provide some guidance on when a restriction to use only F2 and F5 would be appropriate rather than using 1/1000th of the minimum therapeutic dose.
Q4	31.	Comment: HBELs for existing products with well-established clinical safety profile should also be allowed to be established based on full toxicological analyses as per the EMA guide (in a similar way as for highly hazardous products). In such a case HBELs should not be required to be always lowered to 1/1000th minimum therapeutic dose approach. As far as 1/1000th minimum therapeutic dose is concerned it is of note that limits established based on this approach may frequently be too restrictive. It was clearly emphasised in the draft of the EMA guide release for public consultation in January 2013: Pharmaceuticals not considered to be covered under these criteria were 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 was applied concurrently with a maximum permitted contamination of 10 ppm of the previous active substance in the next product manufactured. Whichever of these criteria resulted in the lowest carryover, constituted the limit applied for cleaning validation. However, these limits do not take account of the available pharmacological and toxicological data and may be too restrictive or not restrictive enough. Huge numbers of clearly non-toxic compounds for which residual should not be expected to be lowered below 1/1000th minimum therapeutic dose approach may be given. These include in particular: - most micro- and/or microelements or vitamins, - some endogenous substances (even of chemical origin). Once another case when HBELs should not be expected to be lowered to 1/1000th minimum therapeutic dose is when a manufacturing area is dedicated for a set of compounds, even highly hazardous, sharing both similar

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		chemical structure and similar pharmacological activity (without any risk of contamination of products from other groups). What may be considered in Health-Med's opinion is that "traditional" thresholds (1/1000th or 10 ppm) could be applied for non-highly hazardous products instead of performing any toxicological analysis. We specifically mean that for non-highly hazardous products manufacturers could: 1) apply the "traditional" thresholds (1/1000th or 10 ppm, whatever results in lower carryover), instead of performing toxicological analyses, or 2) perform toxicological analyses (in most cases resulting in less conservative limits). For highly hazardous products relevant toxicological analyses should always be performed, however even for such products lowering respective carryovers to "traditional" thresholds should not be required.
Q4. Can calculations of HBELs be based on clinical data only (e.g. to establish the HBEL on 1/1000th of the minimum therapeutic dose?	32.	Comment: See earlier responses (Q1, Q2). APIC recommends further discussion with industry before publication of the Q&A. Comment: The calculation of HBEL (PDE or ADE) from the minimum Therapeutic Dose (mTD) by dividing this value by 1000 is excessively conservative and it does not take into account any available toxicological data of the drug or active substance. The mTD should be considered as a LOEL. To derive the PDE or ADE from it according the EMA guideline (EMA/CHMP/SWP/169430/2012) the following adjustment factors should be applied: F2: A factor up to 10 (3-10) could be used to account for variability between individuals. F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor up to 10 (3-10) could be used depending on the severity of the toxicity. Using those proposed values and using 1 for factors F1, F3 and F4, the ADE will be in the range of mTD/9 – mTD/100. E.C.Faria et al. show a comparison between the ADE calculated with the EMA guideline and the traditional TD/1000 value for different compounds. The conclusion is clear: the approach TD/1000 leads to unnecessarily tight limits for non-hazardous APIS. Only for anticancer drugs and hormones the ADE values calculated with EMA guideline produce inadequately protective limits and for those compounds production in dedicated facilities is recommended.

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		Ellen C. Faria, Joel P. Bercu, David G. Dolan, Eric J. Morinello, Alison M. Pecquet, Christopher Seaman, Claudia Sehner, Patricia A. Weideman. Using default methodologies to derive an acceptable daily exposure (ADE). Regul. Toxicol. Pharmacol. (2016) doi: 10.1016/j.yrtph.2016.05.026. Proposed change (if any):
Q5	1.	Comment: A: What if LD50 is only toxicological data available for the active substance? Proposed change (if any):
Q5. Q5. Is the use of LD50 to determine health based limits acceptable?	6.	Assuming the statement concerns the API EFPIA agrees in principle with this statement. However, a priori the term LD50 is misleading since these studies are not performed anymore as such. It might be better to refer to acute or single dose toxicity data. As stated, we agree that acute toxicity is not the preferred as a point of departure for HBEL definition especially in case of APIs where much more relevant data is likely to be available. However, relating to intermediates (see also EFPIA proposed Q, under General), acute toxicity data may in some cases be the only experimental data available (as required under REACH). As has been argued for API's, this data may be less adequate, however, in line with good scientific practice it should not completely be ignored. Therefore, it should be indicated how to consider this data in these cases. Proposed change: Please provide more context.
Q&A Q5 Is the use of LD50 to	15.	Comment: 1-In API production we must consider all the compounds used in the chemical or biochemical processes such as

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determine health based limits acceptable		APIs, intermediates and industrial chemicals . LD50 is used as starting point to calculate acceptable residue limits when PDE is not available . 2-When OELs or OEBs are well established for workers safety can these data be used to establish cleaning limits Proposed change (if any):
Question 5	16.	Comment: Applicability to cleaning agents, to well-known excipients and to products without therapeutic doses (Example: Topical products, antiseptics)? Proposed change (if any): N/A
Question 5	16.	Comment: Is the answer to question 5 is to use in all cases the 10ppm? If the value with the LD50 approach is stricter than the 10ppm, is it retained? Proposed change (if any): N/A
Question 5	16.	Comment: Cases of sites using the LD50, what is the deadline for reviewing the criteria? Proposed change (if any): N/A
Q5	19.	Comment: Is the use of LD50 to determine health based limits acceptable? No, LD50, or any other indicator for acute toxicity (e.g. MTD, Acute Toxicity Estimate, discriminating dose) are not an adequate starting point to determine a health based limit.

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		Proposed change (if any): The message should be that the limit should not be based on single dose toxicity studies.
Q5	21.	Comment: We fully agree and thank SWP for the clear statement.
Q&A 5	22.	Is it still acceptance to use LD50 values to determine CV limits for detergents? Are HBELS required for detergents?
Question 5	23.	Comment: This is appropriate for drug substances (drug actives). However, there are situations where the use of an LD50 as a starting point for a HBEL is appropriate, such as for intermediates in small molecule API synthesis or for cleaning agents/detergents. One typical approach for those situations is to use the LD50 to determine the NOEL/NOAEL, and then use the NOEL/NOAEL to determine the ADI (which is essentially the same as a PDE/ADE. Proposed change (if any): Change the answer to the following: “A: The LD50 is not an adequate point of departure to determine an HBEL for a compound that is the drug substance. In some situations, such as for intermediates in small molecule API synthesis or for cleaning agents/detergents, in the absence of other data, the LD50 may be used as the starting point to estimate the NOEL/NOAEL, and then that NOEL/NOAEL may be used to calculate a PDE to be used as the HBEL.”
Q&A 5	24.	Comment: A5 brings the long overdue clarification that the use of LD50 as the point of departure to determine health based limits is not acceptable. The statement is in agreement with the available scientific evidence. The shortcomings of the use of LD50 to derive HBELs have been discussed previously (Faria et al., 2016, Lovsin Barle et al., 2012).
Q5	25.	Comments: We welcome A5 as it brings the long overdue clarification that the use of LD50 as the point of departure to determine health based limits is not acceptable. The statement is in agreement with the available scientific evidence. The shortcomings of the use of LD50 to derive HBELs have been discussed previously (Faria et al., 2016, Lovsin Barle et al., 2012).
Answer to Q5	26.	Comment: As an answer to question 5 (Q5) of the above mentioned document you pointed out that:” LD50 is not

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		an adequate point of departure to determine an HBEL“ We consider that if the lowest available in the data basis LD50 for the respective route of administration is used for the determination of the NOEL according to the methodology given in TR 29 of PDA: where modifying factor MF1 of 1000 is used and further the calculation for determination of PDE continues as described in EMA/CHMP/CVMP/SWP/169430/2012 (applying f=12, f2=10, f3=10, f4=10 and f5=1 as per EMA/CHMP/ICH/82260/2006), the levels of the calculated MACO is extremely severe. The calculated fallowing this methodology levels are in the range of ppb and give a high level of assurance for lack of cross-contamination due to cleaning problems and can guarantee the high quality of the produced medical products. May you please provide me your opinion on the described above methodology! Proposed change (if any): The use of LD50 should be adequately justified.
Q&A 5	28.	Comment: We agree completely with the answer to Question 5. Members of our team have shown that converting an LD50 to an ADE is highly inaccurate and that the cleaning limit derived from it using the current approaches typically lead to unreasonably low limits that cannot be achieved. This has resulted in many companies abandoning the use of cleaning agents, which leads to poorer cleaning, possibly leaving residues behind, and potentially putting patients at risk (see reference below). Walsh A, Ovais M, Altmann T, Sargent EV (2013). Cleaning Validation for the 21st Century: Acceptance Limits for Cleaning Agents. Pharmaceutical Engineering, November/December 2013. Vol. 33 (No. 6). Proposed change: None recommended
Q5	31.	Comment: As far as HBELs determination is concerned, it is noted that for many compounds NOAEL (or NOEL)

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		values are not available and LD50 values are the only toxicological data available. Therefore, in Health-Med's opinion, as long as there are no special safety concerns, NOAEL values should be allowed to be estimated based on LD50 values. One of approaches that has been frequently used in practice is the so-called Layton approach (Layton DW, Mallon BJ, Rosenblatt DH, Small MJ. Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data. Regul Toxicol Pharmacol. 1987 Mar;7(1):96-112). This assumes dividing the LD50 values by an empirical constant 2000, that in most cases derives significantly lower NOAEL values than would be found in the course of tox studies. In general, all alternative approaches to determine health based exposure limits should be considered acceptable if – as stated in the EMA guide – "adequately and scientifically justified".
Q5. Is the use of LD50 to determine health based limits acceptable.	32.	Comment: Neither the question nor the answer is clear. Companies should be encouraged to review all existing toxicity data as part of the risk assessment for manufacturing and cleaning in shared facilities. Please give clarification on the types of toxicity studies that could be used and consider that for established substances and intermediates, LD50 data can be the only data available, whereas for new compounds LD50 data is no longer generated and short-term toxicity studies are reviewed by industry toxicologists together with clinical data to establish risks related to manufacturing and cleaning. Proposed change (if any):
Q6	1.	Comment: A: According to Q6 it seems that traditional cleaning limits (1/1000th of min. therap. dose or 10 ppm) shall be applied regardless the results of HBEL calculations. Please clarify if limits higher than those traditional ones are allowable when justified with toxicological data and other matters concerning cleaning efficacy (risk assessment etc.) for non-highly hazardous products? The same, please explain if limits higher than those traditional ones cannot be ever applied for highly hazardous substances even if justified?

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		What is more, in publication - *Dolan DG, Naumann BD, et al., Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations, Regulatory Toxicology and Pharmacology 43 (2005) 1–9* an approach is presented that for non-mutagenic substance the PDE value is 100 µg per day. Such approach should be also possible to apply. Proposed change (if any):
Q6. How can limits for cleaning purposes be established? (Paragraph 2)	2.	Current text states: For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach. Comment: Per section 1 of EMA/CHMP/CVMP/SWP/169430/2012 (referring to establishing threshold levels based on pharmacological and toxicological data) “These levels can be used as a risk identification tool and can also be used to justify carry over limits used in cleaning validation.” Per section 4.1 “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.” Due to the use of multiple adjustment factors to adjust the NOAEL to account for uncertainty, the PDE values derived per this guidance for establishing carry over limits for cleaning validation contain significant safety margins, which ensure the derived PDE value confidently meets the specified objective stated in section 4.1 (noted above). Proposed change (if any): Therefore, to ensure the Q&A guidance does not imply that a limit which meets the stated objective of section 4.1 requires an additional safety factor please consider rewording this document to state:

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		"For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should not be higher than the traditional cleaning limits approach."
Q6	5.	Comment: Cleaning programs for shared equipment is critical for minimizing the risk of cross contamination. While having the appropriate limits is an essential step, it is just one part of the program. HBELs are conservative by nature but based upon the response to this question it appears that the EMA does not really trust these values and requires further reduction to them to provide a lower cleaning limit. It appears especially for the highly hazardous products EMA wants cleaning limits to be calculated by three methods (HBEL, 1/1000th and 10 ppm) and select the lowest as the acceptance criteria. If the goal is to have robust cleaning programs it may be better to require staged limits (acceptance limits from the HBEL calculation and action/ alert limits at something below which should be just above the level of the data expected or could be the 1/1000th or the 10 ppm based limit), have a robust cleaning development program and robust cleaning verification/routine monitoring. Use of the acceptance limits using the HBEL in the calculation and then assessing it against the actual cleaning results provides an indication of the level of risk the cleaning process represents. For example cleaning data that is very close to the acceptance criteria represents a cleaning program with high risk of failure whereas cleaning data that is very far from the acceptance criteria represents a cleaning program with low risk of failure. There is also a lot of fear of using the HBEL generated limits if the limits are high. In these cases visually clean would be the overriding criteria thereby reducing the acceptance criteria. There is also fear that raising an existing limit would let companies clean less. That is not the intent of using the HBEL generated limit if it is higher. The intent is to show that the risk of failure is low and the expectation is that the cleaning results would remain the same. The area that seems to be misunderstood and not getting enough attention is the cleaning verification/routine monitoring program. Companies that use manual methods for cleaning cannot rely on cleaning validation alone to confirm that the equipment is clean enough for the next product especially when the cleaning limits are below what the eye can detect. Many companies are doing just that – they have manual cleaning that is validated with 3 runs

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		and thereafter only visually inspect for cleanliness even where the cleaning limits are extremely low and the eye cannot detect to that level. (The cleaning verification program usually is weak where every couple years or so some of the sites are verified and companies do find failures in these verification runs!) So in order to determine if the equipment is adequately cleaned to the levels required a chemical analysis is required. By lowering the cleaning limit below that of the HBEL calculated limit most if not all compounds would fall into this scenario. Whereas if the limits were left at the HBEL calculated level, visual inspection could be used for the low risk scenarios and chemical analysis required for the high risk scenarios. Proposed change: "The acceptance criteria should be set by using the HBEL using the guideline methodology (EMA/CHMP/CVMP/SWP/169430/2012) in the cleaning limits calculation for all products (legacy products and new products), as the HBEL does contain all the necessary safety factors. Change the second and third sentences to: The cleaning program should consist of adequate cleaning limits, robust cleaning development, and robust routine monitoring program. Where the cleaning limits are below visual acuity, chemical analysis is required. Risk assessments of the cleaning program should compare the actual cleaning results to the acceptance criteria. High risk cleaning programs are where the results and the limits are close. Delete the last sentence.
Q6. How can limits for cleaning purposes be established?	6.	Comment: We do not agree with the introduction of additional safety factors when using PDE or OEL values as the basis for the calculation of residual limits, as these types of HBEL already consider the worst case situation. There is no need to add a safety factor to account for the uncertainty of the cleaning process because any variability should be accounted for as part of the validation. Good cleaning processes and practices are an essential part of GMP, so for example a high HBEL cannot be used to justify equipment not being 'visually clean'. Proposed change: Although the EMA (EMA/CHMP/CVMP/SWP/169430/2012) guideline may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL (using the guideline methodology). It is the objective of cleaning validation to make sure the actual cleanliness

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		values are consistently achieved, with a high level of confidence that they are below the limits derived from the risk assessment and HBEL, taking into consideration cleaning process capability and analytical method variability. Where cleaning limits historically used by industry for currently marketed products (such as derived from 1/1000th of minimum therapeutic dose), are more conservative than the limits derived from HBEL guideline methodology (PDE), there is no requirement to revise the cleaning limit. Good cleaning processes and practices are an essential part of GMP, so for example a high HBEL cannot be used to justify equipment not being 'visually clean'.
Q6	7.	Comment: It is mentioned that "For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach." Proposed change (if any): For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors and HBEL calculation, the lowest MACO shall be selected as an extreme case"
Q6. How can limits for cleaning purposes be established?	8.	Comment: The answer of question 6 re-introduces the traditional criteria (such as 1/1000th of minimum therapeutic dose and 10 ppm) for establishing limits for cleaning validation. This contradicts the original scientific approach of establishing health based exposure limits. The need for a toxicological evaluation was introduced into the EU GMP Guide, inter alia, just because the traditional criteria are not scientifically based. The substance-specific properties are not taken into account in the case of the 10 ppm criterion, because the limitation is based purely on quantity. In the case of the 1/1000th of the dose criterion, the therapeutic dose is taken into consideration; however, it says nothing about other potential effects of the active ingredient. Moreover, the re-introduction of traditional criteria for cleaning validation would penalize those non-hazardous substances using values more restrictive than the ones that could be applied according to their inherent toxicity.

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		Proposed change: Deletion of the sentence: Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products.
Q6	9.	Comment: Referring to question number 6: Regarding your answer to question no. 6 our company would appreciate more guidance and clarification on the topic, as some items are considered to be in contrast to the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012). Here, the agency recommends the use of scientific derived HBELs (Health Based Exposure Limit) also for non-highly hazardous compounds whereas in the answer a traditional (non-scientific) approach for non-highly hazardous substances is stated. Further it is argued, that the reason for implementing a traditional approach is the inclusion of additional safety margins. However, there are either no (10 ppm) or less (1/1000th dose) safety margins in the traditional approach than in the HBEL concept where toxicological uncertainties are addressed using various adjustment factors. The same is true for highly hazardous compounds where a HBEL always should be preferred over a pure risk based limit (1.5 µg/d). There should always be more confidence in the scientific and product specific approach rather than in a traditional and general risk based concept. The agency should clarify under which circumstances which approach has to be applied. Proposed change (if any): Based on the comments made above, we suggest not distinguishing between non-highly hazardous and highly hazardous compounds and passing on the traditional approach completely. A HBEL should be implemented for all compounds where a sufficient toxicological data base is available. For all other (non-sensitizing) substances the TTC-limit shall be used. Those methodologies are considered as sufficiently scientifically based and conservative enough to be used without further safety factors for the derivation of cleaning limits.

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Q/A6 "The cleaning limits should (2) continue to be based via risk assessment and additional safety margins to help account for (4) uncertainty in the cleaning processes and (3) analytical	10.	Comments: 1) The first two sentences are a hair-splitting interpretation of the Guidance, which says: "These levels (based on HBEL, note added) can be used […] to justify carry over limits used in cleaning validation." To make a difference between "setting limits" and "justifying limits" is questionable construction. If a limit is justified, it is a correct and acceptable limit. EMA cannot say something and its contrary at the same time. The pattern: "although we say you can do it, you should not do it" is not worthy of an authority like EMA. It is not good guidance practice. It is like setting a speed limit at 120 km/h and telling the drivers they will be fined if they drive faster than 100 km/h. Sad to say, I am afraid the Agency discredits itself. 2) In fact, cleaning limits based on HBEL are and continue to be "based via risk assessment and additional safety margins". See the EMA's own methodology to derive PDE. PDEs are conservative values by definition (e.g. lifelong exposure). It can't be justified to add "safety factors beyond the HBEL" (whatever such factors may be) on a cleaning limit based on HBEL, because the HBEL (like PDE) do contain all the necessary safety factors. 3) No need to add a safety factor to account for the analytical variability. The variability is known. It has been determined by the mandatory validation of the analytical methods, and can be taken into account precisely when results are reported. To suggest adding an arbitrary safety factor for analytical variability is contrary to the scientific (and regulatory) principles of method validation. 4) No need to add a safety factor to account for the uncertainty of the cleaning process. To determine and to minimize the uncertainty in the cleaning process is the essence of cleaning validation. It is the objective of cleaning validation to make sure the actual cleanliness values are statistically, with a high level of confidence, below the safe limits based on HBEL. In six sigma talk (process capability): A valid cleaning process must ensure an appropriate margin of safety between the upper process limit and the specification limit. So, there is no need to add "safety margins" to the limits. It is surprising the EMA proposes to do so, because it denotes a questionable understanding of cleaning validation and statistical process control. It is a fallacy to believe that lower limits increase the margin of safety: Only a better cleaning process will. How to validate a cleaning process is out of scope of the EMA Guidance, though. If the EMA intends to give guidance on Cleaning Validation, they should do it in a separate document, which would probably be highly

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variability. cleaning limits should include (2) safety factors beyond the HBEL and should not be higher than the (5) traditional cleaning limits approach.		welcome by industry and inspectors alike. 5) The intention to re-introduce the 10 ppm and 0.1% dose limits after EMA had rightly called them arbitrary values that can be either too low or too high in their concept paper, is a big disappointment. How can EMA, in a Q&A document about HBEL(!), seriously propose a contamination limit (10 ppm) that ignores the nature of the contaminant, completely excludes the knowledge of the product, and is ultimately solely based on the weight of the contaminated product? The traditional argument that the 10 ppm rule "only kicks in when it is lower than 0.1% daily dose" is another fallacy. According to the traditional rules, the 10 ppm rule is ALWAYS enforced: 0.1% daily dose AND 10 ppm (not or!) must be met. If both limits must be met, both limits must be justified independently. The 10 ppm limit has been waiting for a scientific justification for decades and none is in perspective. As a safeguard against too high cleaning limits based on HBEL, the "visually clean" criterion does the job as well as the 10 ppm. To bring back the 10 ppm is a regrettable step back into obscurantism and contrary to HBEL Worse: As disappointing as it is, one could eventually accept that the EMA yielded to the pressure of a few companies or lobbies who wanted to keep the old rules; but it is unacceptable that EMA now wants to force all the companies to go back to the old rules for highly hazardous API. Doing this, the EMA blocks the way to a science and risk based approach and eventually blocks the implementation of the Guidance itself. Proposed change (if any): A: "The cleaning limits should be based on HBEL (PDE, e.g.). The validation of the cleaning process, e.g. the analysis of the cleaning process capability, should show that the cleaning processes ensure appropriate margins of safety to the limits." Comment: Such a disposition would include all the "additional safety factors" intended in the original answer and provide for a (hugely welcome) statistics based approach to cleaning validation. As the Guidance is not on validation, it is better not to give more specific direction as to the extent of the safety margin (like e.g. "at least two sigma to the upper specification limit").

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Q6. (page 2)	11.	Comment: Cleaning limits for “highly hazardous compounds” should not be higher than the traditional cleaning approach. With the PDE aiming at heath based limits, it is surprising that, when indeed determining a PDE (based on health based knowledge/limits), it is NOT allowed to end up with a value higher than the traditional unscientific methods previously used. As a result the following situation may become standard: Carry over limits: PDE or 1/1000th TTD or 10 ppm, whichever is lowest. And with that, all the gains of the PDE approach; more stringent limits where needed, less stringent limits where responsible, would be lost. Having this information in the Q&A is likely to make this the standard approach. Proposed change: - Remove the statement that the old limits may not be exceeded. - Applying a (non health based) upper limit may be warranted in specific circumstance such as carry-over of pharmaceuticals of very low potency (with corresponding high PDE values). Applying 10 ppm is however too stringent. Perhaps applying 0.1% or 1% can be considered?
Q6	12.	Comment: It states that “additional safety margins” should be added to account for cleaning processes and analytical variability. Also the last paragraph says cleaning limits should include “additional safety factors”. We believe the intent is to use process capability to derive the cleaning limits, but as written could be interpreted differently. For example, an inspector could require an arbitrary 100-fold factor below the HBEL. The HBEL is a safe limit and contains adjustment factors already so no additional safety factors should be needed. However, process capability should be considered which is based on cleaning and analytical data. Process capability and cleanings limits based on analytical/process variability are independent for the hazards of the drug. So there should be no separate guidance for highly hazardous drugs compared to non-hazardous drugs.

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		Proposed change (if any): Rephrase the second sentence to "The cleaning limits should continue to be based via a risk assessment taking into account the cleaning process and analytical variability." Remove third sentence and beyond.
Q6	12.	Comment: It states that cleaning limits based on the PDE/HBEL must not exceed the traditional cleaning limit approaches such as 10 ppm or 1/1000 of the minimum therapeutic dose. However, the traditional cleaning limit approach was designed to be a conservative expedient cut-off and not a science-based approach. Typically we find that the HBEL using the PDE approach is higher than the traditional 10 ppm or 1/1000 of the therapeutic dose. The HBEL with appropriate allowance for cleaning process and analytical variability is a safe dose; therefore control below this level to an arbitrary limit is unnecessary. Proposed change (if any): Delete or modify last sentence in Question 6.
Q&A Q6 : how can limits for cleaning purposes be established	15.	Comment : traditional cleaning limits described for non highly hazardous compounds are specific of the drug product industry For API manufacturing common practices are described in APIC guideline as examples from companies Proposed change (if any): Replace current version: the cleaning limits should continue to be based via risk assessment and additional safety margins to help account for uncertainty in the cleaning process and analytical variability . Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product may accomplish this for non highly hazardous products By revised version : cleaning limits should be based on a risk assessment including pharmacological and toxicological data , characteristics of the manufacturing process , uncertainty in the cleaning process and analytical variability

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Question 6	16.	Comment: How can we explain that we can tolerate impurities up to 1% in the finished product (ICH) while we can be on lower criteria in cleaning validation? Considered in our guide but not in the scope of annex 15 (single use and SS system? not only for primary packaging articles) Proposed change (if any): NA
Question 6	16.	Comment: Should the cleaning validation take into account non visible particles on specific product (injectable product with particles level criterion)? Proposed change (if any): NA
Question 6	16.	Comment: In the case of sites already having PDE values calculated for non-highly active products, should these values be exploited to compare them to approaches of 10ppm and 1 / 1000th of the therapeutic dose? Proposed change (if any): N/A
Q6	17.	Comment: We do not agree to the introduction of additional safety factors when using PDE or OEL values as the basis for the calculation of residual limits, as these types of HBEL are already considering the worst case situation, and especially the PDE is a parameter that is based on toxicological and/or human health effect data where no effect is expected even if the person is exposed to the substance during her whole life. Therefore, a PDE for a highly hazardous substance would be expected to have a low PDE and as a consequence, a low allowable residue. The introduction of an additional safety factor would again lead to endless discussions with authorities or during inspections, which is in contradiction with the aim of the guideline to seek clarity i.e. to have an objective criterion to evaluate the criticality of a substance in shared facilities.

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		Proposed change: Please amend the last sentence to read: “For established products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits based on HBEL should not be higher than the applied traditional cleaning limits”.
Q6	19.	Comment: Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non- highly hazardous products. This may be interpreted to suggest that cleaning limits should be established based on the lowest of the PDE, 10 ppm or 1/1000. Proposed change (if any): It is important to clarify that limits based on PDEs are sufficient and that it should not be necessary to determine a PDE, 1/1000th and 10 ppm for every compound and then select the smallest value.
Q6	21.	Comment: One of the problems that have been created with the HBELs and the fact that they are often higher than the traditional limits is that the HBELs are perceived as cleaning targets. It is stated but can maybe put into even clearer words that the minimum expectation of the EMA is that in all cases, the company cleans to its historically proven cleaning capabilities and if the HBEL-derived MACO is lower, cleaning must be improved. If the HBEL-derived MACOs are higher than the traditional cleaning capability, the difference between the two must be seen as margin of safety which should not be intentionally lowered by applying lesser cleaning standards. The mention of the nonsense class of “highly hazardous molecules” is once again unnecessary as the statement made for them is equally correct for low potency compounds – the situation is identical only at different exposure levels. Proposed change: Delete the last 3 lines. Replace the last sentence of paragraph 1 by: “Traditional cleaning approaches used to achieve the 10 ppm or 1/1000 therapeutic dose levels can be considered as “historical cleaning capability” or “good cleaning practice” and should also be applied now and in the future. There should be a sufficient safety margin between the cleanliness that was achieved and the HBEL-derived cleaning reference.”

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Q&A 6	22.	Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL (using the guideline methodology). The cleaning limits should continue to be based via risk assessment and additional safety margins to help account for uncertainty in the cleaning processes and analytical variability. Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products. For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach.
Question 6	23.	Comment: I think the purpose of this paragraph is that there may be effects other than patient safety that may cause cleaning validation limits to be more stringent. Most of the changes below are to clarify this concern. Furthermore, the traditional approach is not "1/1000th of a minimum therapeutic dose or 10 ppm"; as presented in the 1993 Fourman/Mullen publication and in PIC/S recommendations on cleaning validation, the traditional approach is the "more stringent of 1/1000th of minimum therapeutic dose and 10 ppm". I also made a change proposed below that the 10 ppm criterion is not 10 ppm product in anther product, unless the first product is considered the drug substance. I realize this terminology is that used in the Fourman/Mullen 1993 publication, but the use in that publication is misleading. For drug substances in drug product manufacturing, the traditional limit is the "more stringent of 1/1000th of the minimum therapeutic dose and 10 ppm of the drug substance in the next drug product". Finally, in this context it is appropriate to add that the cleaned equipment is also typically expected to be visually clean. Proposed change (if any): Change the answer to the following (note: added or changed words are in bold). "A: Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to exclusively set cleaning limits at the level of the calculated HBEL (using the guideline methodology). The cleaning limits should continue to be based via risk

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		assessment and additional safety margins to help account for uncertainty in the cleaning processes, analytical variability, and other effects such as on product quality and purity. Traditional cleaning limits used by industry for drug substances such as the more stringent of 1/1000th of minimum therapeutic dose and 10 ppm of one drug substance in another product, may accomplish this for non-highly hazardous products. For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits may include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach. Furthermore, after cleaning the equipment should be visually clean, which may be more stringent than a limit based on the HBEL"
Q&A 6	24.	Comment: Robust cleaning procedures are required to prevent cross-contamination and current process capability based on analytical data with respect to cleaning should be maintained. Process capability and process control limits are independent of the hazards of the drug and reflect the cleaning process robustness. The cleaning limits should be validated. The goal is to have as large as possible margin of safety between the acceptance criteria and the results from cleaning which will address process variability. This is what makes the cleaning process less risky (less chance of failure). Lowering the limit to address cleaning process variability does not address the root cause of either human error or inadequate procedures. Visually clean is a requirement and will in effect lower the acceptance criteria for compounds where the HBEL limit is high. Additional factors are not needed for analytical variability since method validation takes this into account. The best practice is to use statistics to evaluate process capability. Most importantly, the hazard of the substances has to be considered only in a context of a risk assessment. A compound could be highly hazardous but easily break down in cleaning solution or not adhere to equipment indicating it is a low risk drug with regard to cleaning.

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		Proposed change: “The acceptance criteria should be set at the level that incorporates the HBEL using the guideline methodology (EMA/CHMP/CVMP/SWP/169430/2012) for all products (legacy products and new products), as the HBEL does contain all the necessary safety factors. Cleaning procedures should strive to reduce residues to the lowest levels that are possible in a consistent manner based on the capability and reliability of the cleaning process, regardless of what carry-over calculations may seem to allow. “Visually clean” criteria have always been applied as an additional acceptance criteria for cleaning, which will in effect lower the acceptance criteria where the HBEL criteria is high. There should be a sufficient safety margin between the cleanliness that was achieved and the HBEL-derived cleaning reference. For legacy products, traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose of one product in another product may be used on an interim basis until calculated HBELs are available. The use of traditional cleaning limits should be justified by a risk assessment. If the HBEL suggests a higher acceptance limit compared to traditional limits based on 1/1000th of the minimum therapeutic dose, this should be viewed as demonstrating an additional margin of safety than previously determined.”
Q6	25.	Comment: A6 states that EMA guideline (EMA/CHMP/CVMP/ SWP/169430/2012) may be used to justify cleaning limits, however it is not intended to be used to set cleaning limits at the level of the calculated HBEL. This statement seems logical; it is a good point that a high HBEL shall not lead to less cleaning and traditional “good cleaning practice” including the criterion “visually clean” should be kept, even if the HBEL is higher than previous limits. However, to force the use of 1/1000 MinDD and 10 ppm criteria is unscientific and unwarranted. The HBEL is a safe limit and contains adjustment factors already; so no additional safety factors are needed. In addition, to do so would be inconsistent with other regulatory programs designed to protect drugs, foods, workers, and the environment. On the cleaning validation side, process capability based on analytical data should be considered. Process capability and process control limits are independent of the hazards of the drug, so there should be no separate guidance based on hazard. The company should clean to its historically proven cleaning capabilities and if the HBEL-derived Maximal Allowable Carry Over (MACO) is lower than the hitherto achieved historical equipment cleanliness, cleaning must be improved However, it should not be stated that companies must continue to use traditional derived MACOs

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		just because they are more stringent or to ask companies that have already implemented HBEL-MACOs for all their portfolio to go back and implement traditionally-derived MACOs in order to have a “margin of safety” against the HBEL-MACOs. HBEL-MACOs should be implemented for every product, in agreement with the initial EMA guidance, to define where the risk to the patient lies, while continuing to clean with the validated method (and achieve the visually clean criteria). The difference between the consistently achieved cleaning results and the HBEL-derived MACO can be considered as a margin of safety of the process (cleaning process capability). The same would apply for new product introduction, where companies should not be encouraged to use traditional methods such as 10 ppm or 1/1000MinDD, which are not appropriate from a toxicological perspective, in order to achieve the presumed margin of safety between the HBEL-MACOs and the traditional-derived MACOs. Adding random factors to the HBEL-MACOs to account for analytical and cleaning variability is unnecessary as the HBEL already includes significant safety factors and it is already very conservative from a toxicological perspective. These random factors to generate a margin of safety were not applied to traditionally derived-MACOs, even though they have proven not stringent enough for certain compounds. The cleaning limits must continue to be based on risk assessment introduced in the ICH Q9 and its applicability to cleaning (including acceptance limits) mentioned in its Annex II.4 and to validation mentioned in Annex II.6, however there is no need to add a safety factor to account for the analytical variability or uncertainty of the cleaning process. The analytical variability is known, it has been determined by the mandatory validation of the analytical methods and can be taken into account precisely when results are reported. Equally there is no need to add a safety factor to account for the uncertainty of the cleaning process. Consistency and the reduction in the variability of the cleaning process is the essence of cleaning validation. It is also the objective of cleaning validation to make sure the actual cleanliness values are statistically achieved, with a high level of confidence they are below the safe limits based on HBELs. A valid cleaning process must ensure an appropriate margin of safety between the upper process control limit and the HBEL based upper specification limit. Validation of a cleaning process, however, is out of scope of the EMA Guidance. The most important message is that the hazard of the substances has to be considered only in a context of a risk

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		assessment. A compound could be highly hazardous but easily break down in cleaning solution or not adhere to equipment indicating it is a low risk drug with regard to cleaning. Proposed change (if any): “The cleaning limits should be set at the level of the calculated HBEL using the guideline methodology (EMA/CHMP/CVMP/SWP/169430/2012) for all products (legacy products and new products), as the HBEL do contain all the necessary safety factors. Cleaning procedures should strive to reduce residues to the lowest levels that are possible in a consistent manner based on the capability and reliability of the cleaning process, regardless of what carry-over may seem to allow. Therefore, “visually clean” criteria must always been applied as an acceptance cleaning criteria. For legacy products traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose of one product in another product may be used until calculated HBEL are available and can be applied for cleaning procedures across the entire product portfolio of a shared facility. There should be a sufficient safety margin between the cleanliness that was achieved and the HBEL-derived cleaning reference. The use of traditional cleaning limits should be justified by a risk assessment.”
Q&A 6	28.	Comment: Paragraph 3 of the Introduction to the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) expresses the intention of the ASTM Standard Guide quite well and this should not be changed. It should be understood by industry that the EMA guideline only provides guidance on selecting the starting point for subsequent cleaning limit calculations which remain unchanged from current practice. Again, the continuation of 1/1,000th or 10ppm level as a starting point for cleaning limit calculations has been shown to impose excessive restrictions on low risk compounds and is lenient on high risk compounds. An accurate Risk Assessment is not possible and ICH Q9 cannot be implemented. The answer to Question 6 should not help to perpetuate this long standing problem. Proposed change:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		A: Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL (using the guideline methodology). The cleaning limits should continue to be based via risk assessment
Q6. 2nd sentence of the answer	30.	Comment: “The cleaning limits should continue to be based via risk assessment and additional safety margins to help account for uncertainty in the cleaning processes and analytical variability.” In our opinion “additional safety margins” do not appear necessary, because a risk assessment has already been carried out at this point that would otherwise be called into question. Proposed change (if any): Please replace … “additional safety margins” … by “including safety margins”
Q6. 2nd paragraph of the answer	30.	Comment: “For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach.” This second paragraph appears contradictory to the guideline on setting health based exposure limits. In our opinion, in accordance to the “Guideline on setting health based exposure limits”, a risk assessment should be carried out also for “highly hazardous products”, since otherwise the PDE concept would have to be questioned. In addition, it should be noted that each facility should be at least "visibly clean". Proposed change (if any): Please delete the second paragraph of the answer.
Q6	31.	Comment: Recommendations provided in Q6 are unclear and considered not to be within the concept of the EMA guide. Necessity of additional safety factors is not clear. It is noted that recovery of swabbing (or other similar activities)

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		is determined in the course of cleaning validation. Such activities in most cases are considered to sufficiently address uncertainty of cleaning performance by imposing relevant safety factors. Moreover, it is not clear why cleaning limits are expected to be lowered to “traditional” thresholds such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product. Reasons for limited reliability of these “traditional” thresholds, including citation of the draft EMA guide are already provided above. It is emphasised that these comments apply to both highly hazardous and non-highly hazardous products.
Q6. How can limits for cleaning purposes be established? Lines 5-7 of Q6. Lines 8-10 of Q6.	32.	Comment: Increasingly, Health Agencies have been requiring manufacturers to establish limits for Cleaning Validation of API manufacturing plants based on toxicological data. When the EMA Guideline was published in June 2015, the industry took it as the guide to calculate such limits based on ADE/PDE values. In fact, the guide says the following under chapter 1. Introduction: Cleaning is a risk reducing measure and carry-over limits for cleaning validation studies are widely used in the pharmaceutical industry. (…) The objective of this guideline is to recommend an approach to review and evaluate pharmacological and toxicological data of individual active substances and thus enable determination of threshold levels as referred to in the GMP guideline. These levels can be used as a risk identification tool and can also be used to justify carry over limits used in cleaning validation. After the publication of the EMA Guideline and as recommended by the requirements from Health Authorities on each inspection to plants, companies have reviewed their Cleaning Validation Master Plans. ADEs were calculated in based on the directions of the EMA guideline and MACOs from those ADEs and from batch sizes of previous and next products redefined. In APIC opinion, the Q&As document draft is changing the approach that industry understood from the initial EMA’s document and creates an unnecessary additional change in Cleaning Validation Plans. APIC agrees to splitting products in 2 categories: highly hazardous and others but we do not see the need of moving back to arbitrary and not scientifically sound limits such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, for the second category of products. ADEs or PDEs calculated according to guideline are based on toxicological data and uncertainty factors. They are more reliable than approaches based on the use of 1/1000th of minimum therapeutic dose or 10 ppm of one

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		product in another product. These are general limits with no specific toxicological base. Additionally, these arbitrary limits are very conservative and, in consequence, the limits for cleaning purposes are very restrictive. The use of ADE or PDE based on toxicological data assures higher limits without losing safety. APIC recommends re-wording of this answer to indicate that a risk based approach is required to manage the risks inherent to compounds as indicated by the established PDE or ADE limits. To maintain risk based approach- deletion of last part of following sentence is proposed. For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL.- Delete- and should not be higher than the traditional cleaning limits approach.
Q7	1.	Comment: A: Could you indicate exemplary active substances of the Ectoparasiticides? Proposed change (if any):
Q7. Can Ectoparasiticides be manufactured or primary packed in common equipment with other categories of medicinal products for human or veterinary use?	6.	Comment: The HBEL as such is used to calculate substance residues allowed on surfaces of production equipment. Therefore it is more appropriate to say that shared use of equipment is possible as long as the residues are allowing it and there is an analytical method to prove successful removal. Proposed change: If the residual limits calculated on the basis of HBEL for Ectoparasiticides cannot support manufacture in common equipment then the Ectoparasiticides should be manufactured in dedicated facilities.
Q7	17.	Comment: The HBEL as such is a parameter that is based on toxicological and/or human health effect data which is used to calculate substance residues allowed on surfaces of production equipment. Therefore it is more appropriate

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		to say that shared use of equipment is possible as long as the residues are allowing it and there is an analytical method to prove successful removal. Proposed change: Please modify the sentence to read: “If the residual limits calculated on the basis of HBEL derivation for Ectoparasiticides cannot support manufacture in shared facilities then the Ectoparasiticides should be manufactured in dedicated facilities”.
Q7	21.	Comment: de facto, this means: yes, it is acceptable under certain circumstances. This is new and should be stated more clearly. Proposed change: Change reply to “Yes, this may be acceptable if HBEL and cleaning capability data justify this.
Q8. What needs to be taken into account when manufacturing Veterinary Medicinal Products for different species in the same facility?	6.	Comment: The last sentence in this answer includes “non-highly hazardous” terminology which as stated before we do not consider appropriate. Proposed change: Edit answer as follows. “The HBEL should be derived considering all data, both clinical and preclinical, and the derivation may use data from the most relevant species.”
Question 8	16.	Comment: How do we account for variations in weight and use of veterinary drugs versus weights and use in humans? The orders of variability between animal species are not comparable to the human! Proposed change (if any): N/A
Q8	17.	Comment: This paragraph seems to clearly demonstrate that it remains a case by case approach for veterinary products manufacturing and that HBEL is not necessarily the most practical criteria. Human data cannot be

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		considered suitable to establish limits for the veterinary. Proposed change: Please introduce a specific animal health toxicological approach into this document.
Q&A 8	28.	Comment: As in our comments to the previous Q&As, references to 1/1,000th and 10ppm are inappropriate and should be removed, and so is the use of the term “highly hazardous products.” Proposed change: A: The guideline on setting health based exposure limits indicates that the carry over limit should generally be derived using the human PDE. However, in cases where there is particular concern relating to known sensitivity of a particular species (e.g. Monensin in horses) a Health Based Exposure Limit (HBEL) approach taking into account specific animal toxicity knowledge should be used.
Q9. How can inspectors determine the competency of the toxicology expert developing the HBEL?	6.	Comment: In the original guideline it is requested to review nonclinical and clinical data, and therefore multiple experts may be involved in developing HBELs. As with all professional roles associated with GMP related systems, the manufacturer should have personnel with the necessary qualifications and practical experience, but these personnel may not be located at the manufacturing facility. Proposed change: If required, the inspectors should evaluate the company's process for developing HBELs to ensure that it involves suitably qualified personnel.
Q9	21.	Comment: experience has shown that there are HBELs and HBEL documents of very poor quality on the market. Many are from highly qualified toxicologists who have no experience in this field/sub-speciality. The reply is good, it would not make sense to ask for higher formal qualification in toxicology.

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Q&A 9	24.	Comment: ISPE welcomes the short note by EMA in relation to proper documentation of the Toxicology expert developing the HBELs (Q9). Hayes et al. (2016) have discussed the HBEL document management, revision, and communication. The authors provide guidance on proper communication of the HBELs that assure change management and information sharing with the contract manufacturers. Furthermore, Olson et al. (2016) provide details on what kind of data the HBEL document should include as well as proof of qualifications of persons who derive and author HBELs. They also point out that transparency and credibility are essential to a company's HBEL program.
Q&A 9	24.	Comment: Only qualified experts should estimate or derive HBELs. These individuals should have the appropriate training and experience, specifically in the area of establishing health-based exposure limits. Proposed change: Add the following after the first sentence: "These individuals should have the appropriate training and experience, specifically in the area of establishing health-based exposure limits. "
Q9	25.	Comment: We welcome the short note by EMA in relation to proper documentation of the Toxicology expert developing the HBELs (Q9). Hayes et al. (2016) have discussed the HBEL document management, revision, and communication. The authors provide guidance on proper communication of the HBELs that assure change management and information sharing with the contract manufacturers. Furthermore Olson et al. (2016) provide details on what kind of data the HBEL document should include as well as proof of qualifications of persons who derive and author HBELs. They also point out that transparency and credibility are essential to a company's HBEL program.
Q&A 9	28.	Comment: EMA should be aware that Question 9 and its answer is fraught with difficulties. Up until now, regulators have never challenged the competency of the persons calculating cleaning limits. Cleaning Validation specialists have come from many different backgrounds, particularly people who have no toxicological education or training yet have been setting cleaning limits based on 1/1,000th of a low clinical dose for many years. Such individuals should have been challenged as to their competence at setting these important GMP limits but they have not been. If the 1/1,000th & 10ppm are permitted to continue to be used, who will be selecting the compounds and doing these calculations?

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		Will this be a qualified Toxicologist or the Cleaning Validation Specialist? If it will continue to be the Cleaning Validation Specialists, will inspectors be evaluating a company's justification of the experience and qualification of the Cleaning Validation specialists? Currently the industry indentifies individuals in their organizations to be Subject Matter Experts (SMEs) and this is true for Cleaning Validation. However, there is no existing certification or qualification for Cleaning Validation SMEs so competency to perform such important calculations cannot be demonstrated or documented. We believe that ALL Health based Exposure Limits should be determined by a person with expertise in Toxicology and our ASTM Standard Guide defines this person as a "Qualified Toxicologist/Pharmacologist". We suggest that Q9 be answered using the proposed ASTM definition. Proposed change: A: Health based Exposure Limits should be determined by a "Qualified Toxicologist/Pharmacologist" who has specific education and training in toxicology/pharmacology and can apply the principles of toxicology to deriving an ADE or PDE value for required process residues. Companies should define these requirements in their internal policies.
Q10	1.	Comment: A: Does the described approach apply also for active substances with limited data used in marketed products? Proposed change (if any):
Q10. How can the HBEL model be applied to early phase Investigational	6.	Comment: Interim (default) HBELs may be required during the early development phase of the novel API, when the dataset for the drug may be insufficient to set a full HBEL. Such limits are by default more conservative than limits calculated on the basis of full data sets. Options not mentioned by the EMA answer are: 1. The (staged) Threshold of Toxicological Concern (TTC) for mutagenic compounds as described by ICH M7.

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Medicinal Products (IMPs) where limited data is available?		Although the TTC is considered to be conservative enough to also cover other types of toxicities, it should be noted that the TTC may not be sufficiently safe in all cases, e.g. for APIs with daily doses in the low µg or ng range. 2. Also related to the note to option 1, the estimated human therapeutic dose should be taken into consideration. 3. Use of relevant comparator data for derivation of a HBEL. 4. OEL monographs (see Q&A 3)
Q/A 10	10.	Comment: The answer is perfect. It comes as a good surprise, particularly after A6. It further highlights the inconsistency of A6: For IMP, which can tolerate higher levels of impurities than commercial products because of the short duration of exposure in clinical tests (see e.g. ICH M7), EMA expects the industry to follow the principles of HBEL, while in A6, EMA accepts the old arbitrary 10 ppm and 0.1% dose rules for commercial products, where the risk is higher than for IMP. Proposed change (if any): none
Q10	12.	Comment: This question misses the TTC approach recommended for IMPs as mentioned in the EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) (section 5.5). Proposed change (if any): Include a statement that a tiered TTC approach based on toxicity can be used to determine the PDE for an IMP.
Question 10	23.	Comment: The answer about IMPs should also reflect what is in the 2014 document, namely that use of a modified TTC approach in the footnote reference #2 (Dolan et al) may be appropriate. Proposed change (if any): Add a sentence at the end as follows:

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		"Approaches such as a staged approach to setting a TTC cited in footnote #2 in the 2014 Guideline (EMA/CHMP/SWP/169430/2012) may be considered."
Q&A 10	24.	Comment: An HBEL is required for compounds manufactured in GMP facilities. This may include pilot plants making material to support clinical trials. By definition, the first in man studies must be performed on the basis of non-clinical data. At the time an investigational new drug (IND) application (or equivalent) is filed, a significant amount of information on the pharmacology, toxicology, intended use, and anticipated clinical dose are available to review and support an HBEL. At this relatively early stage in development, not all studies (e.g., DART) will be available and additional adjustment factors are applied to address the associated uncertainties this implies. Interim default HBELs may be required during the early development phase of the novel API, when the dataset for the drug may be insufficient to set a full HBEL (Hayes et al., 2016). The use of default methodologies in setting HBELs have also been described by Faria et al. (2016). A toxicologist with sufficient expertise will have enough experience to identify appropriate interim HBELs. Such limits are by default more conservative than limits calculated on the basis of full data sets. The inspectors should be mindful of the process in place that periodically reviews assessments depending on the stage of drug development. Finally, this question misses the TTC approach recommended for IMPs as mentioned in the EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) (section 5.5). Proposed change (if any): Include the following statement at the end of the answer: "A tiered TTC approach based on toxicity can be used to determine the PDE for an IMP." (Reference Dolan et al. 2005)
Q10	25.	Comment: We agree with EMA. Interim default HBELs may be required during the early development phase of the novel API, when the dataset for the drug may be insufficient to set a full HBEL (Hayes et al., 2016). The use of default methodologies in setting HBELs have also been described by Faria et al. (2016). A toxicologist with sufficient expertise will have enough experience to identify appropriate interim HBELs. Such limits are by default more conservative than limits calculated on the basis of full data sets. The inspectors should be mindful of the process in place that periodically reviews assessments depending on the stage of drug development. An option not mentioned by EMA answer is a staged Threshold of Toxicological Concern (TTC) for genotoxic

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		compounds as described by ICH M7 (ICH 2015, Bercu et al. (2013). It has to be noted that the 1.5 µg/person/day should only be used for drugs with evidence for mutagenicity, which do not have structural analogies with a high-potency carcinogen, for which there are no compound-specific carcinogenicity data allowing for the derivation of a compound-specific HBEL, and for which mutagenicity is the critical/lead effect of the substance. The TTC is not sufficiently safe in all cases, e.g. for APIs with daily doses in the low µg or ng range. TTC approach is also limited in applicability. A comprehensive risk assessment for mutagenic and genotoxic substances should be completed by a toxicologist to assess whether any additional substance-specific effects indicate the need for a lower HBEL.
Q&A 10	28.	Comment: We agree that HBELs should be established for IMPs and be based on all the available data at that time. Our only comment is that the industry is starting to explore the value of Bayesian Statistics in making reliable predictions and setting HBELs for IMPs based on prior knowledge of other compounds with common structures and related activities could be an application that could help avoid setting excessively low HBELs due to limited data sets at early stages. Proposed change: No changes suggested A: Health based exposure limits should be established based on all available data and as such assessments associated with IMPs should be regularly reviewed for presence of new data. Toxicology experts should also make judgments about the future potential of the material to demonstrate critical effects where key toxicological testing has not been completed (e.g. this may be based on comparison to other similar molecules where available) and any additional adjustment factors that may be appropriate. This would allow manufacturers to assume worst case and make sound judgments on the level of organisational and technical control measures required?
Q&A 10		Comment: In the answer to Question 10 it is stated that “Health based exposure limits should be established based on all available data and as such assessments associated with IMPs should be regularly reviewed for presence of new data.” Please clarify what is meant by “regularly reviewed” in this context. It would be helpful to know the

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		expected (or required) frequency for reviewing and updating an existing HBEL for an IMP. Proposed change (if any): “Health based exposure limits should be established based on all available data and as such assessments associated with IMPs should be regularly reviewed (ideally once per year) for presence of new data.”
Q11	1.	Comment: A: Which substances should be named as “highly sensitising”, is there a definition in any guideline? Proposed change (if any):
Q11. Where products for paediatric populations are manufactured in shared facilities with products intended for administration to adults or to animals, do the HBELs need adjustment?	6.	Comment: Where required and known (e.g. when children are known to be very sensitive population) adjustments for the paediatric population should already be done when calculating a HBEL. Overall, the HBEL should be based conservatively enough to cover all age groups (adult, paediatric, geriatric). Additional measures as proposed (e.g., 100-fold lower for neonates) are essentially a duplication. In general the 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including the children. Therefore there is no need to have different PDEs for adults and children, the same way there is no need to have different PDEs for special populations (e.g., renal impairment). ICHQ3C/Q3D establish PDE values on the basis of a 50 kg body weight for either sex and acknowledge that this relatively low mass provides an additional safety factor against the standard masses. Therefore, the use of all those parameters (general 10-fold adjustment factor of inter-individual variability, 50 kg as default body weight and the most sensitive population as a Point of Departure) is considered appropriate to protect the whole population, including the paediatrics. A separate consideration for paediatric patients has also not been an issue in the previously established cleaning limits, such as 1/1000th of the minimal human dose or 10 ppm. Moreover, children will normally receive a lower absolute amount of any contaminant than adults because they would also receive a (based on body weight) proportionally lower dose of the potentially contaminated product. Proposed change : “No. Overall, the HBEL should be based conservatively enough to cover all age and special groups (e.g. adult,

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		paediatric, geriatric, renal impairment). In cases where knowledge exists of special sensitivity of children for specific API, this needs to be included in the HBEL calculation. In general the 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including the children. Children will normally receive a lower amount of any contaminant than adults because they also receive a proportionally lower dose of the product."
Q11	7.	Comment: Do industry also need to consider the product which can be prescribed by doctors, like recommended for children above 2 years, suppose this product is not manufactured by targeting paediatric population but it is prescribed by doctors and the recommendation is part of PI sheet Proposed change (if any):
Q11	12.	Comment: Question 11 could be problematic in practice because the PDE is usually generated as mg/day by the innovator company for a 50 kg person. The CMO would need to change the number to address paediatrics, or newborns, etc. based on their portfolio. One option to address this is that the PDE could be adjusted to reflect lower body weights. This could be done by multiplying by the body weight of the next drug (e.g., 0.5 kg newborn) and dividing by 50 kg. Proposed change (if any): If the PDE is reported as a mg/day dose, then the dose can be adjusted on a body weight basis by multiplying the paediatric body weight of the next drug and dividing by 50 kg.
Answer Q11	13.	Comment: How does this answer combine with 1/1000th of the minimum therapeutic dose of Question 4?
Q11	17.	Comment: The HBEL as such is a parameter that is based on toxicological and/or human health effect data which is used to calculate substance residues allowed on surfaces of production equipment. Therefore it is more appropriate to say that shared use of equipment is possible as long as the residues are allowing it and there is an analytical method to prove successful removal. In the case of paediatric formulations, the body weight would be adopted to

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		the most critical individual. This needs to be reflected in the answer to the question. Proposed change: Please amend the sentence in that way: "In such facilities the standard body weight value for adults of 50 kg used for calculating the HBEL should be related to a lower body weight value (e.g., children: 10 kg, newborns: 3.5 kg, prematurely born newborns: 0.5 kg) and used for the determination of residual limits for all relevant products in order to reflect the worst case situation".
Q11. Where products for paediatric populations are manufactured in shared facilities with products intended for administration to adults or to animals, do the HBELs need adjustment?	21.	Comment: HBEL should generally be based conservatively enough to cover all age groups (adult, paediatric, geriatric). Additional measures as proposed (e.g., 100-fold lower for neonates) are generally not needed. The 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including children [Dourson M, Charnley G, Scheuplein R. Differential sensitivity of children and adults to chemical toxicity II. Risk and regulation. Regul Toxicol Pharmacol 35, 448-467, 2002]. Exceptions calling for additional caution (i.e., additional factors leading to lower HBELs) include drugs with risk for significantly higher or unique toxicity in paediatric populations compared to adults (e.g., as indicated by results from juvenile animal studies). Children will normally receive a lower dose of the contaminant than adults because they also receive a proportionally lower dose of the contaminated product. If a child is more sensitive than an adult based on a kg/kg or m2/m2 comparison, the pediatric data (i.e. the data from the more sensitive subpopulation) should be taken as a starting point for the calculation of the HBEL for everyone. Care must be taken in drug product manufacturing if a whole batch is formulated for a pediatric population of a body weight of <50 kg. Here, in the MACO calculation, the HBEL needs to be adjusted to take into account the weight of the recipient of one therapeutic dose. Proposed change (if any): A: The adjustment factors commonly used for HBEL determination are generally conservative enough to cover all age groups including children. Where a product has shown significantly higher or unique toxicity in paediatric populations compared to adults on a kg/kg or m2/m2 basis (e.g., as indicated by results from juvenile animal studies), the pediatric/juvenile data should be used as a starting point to derive the HBEL.
Q&A 11	24.	Comment: Application of the HBELs to paediatric formulations has been discussed by Hayes et al., 2016.

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		Adjustments for the paediatric population may be already done when calculating a HBEL. An additional adjustment factor may be considered for the HBEL when used with drugs intended for neonates or infants (Sussman et al., 2016). Overall, the HBEL should be based conservatively enough to cover all age groups (adult, paediatric, geriatric). Additional measures as proposed (e.g., 100-fold lower for neonates) are not needed. In general the 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including the children (Dourson et al., 2002). For drugs where children are known to be very sensitive population, this is typically adjusted by the experts while calculating the HBEL. Therefore, if the age (and body weight) is taken into account when selecting the critical effect in paediatric population, and potentially lowering the value with additional adjustment factor, there is no need to have different PDEs for adults and children, the same way there is no need to have different PDEs for special populations (e.g., renal impairment). Therefore, the use of all those parameters (general 10-fold adjustment factor of inter-individual variability, 50 kg as default body weight and the PoD from the most sensitive population) is considered appropriate to protect the whole population, including the paediatrics. A separate consideration for paediatric patients has also not been an issue in the previously established cleaning limits, such as 1/1000th of the minimal therapeutic dose or 10 ppm. Children will normally receive a lower dose of the contaminant than adults because they would also receive a proportionally lower dose of a potentially contaminated product. When a doctor is prescribing a drug to a paediatric patient, the dose is often adjusted to the lower child's body weight, so an adult dose of 10 mg/day which includes 1 µg/day of contaminant at the PDE that reduced to 5 mg/day for a child results in a concomitant reduction in the potential exposure, which in this example will also be cut in half. Therefore, in this case, the adjustment already provides an additional Margin of Safety (MoS). In cases where the above toxicological considerations are not considered in the derivation of the HBEL, the risk to paediatric patients must be addressed as part of the risk evaluations and choice of appropriate exposure controls. The appropriate subject matter experts involved to make this determination. Proposed change: Replace with the following: "Not necessarily. If the HBEL does not specifically address potential susceptibilities of the paediatric patient population receiving the subsequent product, adjustments may be required in cleaning limits or other administrative or technical measures to ensure a sufficient margin of safety. As a unique attribute of every API, the HBEL does not need to be specifically adjusted to paediatric use. Overall, the HBEL

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		should be based conservatively enough to cover all age groups (adult, paediatric, geriatric). In general the 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including the children (Dourson et al., 2002). In cases where the above toxicological considerations are not adequately considered in the derivation of the HBEL, the risk to paediatric patients must be addressed as part of the risk evaluations and choice of appropriate exposure controls. The appropriate subject matter experts should be involved to make this determination."
Q11	25.	Comment: HBEL should generally be based on the most critical endpoint and should be conservative enough to cover all subpopulation groups (paediatrics, adults, and geriatrics). Actually, the 10-fold adjustment factor for intraspecies variability also covers age-related variability, including children (Dourson et al, Regul.Toxicol.Pharmacol. [2002] 35, 448-467). In case of drugs inducing significantly higher toxicities to paediatric population than in adults (e.g., as indicated by juvenile animal studies), the "point of departure" for calculating the HBEL shoud be this particular juvenile toxicity study. Proposed change (if any): Replace the answer by: "No. As a unique attribute of every API, the HBEL does not need to be specifically adjusted to paediatric use. Overall, the HBEL should be based conservatively enough to cover all age groups (adult, paediatric, geriatric). In general the 10-fold adjustment factor commonly used to allow for inter-individual human variability also covers age-related variability including the children (Dourson et al., 2002), although a more recent analysis suggests that a 15-fold adjustment factor may be more appropriate (Streeter and Faria, 2017). Children will normally receive a lower dose of the contaminant than adults because they also receive a proportionally lower dose of the contaminated product."
Q&A 11	28.	Comment: It is our understanding that paediatric considerations are already factored into the HBEL calculations so no further adjustments are necessary. In addition, children typically receive lower dosages of drug products compared to

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		adults so this also provides a level of protection. Proposed change: A: No. HBELs do not need to be adjusted based on paediatric use as it is expected that HBELs should be protective of all individuals, including any sensitive population.
Q&A 11	29.	Comment: In the answer to Question 11 it is stated that "…the standard body weight value for adults of 50 kg used for calculating the HBEL should be replaced by a lower body weight value (e.g., children: 10 kg, newborns: 3.5 kg, prematurely born newborns: 0.5 kg) and used for HBEL determination for all relevant products in order to reflect the worst case situation." This is not consistent with the guideline where it is stated on page 5 that the PDE (i.e., HBEL) value should be calculated on a mg/kg bw basis rather than on a per person basis. Please clarify the apparent discrepancy between the use of body weight for PDE/HBEL calculations that are cited in the guideline and in the Q&A document.
Q12	5.	Comment: ICH Q9 defines risk as "The combination of the probability of occurrence of harm and the severity of that harm". The inherent properties of a compound relate to the hazard or the harm the compound can do to a patient where the PDE is an indication of the level of harm. The probability of occurrence (for cross contamination) is related to the controls that prevent undue exposure. For example a company is manufacturing Methylphenidate where the risk of manufacturing Methylphenidate varies based on the controls in place. • High risk manufacturing would be where the compound is handled in open processes with manual cleaning processes and inadequate cleaning verification, • Medium risk manufacturing would be where the compound is handled in semi-closed processes with manual cleaning processes with adequate cleaning verification • Low risk manufacturing would be where the compound is handled in closed processing with automatic cleaning • No risk if manufacturing of this compound is in a dedicated facility or not made by the company In all cases the hazard/harm is the same, the variable is the manner in which it is controlled during processing which varies the risk level.

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		Proposed change: Change the word risk in the following sentence to harm. "It is expected that the higher the hazard of products/active substances, the higher the inherent harm and the more significant organisational and technical control measures will be required."
Q/A 12	10.	Comment: The last sentence is absolutely right. It highlights once more how regrettable and how incoherent A6 is with the general intention of the Guidance. Proposed change (if any):
Q12	12.	Comment: Question 12 states "It is expected that the higher the hazard of products/active substances, the higher the inherent risk." This statement is not always true. Potential for exposure affects risk just as much as the inherent hazard of the drug. For example if the drug easily breaks down in the cleaning solution, or doesn't adhere to equipment these may indicate a low risk drug. Control measures should be dependent on the outcome of the quality risk assessment regardless of the hazards of the drug. Proposed change (if any): Remove "It is expected that the higher the hazard of products/active substances, the higher the inherent risk and the more significant organisational and technical control measures will be required."
Q&A 12	24.	Comment: It should not be assumed that a substance with higher hazards also has higher risks. The HBEL takes the higher hazard into account by use of appropriate adjustment factors. The risk reflects both the hazard (already addressed by the HBEL) and the level of exposure. If there are concerns about the pathways and extent of potential exposure (e.g., with manual vs. automated cleaning), then additional safety measures, such as more frequent periodic verification analytically, may be appropriate. Proposed change: Delete the second to last sentence, i.e.: "It is expected… will be required" and add the following after the last sentence: "The HBEL takes the higher hazard into account by use of appropriate adjustment factors.

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		The risk reflects both the hazard (already addressed by the HBEL) and the level of exposure. If there are concerns about the pathways and extent of potential exposure (e.g., with manual vs. automated cleaning), then additional safety measures, such as more frequent periodic verification analytically, may be appropriate."
Q12	25.	Comment: We take positively note that the EMA confirms that the HBELs provide an accepted safe level of cross contamination and they should be used to justify cleaning limits as a part of the requirement for a quality risk management process as outlined in GMP Chapter 5 section 20.
Q&A 12	28.	Comment: In our view, the HBEL is the prerequisite starting point for compliance with GMP Chapter 5 section 20. As stated in your answer, the HBEL provides the insight into the risk posed by the molecule. Without the HBEL and toxicological review it is impossible to make all the necessary and appropriate decisions for contamination control, dedication, etc. This is another good reason why traditional cleaning limits based on 1/1,000th of a low clinical dose and 10ppm should never be used. They are inconsistent with GMP Chapter 5 section 20. Proposed change: No changes suggested A: Once the health based assessment has been completed and HBEL confirmed, these data should be used via a Quality Risk Management process to assess if current organisational and technical control measures are adequate, or in the case of new equipment/facility to determine what control measures are required. It is expected that the higher the hazard of products/active substances, the higher the inherent risk and the more significant organisational and technical control measures will be required. Health based exposure limits provide an accepted safe level of cross contamination and they should be used to justify cleaning limits.
Q13. Is it acceptable to simply segregate highly hazardous	6.	Comment: Again, the HBEL derivation includes hazard evaluation, dose-response assessment, and risk characterization, so it is not necessary to distinguish between "highly hazardous" and "non-highly hazardous" compounds. The quality risk management process includes scientifically justified cleaning risk analysis for the identification of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
products in a dedicated area as a means of controlling risk of cross contamination?		risks and the appropriate adoption of risk mitigation measures to control cross contamination. Proposed change: “Manufacturers must be aware of the risks associated with the substances manufactured in their facilities. Quality risk management incorporating relevant toxicological and other scientific information should be used to evaluate risks and establish appropriate measures to prevent cross contamination.”
Q13	17.	Comment: Dedicated area is a notion which remains ambiguous, what does it mean compared to dedicated equipment, isolation equipment etc? Proposed change: Please clarify. Please provide a definition in the Guidance regarding dedicated equipment, area…
Q13	21.	Comment: There is a big confusion about the terms “segregated” and “dedicated” and it is also reflected here. “Dedicated” is a term that describes the use of a facility (i.e. it is only used for one product or one group of closely related products. “Segregated” describes the physical characteristics of a facility (e.g. walls, airlock, separate access, separate HVAC system). Segregation is not the object of the questions and the term has no place in this answer. Proposed change (if any): Replace sentence 1 and 2 by: “Manufacturers cannot simply place several hazardous products into a facility dedicated to such highly actives. This will reduce the risk of cross-contamination of these products into products produced outside this dedicated area, but undue cross-contamination between the products inside the facility dedicated to highly actives must also be avoided.
Question 13	23.	Comment: While the answer addresses making more than one different highly hazardous products in a dedicated facility is not the sole means to address patient safety, there should be a statement that a dedicated facility or area for a single compound does address patient safety from a cleaning validation perspective. However, there may be other issues such as operator procedure, air handling and the like, even in the situation of a single highly hazardous compound being made in a dedicated facility or area. It would be helpful to clarify that situation.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change (if any): Add at the end of the answer the following: “The manufacture of a single highly hazardous product in a dedicated facility or dedicated area may address cleaning validation issues. However, in such a situation, contamination from other routes of exposure, such as by operator practices and by air handling systems, should also be addressed.”
Q13	25.	Comment: We appreciate EMA confirming that it is the responsibility of the manufacturers to be aware of the risks associated with the drugs manufactured in their facilities. A quality risk management process includes scientifically justified cleaning risk analysis for the identification of risks and the appropriate adoption of risk mitigation measures to control cross contamination. Proposed change (if any): “Manufacturers cannot just segregate highly hazardous products from other lower risk products as a means of dealing with the risk to patient safety. Manufacturers must be aware of the risks associated with the substances manufactured in their facilities. Scientifically justified cleaning risk analysis has to be provided to show high risks and risk mitigation measures must be in place to control cross contamination.”
Q&A 13	28.	Comment: In our minds, the words "simply" and "highly hazardous" cannot be used in the same sentence when discussing the control of risk. The answer provided seems totally appropriate, yet this answer is out of alignment with answers above (Q4, Q6) that endorse the continued use of non health based and arbitrary limits or default limits (Q14). As stated above (comments to Q2, Q4 and Q8), any references to “highly hazardous products” should be deleted from the answer. Continued use of “certain classes” type of approach to dedication or segregation of facilities would nonetheless create confusion in the industry. The Q&As should not deviate from the fundamental principles, to managing cross-contamination risks, enshrined in Chapter 3 (Section 3.6) and Chapter 5 (Sections 5.17 to 5.21) of the EU GMP guidelines. The “necessity for and extent of” dedication or segregation of facilities should be an outcome of a Quality Risk Management exercise - and that should be the bottom line.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: None suggested A: Manufacturers should not segregate or dedicate facilities based on generalized classes of compounds. The approach taken to address cross-contamination between products produced in a manufacturing facility, including implementation of appropriate technical and organisational control measures, should be the outcome of a Quality Risk Management process, comprised of a scientific evaluation of all available knowledge and data as described in EMA's Annex 15 Chapter 4. The measures to prevent cross-contamination should be commensurate with the risks.
Q13	31.	Comment: It is fully agreed that it shall not be acceptable to simply segregate all highly hazardous products in one dedicated area as a means of controlling risk of cross contamination. However, as noted in respect to Q4, if an area is dedicated for a group of compounds, even highly hazardous, sharing both similar chemical structure and similar pharmacological activity, higher HBELs and – consequently – higher cleaning limits could be acceptable than in a case where there is a risk of contamination of products from other groups.
Q14. Is the application of the Threshold of Toxicological Concern (TTC) as applied in the guideline of mutagenic products of 1.5 µg/person/day concept an acceptable default approach to	6.	Comment: The 1.5 µg/day cannot be considered a default for all substances as is suggested here. Proposed change: TTC approaches as described in the guideline are considered to be conservative enough to cover mutagenic and other toxicity end-points and can be considered to derive health-based exposure limits if adequately justified. Therefore, in general the 1.5 µg/day TTC level defined for mutagenic impurities can be acceptable given that other relevant aspects that may require further lowering of the HBEL have been considered such as: - APIs with daily doses in the low µg or ng range - Structural analogies with a high potency mutagenic carcinogen (so called cohort of concern, e.g. aflatoxin-like, azoxy- and nitroso-compounds)

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establish an HBEL?		
Q14	12.	Comment: The EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) proposes a tiered TTC-approach in addition to the mutagenic impurities guideline. Proposed change (if any): Include “A tiered TTC approach such as those found in Kroes et al. (2004), Munro et al. (2008), Dolan et al. (2005), Bercu and Dolan, 2013, and Stanard et al. (2015)*, are acceptable as well for non-mutagenic compounds. * Note Stanard et al., 2015 was not available at the time of the original EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) but was developed to derive a TTC number for oncology products that have DART effects.
Q14	17.	Comment: The notion of TTC does not exist in Veterinary industry Proposed change: Please consider including Animal Health specific criteria and calculations into this document.
Q14	19.	Comment: Is the application of the Threshold of Toxicological Concern (TTC) as applied in the guideline of mutagenic products of 1.5 µg/person/day concept an acceptable default approach to establish an HBEL? Proposed change (if any): This needs to make far clearer that the TTC would only typically be applied where there is evidence of potential mutagenicity.
Q14	21.	Comment: The answer is incorrect. The 1.5 mcgr/d cannot be a default for any and all molecules as is suggested here! It only applies for genotoxic molecules where a) genotoxicity is the lead/critical effect of the molecule and b) there are no substance-specific genotox data that would allow the derivation of a substance-specific HBEL. Finally, in the EMA guideline, to be totally correct, the 1.5 mcgr/d limit refers to genotoxic and not to mutagenic substances (although the latter is a subgroup of the former) and excludes certain very potent genotoxics. We have examples of substances with a PDE below 1.5. mcgr/d that are genotoxic and which do not belong into one of the “highly genotoxic” categories. In these substances effects other than genotoxicity drive the PDE.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change (if any): Delete the proposed answer. Replace by: "The 1.5 mcgr/d can only be used if all of the following conditions (a – d) are fulfilled: a) there is evidence that the substance is genotoxic, b) it does not have structural analogies with a high-potency carcinogen, c) genotoxicity is the actual lead/critical effect of the substance, i.e. no other effects appear at doses <1.5 mcgr/day and d) there are no substance-specific genotox data allowing for the derivation of a substance-specific HBEL."
Q&A 14	24.	Comment: The EMA guideline (EMA/CHMP/ CVMP/ SWP/169430/2012) proposes a tiered TTC-approach in addition to the mutagenic impurities guideline. The TTC value of 1.5 ug/day, as recommended in ICH M7, only applies to mutagenic substances. It may or may not be sufficiently protective for other endpoints. Depending on the substance-specific data, a lower or higher HBEL may be appropriate. An option not mentioned by EMA answer is a staged Threshold of Toxicological Concern (TTC) for genotoxic compounds as described by ICH M7 (ICH 2015, Bercu and Dolan (2013). It has to be noted that the 1.5 µg/person/day should only be used for drugs with evidence for mutagenicity which do not have structural analogies with a high-potency carcinogen, for which there are no compound-specific carcinogenicity data allowing for the derivation of a compound-specific HBEL, and for which mutagenicity is the critical/lead effect of the substance. The TTC is not sufficiently safe in all cases, e.g., for APIs with daily doses in the low µg or ng range. TTC approach is also limited in applicability. A comprehensive risk assessment for mutagenic and genotoxic substances should be completed by a toxicologist to assess whether any additional substance-specific effects indicate the need for a lower HBEL. Proposed change: Add: "It has to be noted that the 1.5 µg/person/day should only be used for drugs with evidence for mutagenicity which do not have structural analogies with a high-potency carcinogen, for which there are no compound-specific carcinogenicity data allowing for the derivation of a compound-specific HBEL, and for which mutagenicity is the critical/lead effect of the substance. The TTC is not sufficiently safe in all cases, e.g., for APIs with daily doses in the low µg or ng range. TTC approach is also limited in applicability. A comprehensive risk assessment for mutagenic and genotoxic substances should be completed by a toxicologist to assess whether any additional substance-specific effects indicate the need for a lower HBEL. A tiered TTC approach such as those found in Dolan et al. (2005), Bercu and Dolan, 2013, and Stanard et al. (2015), are acceptable as well for non-mutagenic

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		compounds. More discussion and guidance should be provided on this in future Q&A editions." References Bercu, J. P., & Dolan, D. G. (2013). Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul Toxicol Pharmacol, 65(1), 162-167. http://dx.doi.org/10.1016/j.yrtph.2012.06.012 Dourson, M., Charnley, G., & Scheuplein, R. (2002). Differential sensitivity of children and adults to chemical toxicity. II. Risk and regulation. Regul Toxicol Pharmacol, 35(3), 448-467. Faria, E. C., Bercu, J. P., Dolan, D. G., Morinello, E. J., Pecquet, A. M., Seaman, C., Sehner, C., & Weideman, P. A. (2016). Using default methodologies to derive an acceptable daily exposure (ADE). Regul Toxicol Pharmacol, 79 Suppl 1, S28-38. http://dx.doi.org/10.1016/j.yrtph.2016.05.026 Hayes, E. P., Jolly, R. A., Faria, E. C., Barle, E. L., Bercu, J. P., Molnar, L. R., Naumann, B. D., Olson, M. J., Pecquet, A. M., Sandhu, R., Shipp, B. K., Sussman, R. G., & Weideman, P. A. (2016). A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing - Operational considerations. Regul Toxicol Pharmacol, 79 Suppl 1, S39-47. http://dx.doi.org/10.1016/j.yrtph.2016.06.001 Lovsin Barle, E., Looser, R., Cerne, M., & Bechter, R. (2012). The value of acute toxicity testing of pharmaceuticals for estimation of human response. Regul Toxicol Pharmacol, 62(3), 412-418. Olson, M. J., Faria, E. C., Hayes, E. P., Jolly, R. A., Barle, E. L., Molnar, L. R., Naumann, B. D., Pecquet, A. M., Shipp, B. K., Sussman, R. G., & Weideman, P. A. (2016). Issues and approaches for ensuring effective communication on acceptable daily exposure (ADE) values applied to pharmaceutical cleaning. Regul Toxicol Pharmacol, 79 Suppl 1, S19-27. http://dx.doi.org/10.1016/j.yrtph.2016.05.024 Sussman, R. G., Naumann, B. D., Pfister, T., Sehner, C., Seaman, C., & Weideman, P. A. (2016). A harmonization effort for acceptable daily exposure derivation - Considerations for application of adjustment factors. Regul Toxicol Pharmacol, 79 Suppl 1, S57-66. http://dx.doi.org/10.1016/j.yrtph.2016.05.023 Teasdale, A., Naumann, B.D., Allison, G., Luo, W., Callis, C.M., Shipp, B.K., Rutter, L., Seaman, C. (2015). EMA guideline on setting health-based exposure limits. Pharm Technol, 40 (1), 58-62.
Q14	25.	Comment:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		We agree with EMA. However, the TTC approach of 1.5 µg/person/day cannot be used as a default value for all compounds. It can be used for genotoxic compounds IF they do not belong to the “cohort of concern” (aflatoxin-like, azoxy- and nitroso-compounds) and IF all other critical effects lead to higher values than the TTC. However, there are now more and more highly potent compounds with therapeutic doses in the µg or ng range for which such approach would be insufficient to cover all potential hazards. Proposed change (if any): Replace the answer by: “The use of the 1.5 µg/person/day concept can only be done if a substance fulfils all the following criteria: 1) There is evidence that the substance is genotoxic 2) It does not have any structural analogies with highly-carcinogenic compounds of the “cohort of concern” (aflatoxin-like, azoxy- and nitroso-compounds) 3) There are no compound-specific carcinogenicity data allowing the derivation of a substance-specific HBEL, 4) Genotoxicity is the critical/lead effect, i.e, no other effects appear at doses < 1.5 µg/day. However, this TTC approach is not sufficiently safe in all cases, e.g., for APIs with daily doses in the low µg or ng range. A comprehensive risk assessment for mutagenic and genotoxic substances should be completed by a toxicologist to assess whether any additional substance-specific effects indicate the need for a lower HBEL”
Q&A 14	28.	Comment: The TTC value of 1.5 µg/person/day, as proposed by Kroes et al. (2004) for mutagenic substances, do not strictly apply to substances that belong to the ‘‘Cohort of Concern’’ groups (i.e., five structural groups of highly potent carcinogens which are aflatoxin-like compounds, N-nitroso-compounds, azoxy-compounds, steroids, and polyhalogenateddibenzo-p-dioxins and –dibenzofurans). In addition, the TTC approach also do not apply to: heavy metals, compounds with extremely long half-lives and proteins (Kroes et al. 2004). Hence, the value of 1.5 µg/person/day cannot be used explicitly as a default approach for establishing HBELs.

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		Default limits, such as the various TTCs, are only for use when no data are available. This is never true for drug compounds; pre-clinical and clinical data are always being developed and available for use. Use of TTCs may have use for investigational compounds but only in very early stages before specific data are available. Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G; European branch of the International Life Sciences Institute (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol. 2004 Jan;42(1):65-83. Proposed change: A: Default values may only be used when limited toxicity data are available for a substance-specific risk assessment, provided the substance is not a heavy metal, a protein, a highly sensitising substance and do not belong to any of the ‘‘Cohort of Concern’’ groups (i.e., aflatoxin-like, N-nitroso-, azoxy-, steroids, and polyhalogenateddibenzo-p-dioxins and –dibenzofurans). The default limit should be replaced with HBEL as soon as data are available for a Risk Assessment.
Q14	31.	Comment: Application of the threshold of toxicological concern (TTC) is fully supported in cases discussed in respect to Q4, i.e. for non-highly hazardous products when manufacturers choose to apply the “traditional” thresholds instead of performing toxicological analyses. It is however recommended clarifying what approach should be applied for substances with therapeutic doses below 1.5 mg (i.e. for substances for which 1/1000th therapeutic dose would results in values below TTC of 1.5 µg/day). In Health-Med’s opinion, provided that there are no special safety concerns, threshold of 1.5 µg/day should be valid as long as respective residues would results in reasonably low parts of therapeutic doses (even if higher than 1/1000th part). In the most “safe” case, when the compounds concerned are present in normal diet, are present endogenously or otherwise are not linked with any risk, exposures equivalent to TTC of 1.5 µg/day could be acceptable as long as do not exceed e.g. 1/20th therapeutic dose. Obviously there are compounds with so low therapeutic doses for which application of TTC of 1.5 µg/day would

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		result in clearly unacceptable exposures. More clarification on this issue is recommended to be provided.