Connecting People, Science and Regulation®

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26 June 2013

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: 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)

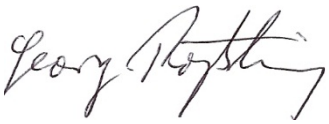
To the Health and Consumers Directorate-General:

PDA is pleased to provide comments on this guideline submitted for public consultation. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our review was completed by an international group of expert volunteers with experience in investigational medicinal products, regulatory affairs and GMP on behalf of our Regulatory Affairs and Quality Advisory Board.

PDA supports the concept of health based exposure limits and welcomes the guidance as advocating a risk based approach. PDA advocates flexible approaches for products currently manufactured in shared facilities to avoid interruption of supply of essential medicines. We also ask that the guideline make it clear that the approach described therein is not the only acceptable one. Any scientifically justified, toxicological, risk based approach with a documented rationale should be acceptable.

If you have any questions, please contact me.

With very best regards,



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cc: Richard Johnson, PDA, Rich Levy, PDA

28June2013

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

Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
1	PDA supports the concept of health based exposure limits and welcomes the guidance as advocating a risk based approach. PDA advocates flexible approaches for products currently manufactured in shared facilities to avoid interruption of supply of essential medicines. We also ask that the guideline make it clear that the approach described therein is not the only acceptable one. Any scientifically justified, toxicological, risk based approach with a documented rationale should be acceptable.	
2	The term Permitted Daily Exposure (PDE) originates in ICH Q3C referring specifically to residual solvents. The ICH definition is different to the use of the term in this document. The data set available for active substances, where extensive pre-clinical and clinical data in animals and human is much greater than for solvents. As such the uncertainty associated with active substances is less and the adjustment factors are molecule specific vs default for solvents. Therefore PDA recommends using the term Health Based Exposure Limits throughout the document allowing companies the flexibility to select and justify their approach e.g. PDE, ADE, TTC.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Proposed change: Add a reference to the origin of the term PDE in ICH Q3C but use the term Health Based Exposure Limits to replace PDE throughout the document.	
3	The document should allow for the use of NOAELs, which are the commonly used endpoint in pharmaceutical industry toxicology studies, in the derivation of a Health-Based Limit. **Proposed change:** Replace “NOEL” with “NOEL or NOAEL” throughout the document.	
4	The PDE values specified in this guideline are values for safe exposure “every day for a lifetime” There are cases where the subsequently manufactured product is administered for a short time (e.g. anaesthetic) or as intermittent doses (weekly, monthly), certain patient populations etc. There should be flexibility in setting limits using a risk based approach. **Proposed change:** Where the next product is known (as applied in cleaning validation), the health based limit may be modified based on factors such as frequency of administration, patient population and duration of use.	
5	Regarding active substances with sensitizing potential (as in section 4.1.4), the concern here is for highly sensitizing substances without a threshold value. As	

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	currently written, the guidance could be misinterpreted as including any compound with some immunogenic potential. Immunogenicity responses are not created equal and many compounds with some immunogenic potential (e.g., biopharmaceuticals) could be included if the language is not clear. **Proposed change:** Change language throughout the document from "sensitizing potential" to "**certain highly sensitizing materials where no threshold value can be identified.**"	
6	The proposed Risk Report template does not allow companies to account for all data types or to be flexible in selecting their approach to the risk assessment and presentation of data. The use of check boxes seems to negate the risk based approach. **Proposed change**: require companies to prepare a report but allow each company to select the appropriate format that best reflects their risk assessment and the data set to be presented.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 44		Comment: PDA recommends avoiding using the absolute term "all" and rephrasing to indicate that the level should be the outcome of scientific review of relevant, available data. **Proposed change:** The derivation of a health-based exposure limit, such as permitted daily exposure limit (PDE), acceptable daily exposure (ADE) including the Threshold of Toxicological Concern (TTC) concept, should be the result of a structured scientific evaluation of ~~all~~ relevant, available pharmacological and toxicological data including both non-clinical and clinical data.	
Line 48		The scope of the guideline is currently very broad, applying to the entire product lifecycle. Consequently, it should recognize that as empirical data are acquired during development, adjustment factors will need to be modified, as will the health based limit, to reflect the iterative nature of the drug safety assessment process. **Proposed Change:** As drug candidates move through development, the amount and types of available data increase, reducing the uncertainty, so the health-based limit should be reviewed and, if necessary, changed based on the new information.	
Lines 83-98		Comment: PDA recommends including some additional references as identified below.	

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		Proposed change: Add the following references: WHO Guidance (2005), *Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose / Concentration-Response Assessment*. Harmonization project document No. 2, Geneva, Switzerland, World Health Organization ISPE Risk-MaPP (2010) – Risk-Based Manufacture of Pharmaceutical Products. Volume 7, First Ed. Guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006) Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) 15-March 2010. Regulation (EC) No 470/2009 (Article 6) for establishing residue limits of pharmacologically active substances in foodstuffs of animal origin.	
Line 170-173		Comment: Other adjustment factors besides F2 and F5 may be based on human data. F3 and F4 equivalents, as well as UF_D, are often used. **Proposed change:** Delete ~~F2 and potentially F5 would need to be applied when deriving a PDE on the basis of human…~~ and replace with F2, F3, F4 and F5 are often applied when deriving health-based exposure limits on the basis of human data.	
Lines 176 - 179		Comment: Using the lowest limit need not apply when adequate human data is available. A limit derived from animal data is often lower than one derived from human data since the adjustment	

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		factors are larger. However, human data are more relevant. **Proposed change:** Human data may be used to derive a health based limit in preference to animal data. However, there are some effects (e.g., reproductive or developmental toxicity) that are not evaluated in clinical trials prior to approval, and in those cases the lowest limit should be used.	
Line 209		For large molecules, if the subsequent product is orally administered, then zero bioavailability can be reasonably assumed for the residual large molecule. **Proposed change :** Add the underlined text "...~~PDE~~ health based limit calculation. <u>For large molecules, oral bioavailability is negligible, and there is no expectation for the generation of data to support this assumption</u>. It is expected that the route-to-route extrapolation will be performed on a case-by-case basis.	
Lines 212 - 222		Comment: The residual genotoxic actives should have the same limit as genotoxic impurities. Applying a lower limit of 0.15 mcg/day for genotoxic residual actives is inconsistent with current PDE practices (e.g. ICH Q3C and EMA genotoxic impurities guidance from 2006). In addition, for genotoxic residual actives in compounds used as anticancer agents the limits for genotoxic residual actives should be higher as per ICH S9	

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		Proposed change: Revise the paragraph to be consistent with the current genotoxic impurities guideline whereby a limit of 1.5 ug/person / day is allowed for genotoxic residual active substances.	
Line 239-254		Comment: The approach for setting health-based limits for large and small molecules should be the same. In addition pharmacodynamic studies **are** used to derive an effect-level and are rarely dosed to a NOEL so that ruling out the use of LOEL appears inappropriate. The requirement to do so is inconsistent with the principles of the 3Rs of humane animal experimentation (reduction, refinement and replacement) in its obligation to undertake additional animal studies to derive NOEL levels for all effects or pharmacodynamic endpoints when a NOEL or NOAEL can be extrapolated from existing data. Proposed change (if any): Delete the section (lines 239-254).	
Lines 260-261		Comment: PDA is not aware of any recorded incidence of human male-mediated teratogenicity in pharmaceuticals and does not believe this should be included in the guideline unless specific incidences can be provided. **Proposed Change**: delete lines 260 - 261	
Lines 267-269		Comment: The guidance does not provide clear guidance when there is a lack of data such as reproductive and developmental	

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		effects. PDA feels that there is enough scientific data in the literature to provide better guidance. Moreover, flexibility should be allowed to provide limits based on potential toxicity based on the pharmacology of the drug (e.g., a compound whose pharmacological effect can cause developmental toxicity). Data in the literature support TTC values developed from non-carcinogenic effects, including developmental toxicity: (Dolan et al. 2005 Regul Toxicol Pharmacol. 43(1):1-9.; Bercu and Dolan 2013. Regul Toxicol Pharmacol. 65(1):162-7; van Ravenzwaay et al. 2012. Regul Toxicol Pharmacol, 64(1), 1-8; van Ravenzwaay et al. 2011Regul Toxicol Pharmacol 59(1), 81-90) **Proposed change :** Remove lines 267-269 and add: The following limits are acceptable when there are gaps in toxicity data for an active substance (Dolan et al. 2005 Regul Toxicol Pharmacol. 43(1):1-9.: • Not likely to be potent, highly toxic or carcinogenic – 100 ug/day • Highly potent or toxic – 10 ug/day • Mutagenic or likely carcinogenic – 1.5 ug/day If the facility is used for early-phase (Phase 1) material, a 10-fold adjustment factor is acceptable because of the limited duration of exposure to the residual active compound (Bercu and Dolan 2013, Regul Toxicol Pharmacol. 65(1):162-7). Also,	

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		evaluation of pharmaceuticals with a similar mechanism of action may be used to fill in data gaps.	

Please add more rows if needed.