PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

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Reference: 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)

Dear Sir/Madam:

PDA fully supports the concept of health based exposure limits that is outlined in the guidance as it advocates a risk based approach. PDA additionally advocates flexible approaches for products currently manufactured in shared facilities to avoid interruption of supply of essential medicines. Finally, PDA recommends that a scientifically justified, toxicological, risk based approach with a documented rationale should be used and makes reference to an earlier "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA/CHMP/SWP/598303/2011) a precursor to "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).

PDA would like to highlight that in this earlier paper EMA had stated, - "In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall Quality Risk Management in shared facilities." This concept is contradicted by some of the answers in current Q & A paper. Please see attached detailed comments.

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 comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and development including members of the Pharmaceutical Water Interest Group representing the PDA Board of Directors and PDA Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me (klar@pda.org).

Sincerely,

Falk Klar
General Manager, Vice President, PDA Europe

CC: Richard Johnson, PDA; Richard Levy, PDA; Denyse Baker, PDA

<30 April 2017>

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:

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).

DEFINITIONS

Critical:

Any of the following factors could make a comment "critical" for purposes of this analysis. Determination is left to task force members who developed the comments. Note, comment criticality is based on the most important aspects of the specific document or text concerned. Criticality of the draft document relative to other guidance should not be considered when assessing comments. Critical is defined as:

- Comment has a major impact on patient safety or product quality
- Not adopting the comment will have a large/major impact on the industry or process (i.e. greater than 1 year to become compliant; financially greater than $1M Euros to implement;)
- Not adopting the comment will lead to difficult or complex to implement changes that may impact multiple quality and/or operating systems

Non Critical:

Everything else

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Critical Comment (Y/N)?	Outcome (if applicable) *(To be completed by the Agency)*
1.	PDA fully supports the concept of health based exposure limits that is outlined in the guidance as it advocates a risk based approach. PDA advocates flexible approaches for products currently manufactured in shared facilities to avoid interruption of supply of essential medicines. PDA makes a reference to an earlier "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA/CHMP/SWP/598303/2011) a precursor to "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). PDA reminds that in this paper EMA had stated, - "In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall Quality Risk Management in shared facilities." This concept contradicts some of the answers in Q & A paper. PDA recommends that a scientifically justified, toxicological, risk based approach with a documented rationale should be used.		

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')*	Critical Comment (Y/N)?	Outcome *(To be completed by the Agency)*
Q4.	Name (First & Last)	Comment: Remove references to 1/1000th of the minimum therapeutic dose based on the approach described in the "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA/CHMP/SWP/598303/2011). While the clinical data may be use to establish HBEL, the standard adjustment factors should be utilized as already described in the ISPE Risk-MaPP Guideline and the EMA/CHMP/SWP/598303/2011. Proposed change (if any): Remove "(e.g. to establish the HBEL on 1/1000th of the minimum therapeutic dose)" from title of the question Remove "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." At the end of the question.	Y	Decision to Submit/ withdraw comment
Q6				

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')*	Critical Comment (Y/N)?	Outcome *(To be completed by the Agency)*
		Comment: Remove references to 1/1000th of the minimum therapeutic dose and 10 ppm based on the "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA/CHMP/SWP/598303/2011) Proposed change (if any): Remove "...additional safety margins..." as the HBEL already provides all the adjustment factors necessary to achieve a very conservative cleaning limit (see definition of ADE/PDE) Remove "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." Remove "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". As stated above, the HBEL already provides all the adjustment factors necessary to achieve a very conservative cleaning limit (see definition of ADE/PDE) and no additional factors should be applied as this does not provide any additional safety to the patient but creates an unnecessary burden to industry.		

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')*	Critical Comment (Y/N)?	Outcome *(To be completed by the Agency)*
Q8		Comment: Change reference to question 6 (after making suggested changes) citing risk based assessment as an example. Proposed change (if any): Change last sentence to read "For non-highly hazardous products the approach described in the response to question 6 can also be applied (e.g. risk based assessment).		

Please add more rows if needed.