26 June 2013

European Medicines Agency
7, Westferry Circus
Canary Wharf
London
E14 4HB

Dear Sir or Madam,

EMA/CHMP/CVMP/SWP/169430/2012

Thank you for the opportunity to comment on the proposed Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities.

This is clearly a complex and important subject. There were numerous issues raised by ISPE members in relation to the proposed guidance document and I suspect members of other interested parties will also raise many issues.

If additional comment detail is required ISPE would welcome any opportunity for its SME to collaborate with the EMA SWP in further developing this guidance document. This could be in the form of teleconferences, focus group meetings, consultations and workshops etc as required. The aim of such collaboration would be to ensure that the final version of the document incorporates the best science in setting health- based exposure limits which is in the best interests of both the EMA and industry.

Yours sincerely,

President/CEO, ISPE

ISPE Headquarters
600 N. Westshore Blvd. | Suite 900 | Tampa, FL 33609 | USA | TEL +1-813-960-2105 | FAX +1-813-264-2816
www.ISPE.org

26 June 2013

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: ISPE

600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
1-813-960-2106
http://www.ispe.org

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).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Comment: The Guideline suggests the use of prescriptive adjustment factors. Such an approach is restrictive in that it will not allow industry to take advantage of the existing vast quantity of data and science available on medicinal products This approach may also limit future scientific development. A more open risk based approach that encourages industry to use good science rather than trying to fit the very narrow band of prescriptive factors detailed in the document would be more in line with other regulatory initiatives. Proposed change: Allow companies to take full advantage of the science and data they have at their disposal to more accurately select adjustment/safety factors in determining the threshold values. The company would be expected to justify the selection of these factors with the data/science used to determine the threshold values.	

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

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)
36-39		Comment: Cleaning is not the only manner in which cross contamination can occur. Other methods exist eg mix-up, mechanical and airborne transfer. Proposed change (line 37): Hence, residues of an active substance may be available to contaminate other medicinal products produced in the same facility by one or several modes; mix-up, retention, mechanical transfer or airborne transfer.	
42-45		Comment: A rational for not using other values such as Acceptable Daily Exposure (ADE) or Acceptable Daily Intake (ADI) as a threshold valve is not provided. Proposed change (line 42) : The derivation of a threshold value (permitted daily exposure (PDE), acceptable daily exposure (ADE), acceptable daily intake (ADI)) or threshold of toxicological concern (TTC)) should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data.	

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52-62		Comment: This section implies a narrow focus i.e. to set cleaning limits whereas the detail in the guideline suggests a broader approach i.e. to set limits for managing the risk of cross contamination as a whole. To reflect this broader approach other modes of transfer could be included in this section e.g. mix up, mechanical transfer and airborne transfer. Proposed change (line 52): Pharmaceuticals not considered to be covered under these criteria were addressed by several processes designed to minimize the risk of cross contamination such as mix-up prevention, gowning, decontamination/wipe down of materials and cleaning validation processes involving reduction of the concentration of residual active substance to a level where the maximum carryover from the total equipment train would result in no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured.	
80-82		Comment: Exactly why the risk assessment report has been given this title is not clear. The information provided in this risk assessment report more closely resembles risk identification i.e. only one of the risk assessment processes identified in ICH Q9. Proposed change (line 80): The guideline also outlines how the data on which the threshold value is derived should be presented in the risk identification report…..	

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105		Comment: There is a lack of clarity on setting some threshold values e.g. dosing "every day for a lifetime" is a scenario that isn't applicable to development products or products such as antibiotics; Proposed change (line 105): Clarity should be provided on setting threshold values for different situations.	
108		Comment: The term NOEL as defined in the guideline more closely reflects the term NOAEL (no observed adverse effect). This will give rise to confusion. Proposed change (line 108): (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects	
113		Comment: The adjustment factors are in line with those recommended in ICH Q3C (R4). They are however different from those recommended in REACH (European Chemicals' Regulation), which may result in 2 different limits for the same population under the different regulations. As the document will apply to sites in third countries manufacturing for the EU these assessment factors may also not be the same as those used in different parts of the world. A prescriptive non flexible approach will be difficult for companies to manage. Proposed change (line 113): Either do not state the exact assessment factors in the document or give them as examples which are not mandatory.	

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116		Comment: Replace "carryover limits" with "acceptance limits" to more accurately reflect the management of cross contamination rather than only cleaning validation. Proposed change (line 116): In relation to the establishment of acceptance limits…	
124		Comment: Replace "carryover limits" with "acceptance limits" to more accurately reflect the management of cross contamination rather than only cleaning validation. Proposed change (line 124): The derivation of acceptable limits will need to take account of the dose to be administered….	

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132-140		Comment: This guideline would apply to Investigational medicinal products: for early R&D stages, there is too little information available to set limit values. There is insufficient guidance on when to initiate an assessment (i.e. how early in development) and then how frequently this should be reassessed/updated. The guidance given does not provide for full use of the TTC concept where there is a staged approach to the value depending on the likely characteristics of the compound. This may have a significant impact during early development where safety data is continually evolving. By comparison to OEL, this would not normally set this before the siting decision when reprotox, ADME, genotox, 6 month rodent data, and some Phase I and II data are available. If limits are set too early, the lack of data needs to be compensated with an extra assessment factor, and the resulting threshold value is likely to be very low. Proposed change (131): Provide additional discussion within the guidance document on the use of the TTC concept for early stage products.	

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138-140		Comment: The following statement while apparently reasonable is very difficult to interpret practically: "If data sets are incomplete, the identified gaps need to be critically assessed with regard to the uncertainty impact this might have on deriving a reliable health based' exposure limit." Clarity is required as to EMA's expectations. Proposed change (line 138): Add clarity as to EMA's expectations in this situation. Possibly by adding an example.	
146		Comment: Reproductive and developmental toxicity should always be evaluated against other data and points of departure to ensure that the male, female, and unborn are all protected by the threshold value. Proposed change (line 146): Add at the end of the paragraph "It is important to always compare reproductive and developmental toxicity to other sensitive endpoints to ensure protection of the male, female, and unborn."	

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148-154		Comment: The text describes the NOAEL rather than the NOEL Proposed change (line 148): For all critical effects identified, a NOAEL should be established. The NOAEL is the highest tested dose at which no "critical" effect is observed. If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value. If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used. A NOAEL based on clinical pharmacodynamic effects should correspond to the highest dose level tested which is considered therapeutically inefficacious.	
150-151		Comment: If several animal studies are used the lowest NOEL may not give lowest PDE. Is the use of the lowest (NOEL/F1) not just lowest dose NOEL more applicable here ? Proposed change (150): If the critical effect is observed in several animal studies, the critical effect producing the lowest threshold value should be used.	
164		Comment: Uncertainty factors are based on ICH Q3C residual solvents. There is much more toxicology data available for biopharmaceuticals than solvents which may allow for uncertainty factors less than 10. Proposed change (line 164): F3: A factor of 1-10 to account for repeated dose toxicity studies of short duration	

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220-223		Comment: This section states that "in the case of residual active substances without a threshold, a limit dose corresponding to a theoretical 1 x 106 excess lifetime cancer risk should be applied, i.e., 0.15 µg/person/day, or 0.0025 µg/kg bw." Neither residual active substances nor impurities benefit patients therefore the basis for the ten- fold reduction on the TTC for genotoxic APIs relative to impurities is not scientifically supported Proposed change (line 221) : Delete the statement.	
228-238		Comment: Further clarification on defining a sensitising reaction and the ability to determine threshold values for all routes of exposure is required as most monoclonal antibodies (foreign protein) will elicit some immunological response and potential for acute allergic reactions. This section should be specific to highly sensitising agents without threshold values. Proposed change: Change "sensitizing materials" to "certain highly sensitizing materials where no threshold value can be identified" throughout.	

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239-254		Comment: The approach for setting threshold values for therapeutic macromolecules and peptides should be no different than for small molecules. Both pharmacological and off-target, adverse effects from non-clinical and clinical studies should be considered. Proposed change (mid line 247): it is not considered acceptable to derive a health-based exposure limit based solely on the pharmacodynamic effects; toxicity must also be considered.	
240-250		Comment: Section 4.1.5 on protein-based Biopharmaceuticals does not reflect destructive cleaning, that leads to complete degradation of the protein drug. Proposed change: additional text to be added to section 4.1.5: "The cleaning of the manufacturing equipment should be performed with caustic solutions under conditions that ensure complete degradation of the protein-based Biopharmaceutical into a crude mixture of pharmacologically inactive biological compounds (eg. peptide fragments or amino acid derivatives). In this case the calculation of a PDE based on the pharmacological activity of the original intact Biopharmaceutical drug is no longer justified. Instead, the acceptable level of potentially present residual soil on the inner surface of the manufacturing equipment should be expressed in relation to the cleaning process capability."	

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255-269		Comment: This guidance in this section is not clear. Lines 256-266 seem to imply the use of the threshold of toxicological concern concept when insufficient data is available yet lines 267-269 appear to indicate that if insufficient data is available the substance should be manufactured in a dedicated facility. Proposed change: Delete line 267-269.	
260-269		Comment: The use of genotoxicity threshold for male-specific drugs without reproductive toxicity data is confusing. Segregation does not automatically apply to reproductive or developmental toxins. Proposed change: Delete lines 267-269. Add the following at the end of the section "in the absence of reproductive or developmental data, an uncertainty factor for data incompleteness should be applied when calculating the threshold value."	
267-269		Comment: if 267 to 269 is retained (see comment above) reduction to a threshold and the ability to establish a threshold do not seem sufficient. Other aspects might be existence and validation of analytical techniques to detect at levels less than or equal to the established threshold. Proposed change (267-269): In case the level of residual active substance cannot be reduced to the established threshold value, where analytical methods are insufficient for detection of residual active substance less than or equal to the established threshold or when insufficient data are available to establish a threshold value, the active substance should be manufactured in a dedicated facility.	

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270		Comment: Biological Products Determination of health based exposure limits assumes residual product after cleaning is active and the level of activity is comparable to product activity prior to exposure to cleaning agents and conditions. Biological product cleaning procedures are generally designed to expose product contact equipment to extremes of pH (<2 and >13) and temperature (60-80°C) for several minutes. Under these conditions, biological products are known to degrade and denature rapidly, and are therefore likely to become pharmacologically inactive. If it can be demonstrated that the biological product becomes inactive after exposure to applicable cleaning conditions, the determination of health based exposure limits may not be required. Proposed change: Add additional text under 4.1 Specific Considerations section 4.1.7 "Intact and properly buffered product is used in methods for determination of threshold values as well as in the determination of critical effects from toxicity studies. However, for biological products, exposure during cleaning to the cleaning agents and conditions would degrade and denature the biological product and render it inactive. Therefore, the threshold value and critical effect data suggested for use in determination of the proposed health based exposure limits would not be reflective of the phenomenological aspects of the cleaning process and actual product activity of potential residual product on equipment. If product inactivity after exposure to cleaning conditions can be demonstrated, determination of health based exposure limits as proposed should not be required."	

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270-281		Comment: The principles of ICH Q9 are being adopted in the EU GMP Guide and the document is referenced in part 3 of the Guide. A consistent approach to terminology is expected as such the report really discusses the Risk Identification phase of the ICH Q9 process which is the first step of the Risk Assessment phase. A Risk Assessment report should encompass not only Risk Identification but Risk Analysis and Risk Evaluation which would use the information developed based on this guideline to analyze and evaluate the risk. Proposed change (line 270): Change "risk assessment report" to "risk identification report". …the initial page of any prepared risk identification report should be in the form of a summary of the process….	
302-328		Comment: This summary sheet is confusing as the title relates to Risk Assessment (which include Risk Analysis and Risk Evaluation that are not addressed) but the content relates to Risk Identification. The purpose of the check boxes is not stated. Is it expected that they will for example flag a special review? Proposed change (line 302): Change title to Summary of Risk Identification Report. Provide an explanation on how this summary is to be used.	

Please add more rows if needed.