28 March 2017

Submission of comments 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:

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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).

1. General comments

General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
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 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	

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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.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	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)*
Q1	**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."	
Q2	**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	

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	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”	

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	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."	
Q3	**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	

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	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 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	

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	available, this may easily be used to prepare a PDE rationale as well." Delete the last sentence.	
Q4	**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.	

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	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 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.”	
Q5	**Comment**: A5 brings the long overdue clarification that the use of LD50 as the point of departure to determine health based limits is	

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	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).	
Q6	**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.	

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	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. **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	

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	demonstrating an additional margin of safety than previously determined."	
Q9	**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.	
Q9	**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. "	
Q10	**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	

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	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)	

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Q11	**Comment**: Application of the HBELs to paediatric formulations has been discussed by Hayes et al., 2016. 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	

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	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 should be based conservatively enough to cover all age groups (adult, paediatric, geriatric). In general the 10-fold adjustment	

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	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."	
Q12	**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. 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	

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	measures, such as more frequent periodic verification analytically, may be appropriate."	
Q14	**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-	

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	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 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	

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	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.	

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