



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

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)

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Comments should be provided using this [template](#). The completed comments form should be sent to adm-gmdp@ema.europa.eu



Q1. Do companies have to establish Health Based Exposure Limits (HBELs) for all products?

A: Yes, HBELs should be established for all products. HBELs for highly hazardous products are expected to be completed in full as per the EMA guide (EMA/CHMP/CVMP/SWP/169430/2012) or equivalent. 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.

Q2. What products/active substances are considered to be highly hazardous?

A: Highly hazardous products are those that can cause serious adverse effects at low doses and that therefore would benefit from a full toxicological assessment in order to derive a safe HBEL.

Highly hazardous products are identified based on their inherent toxicological and pharmacological characteristics and include the groups below (this list is not an exhaustive list and if evidence is available indicating that the product may cause adverse effects at low doses by other mechanisms it should be considered as highly hazardous).

Manufacturers should consider, via a safety assessment against the guidance below, if products/active substances should be considered highly hazardous. Evidence indicating a product or active substance falls within any of the categories below should result in a product being considered highly hazardous. 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.

1. Genotoxic (specifically mutagenic) compounds that are known to be, or highly likely to be, carcinogenic to humans. Compounds of this group are easily identifiable, since genotoxicity would be related to the pharmacology, e.g. as DNA alkylating cytostatics, and their use is usually restricted to oncology indications with respective warning statements in the Summary of Product Characteristics.
2. Compounds that can produce reproductive and/or developmental effects at low dosages, for example where evidence exists of such effects being caused by a clinical dose of <10 mg/day (veterinary dose equivalent 0.2 mg/kg/day) or dosages in animal studies of ≤ 1 mg/kg/day.
3. Compounds that can produce serious target organ toxicity or other significant adverse effects at low doses, for example where evidence exists of such effects being caused by a clinical dose of <10 mg/day (veterinary dose equivalent 0.2 mg/kg/day) or dosages in animal studies of ≤ 1 mg/kg/day.
4. Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg).
5. Compounds with a high sensitising potential.

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?

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: $PDE (\mu\text{g}/\text{day}) = OEL (\mu\text{g}/\text{m}^3) \times 10 \text{ m}^3$ (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 $\mu\text{g}/\text{day}$ or lower the product should be considered as highly hazardous.

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)?

A: 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.

Q5. Is the use of LD50 to determine health based limits acceptable?

A: No, LD50 is not an adequate point of departure to determine an HBEL.

Q6. How can limits for cleaning purposes be established?

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 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.

Q7. Can Ectoparasiticides be manufactured or primary packed in common equipment with other categories of medicinal products for human or veterinary use?

A: If HBEL data cannot support manufacture in shared facilities then the Ectoparasiticides should be manufactured in dedicated facilities.

Q8. What needs to be taken into account when manufacturing Veterinary Medicinal Products for different species in the same facility?

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. For non-highly hazardous products the approach described in the response to question 6 can also be applied.

Q9. How can inspectors determine the competency of the Toxicology expert developing the health-based exposure limit?

A: Inspectors should evaluate the company's assessment of the competence of their expert in the field by reviewing justification of experience and qualification.

Q10. How can the HBEL model be applied to early phase Investigational Medicinal Products (IMPs) where limited data is available?

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.

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?

A: In such facilities 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.

Q12. What role do HBELs play in meeting the requirements of GMP Chapter 5 section 20?

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 products in a dedicated area as a means of controlling risk of cross contamination?

A: Manufacturers cannot just segregate highly hazardous products from other lower risk products as a means of dealing with the risk to patient safety. This may protect less hazardous products from contamination but it does not address the possibility for cross contamination between highly hazardous products. The approach taken to address cross contamination between individual highly hazardous products produced in the same dedicated area should be justified taking account of the clinical application and toxicological profile of the individual products within the group of products manufactured in the dedicated area. This should include implementation of appropriate technical and organisational control measures.

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 establish an HBEL?

A: Yes, except in the case of highly sensitising active substances and products.