

Cleaning Memo for August 2017

EMA's Q&A Clarification: Part 2

This is a continuation of last month's Cleaning Memo dealing with the EMA's recent Q&A on HBELs for cleaning validation. Please read that July document before jumping into this one. This month we will cover Questions #6 through #14. As mentioned last month, care must be used in trying to understand what the EMA means by a "product". In many cases I believe they are referring to a drug active (or drug substance), but in other cases they are referring to a drug product. Note also that the EMA sometimes refers to a "compound", which in this context probably means a drug active.

Question #6

The first five questions were about setting HBELs. This question addresses how to set limits for cleaning validation purposes. It states that limits should not be set on a calculated HBEL alone, but other factors should be considered. Those other factors include "uncertainty in the cleaning process and analytical variability". Although not stated by the EMA's answer, I would add factors such as effects on product quality and product purity as possibly affect cleaning validation limits, even though those factors are not part of a *health* based exposure limit. For *non-highly hazardous products*, the EMA states that this can be achieved by "traditional cleaning limits used by the industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product". This is additional support for *not* requiring a full PDE assessment for these non-highly hazardous products. Although not clearly stated by the EMA, the traditional industry approach for these non-highly hazardous active has been the *more stringent* of 0.001 of a dose and 10 ppm in the next drug product, not an "either/or, choose one".

For highly hazardous products, the EMA also states that limits beyond the HBEL may be appropriate, and then further states that limits for highly hazardous products "should not be higher than the traditional cleaning limits approach". This is apparently a reference to "traditional approach" mentioned earlier in Question #6, namely the idea of 0.001 of a dose and 10 ppm in the next product. If this is the case, what it means is that for highly hazardous products, the limit for an active should be the *most stringent* of these three criteria:

- Calculated HBEL by PDE or TTC criterion for active
- 1/1000th daily dose of the active in the next drug product
- 10 ppm of active in the next drug product

Question #7

This answer states that Ectoparasiticides may be manufactured in shared equipment with other human or veterinary products only if supported by HBEL data. No comment by me is necessary.

Question #8

This question deals with veterinary products for different species manufactured in the same facility. For highly hazardous products with known sensitivity with certain species, the HBEL should take into account “specific animal toxicity knowledge”. For products not highly hazardous, the traditional approach (0.001 dose and 10 ppm) mentioned in Question #6 may be used.

Question #9

This question deals with how one determines that the toxicologist performing the HBEL assessment is a competent toxicologist. The answer given is to review the person’s “experience and qualifications”.

Question #10

This question deals with HBELs for early phase IMPs (clinical trial products). The answer given is basically to evaluate “all available data” and to update the assessment as new information is available. Furthermore, it may be appropriate to use the “read across” approach by evaluating data from similar molecules as well as any other “appropriate” adjustment factors based on worst case assessments where knowledge is less than complete.

Question #11

This question deals with pediatric products that are made in shared equipment/facilities with products for adults or for animals. The EMA states that the HBEL in this situation should be based not on the adult human weight of 50 kg, but on weights of 10 kg for children, 3.5 kg for newborns, and 0.5 kg for prematurely born newborns. I assume this is mainly for setting limits for the human adult and animal product where residues could potentially transfer to products for the pediatric population. However, those lower weights should also be considered for pediatric products following other pediatric products.

Question #12

This deals with the question of the relationship of HBELs to the requirements of GMP Chapter 5 section 20. This section of the EU GMPs deals with a Quality Risk Management assessment that “should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family.” The EMA’s answer is that HBELs should be used to justify cleaning limits. In this context, I am reminding you that HBEL values are not determined just by PDE or TTC calculations. According to the EMA answers in this document, the 0.001 dose criterion also comes into play under the HBEL umbrella.

Question #13

This question deals with the appropriateness of segregating highly hazardous products in a dedicated area (apart from non-highly hazardous products). While such an approach may prevent cross-contamination of the highly hazardous products into the non-highly hazardous products, such segregation *alone* does not address the issue of cross-contamination *between* highly hazardous products. It is still necessary to perform a

toxicological evaluation of each highly hazardous product to ensure that it does not cross-contaminate another highly hazardous product. In other words, it is *not* adequate to claim that the residue of one mutagenic product in another mutagenic product is not an issue; it clearly *is* an issue.

Question #14

This answer deals with the application of the TTC guide of 1.5 µg/day to mutagenic products as an “acceptable default” approach. The answer given is “Yes” *except* for highly sensitizing compounds. This should not be misread to think the EMA is allowing the TTC approach for *all* highly hazardous products. It is merely saying that the TTC approach is acceptable for mutagenic products, but *not* if those mutagenic products are also highly sensitizing products.

This finishes my observations and comments on the specific questions in this draft document. Two additional comments may be helpful. One is that even though a visually clean criterion is not mentioned in either the 2014 document or in the draft Q&A, it is probably still an expectation that the equipment be visually clean in a product to product validated cleaning process. The second is that the EMA appears to be making a *distinction* between a health based exposure limit (HBEL) and a cleaning validation limit. A HBEL only deals with patient safety issues. It *must* be considered in arriving at a cleaning validation limit. However, a cleaning validation limit should consider other relevant factors, such as the 10 ppm criterion (dealing with product purity issues) and the visually clean criterion (dealing with GMP expectations).

Care should be used in applying the principles in this draft Q&A until such time as it is finalized. However, this Q&A document is, as I expressed in my written comments to the EMA, “a breath of fresh air”. Let’s hope that the basic principles in the EMA’s draft document appear in the final version of the Q&A.