

Cleaning Memo for July 2017

EMA's Q&A Clarification: Part 1

The EMA issued its draft Q&A on health based exposure limits in December 2106. The official title is “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)”

There has been surprisingly little attention to this Q&A in the various pharmaceutical journals and internet news sites. My original intention was to wait until a final document is issued before discussing it in a Cleaning Memo. However, I have changed my mind because of the radical departure this is from the way the industry seemed to be going.

For those of you that are not familiar with this document, it is a series of fourteen (14) questions and answers relating to implementation of Health Based Exposure Limits (HBELs). Before I start on the 14 questions, a discussion of HBEL versus PDE values requires some clarification. The more general term is HBEL. PDE is only one method to derive a HBEL. Unfortunately the 2014 EMA is sometimes read as requiring PDE values for all actives. It should be clear from reading that document that a PDE is only one avenue for establishing a HBEL. That 2014 document also discusses using the TTC concept for genotoxic materials, as well as stating for certain products, like biotechnology actives and product where the most relevant safety data is on humans, the PDE formula *may not* be appropriate.

That said, the wording of the EMA document may contribute to that misreading. The beginning of Section 4.1 states “The procedure proposed in this document for determination of health based exposure limits for a residual active substance is based on the method for establishing the so-called Permitted Daily Exposure (PDE)....” Obviously the PDE is not the *only* procedure to establish a HBEL given in that 2014 document. In addition, Section 6 of the 2014 document is titled “Reporting of the PDE determination strategy”; it would seem appropriate if there were other means of determining a HBEL, that section should have been titled “reporting of the HBEL determination strategy”. Fortunately the new draft Q&A clarifies this and emphasizes the general idea of a HBEL as compared to one embodiment of it (the PDE).

However, this should be reminder to us all that words and wording can make a difference, and that a careful reading of original regulatory documents should always be considered. So take that into consideration as I present a summary and critique of the new draft Q&A. These comments are given for each of the questions as listed in that new draft document. As you read my comments, you should be referring to the EMA document at the same time. In addition, 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 that the EMA sometimes refers to a “compound”, which in this context probably means a drug active.

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Question #1

The first question states that “HBELs should be established for all products.” That is fairly clear; “all products” is *all* products. However, the answer goes on to state that for “highly hazardous products” the HBEL is “expected to be completed *in full* per the [2104] EMA guide ... or equivalent.” [Emphasis added] Question #2 covers highly hazardous products and Question #4 covers those that are *not* highly hazardous.

Question #2

In this question the EMA defines a highly hazardous product as one that “can cause serious adverse effects at low doses”. It lists certain categories (which is not an exhaustive list) of compounds that should be considered highly hazardous. The list includes genotoxic/mutagenic compounds that could be carcinogenic, compounds with reproductive or developmental effects, compound with specific serious target organ toxicity, highly potent compounds (those with a daily therapeutic dose of <1 mg/day in humans), and compound with that are highly sensitizing.

I also find it difficult to clearly define what I mean by highly hazardous actives. While I am not fully comfortable with the EMA’s descriptions, I don’t think I can come up with a better list. One area to consider carefully when an assessment is being made using these criteria is the emphasis on effects at “low doses” (<10 mg/day) for mutagenic and reproductive effects. I would think that compounds that were mutagenic should have a full PDE or TTC assessment even if the daily dose was greater than 10 mg/day. I have not yet covered question #4, but it doesn’t make sense to me (as a non-toxicologist) to make that distinction based on the daily dose. There should be a distinction between the daily therapeutic dose and the dose at which highly hazardous effects are observed.

The second area of concern is listing “highly potent” compounds, those with a daily dose of < 1 mg/day, as highly hazardous. My assumption here is that the EMA is referring to “potent” compounds that are not mutagenic, etc. With other things being equal I would be more concerned about the safety effect of a potent compound as compared to a non-potent compound. But if the major safety concern for the highly potent compound is the therapeutic effect, then the safety concern from 0.001 of a therapeutic dose of a highly potent compound should not be of more concern as compared to 0.001 of a therapeutic dose of a non-potent compound. In my comments to the EMA I recommended that this be changed.

Question #3

This question addresses the applicability of using OEL or OEB values to “support” an assessment of whether a product is highly hazardous or not. The EMA’s answer is “Yes”, for determining a *preliminary* PDE. The typical formula of multiplying the OEL/OEB value by 10 m³ of air is given. The EMA adds that adjustment factors based on the target population and on administration routes may be needed. It also states that PDE values determined in this way that are less than or equal to 10 µg/day should be considered highly hazardous. I am unclear why this last statement is given as to a “highly hazardous” category. My speculation is that the OEL only gives a *preliminary* PDE. If

this preliminary PDE is at or below 10 µg/day, then a *full* evaluation should be done to establish the PDE using the approach given in the 2014 document. If the OEL/OEB approach gives a value above 10 µg/day, then that compound can be considered non-hazardous and the approach given in Question #4 could be used. However, this is *my* speculation of the intent here, and I may be wrong.

Question #4

This is the one I think (or hope) should clearly survive in the final Q&A. This is dealing with products that don't belong to the highly hazardous category and have a "favorable therapeutic index". I think a description of what this means is given later in the answer as compounds where the "pharmacological activity would therefore be the most sensitive/critical effect", with the therapeutic dose being the point of departure for determining the HBEL. Here is the key sentence in full:

"Under these circumstances, HBEL based on the 1/1000th minimum therapeutic dose approach would be considered as sufficiently conservative and could be utilized for risk assessment and cleaning purposes."

This appears to mean that for compounds that are *not* highly hazardous (as defined in Question #2), 0.001 of a dose can be used as the HBEL, and it is not necessary to do a full PDE assessment as given in the 2014 guide.

That said, I believe it would still be prudent to perform a preliminary PDE based on the OEL/OEB if that OEL/OEB data is available.

Question #5

This answer states that an LD₅₀ value is *not* an "adequate point of departure to determine an HBEL." My only concern here is that perhaps the context of that statement is limited to actives. Clearly for actives there has to be relevant data other than an LD₅₀ study. However, for cleaning agents and for intermediates in API synthesis, LD₅₀ data may be the only relevant safety data available. I hope that this answer is interpreted only in the context of drug actives. We'll have to wait and see what is in the final Q&A document.

There are nine more questions and answers to cover. We continue in August with those.