Cleaning Memo for June 2018
The EMA Q&A "Clarification" on Limits

The EMA issued it clarifying Q&A on limits in shared facilities on April 19, 2018. This was a "final" document with changes from the draft version issued in January 2017. I say it was a clarifying document. However, in my view it just muddied the waters further as compared to the clear statements made in the draft document. That said, it is probably not as bad as it looks on first glance, providing you read it *carefully*. In this Cleaning Memo and over the next several months I will try to explain what is being said and what is not being said in this Q&A document. This month, I just focus on the issue of Health Based Exposure Limits (HBELs) and the traditional way limits were set (hopefully you know what the traditional way is). As you read what follows, note that some statements will refer to the *final* document and some statements will refer to the earlier *draft* document.

First, the EMA is clear in its answer to Question #1. HBELs are required for *all* "medicinal products". This is a slight change from the draft document, which required HBELs for all "products". I might be reading too much into this change, but it might mean that HBELs, as defined in this document, are not required for cleaning agents and for intermediates (in small molecule API synthesis). Now it should be clear that toxicological evaluations should be part of setting limits for cleaning agents and intermediates. However, in many instances the most relevant toxicity information is short term toxicity information such as animal LD_{50} values. And, if we jump to Question #10, LD_{50} "is not an adequate point of departure to determine a HBEL for drug products". This has a slight twist from the draft document where the final clarifying phrase "for drug products" is *absent*. Does this mean that LD_{50} values can be a starting point for a HBEL for detergents and intermediates (which clearly are *not* drug products)? We might have to wait for a further clarifying Q&A from EMA on this issue.

Second, the answer to Question #2 merely states the obvious that there is a hard continuum (with no cut-off points) in evaluating the level of risk from any hazard. While this should not come at a surprise, it is a change from Question #2 in the *draft* document which made a distinction between defined *highly hazardous products* and those that were *not* highly hazardous. Yes, that distinction does involve a cut-off point, but it is reasonable cut-off point like those used when a qualified toxicologist establishes OEL bands for worker safety purposes (those bands do have hard cut-off points, although everyone realizes that the distinction between a value of 0.99 and 1.01 may not be significant). Having hard cut-off helps us make useful distinctions in the real world, as opposed to theoretical (but clearly true) assertions. It seems to me that the distinction between an active where the therapeutic effect is the point of departure and an active where there is a significant other effect of the active (giving a different point of departure) is a valid one. We should also remember that for Risk-MaPP and the EMA, the point of departure for their efforts was to find some way to set limits for "certain" actives (which were the highly hazardous ones) where the traditional dose-based criteria were *not* applicable.

Third, we have arrived (at least for this Cleaning Memo) at Question #6. The question here is "How can limits for cleaning purposes be established?". The first sentence of that answer is the same one given in the draft document: "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." I think what this suggests is that there is a distinction between a HBEL and a cleaning validation limit. My take on this (if you've followed my writings, you know where I'm going) is that the HBEL is a requirement to insure patient safety and the cleaning validation limit should meet this requirement *at a minimum*. However, the cleaning validation limit may be *more stringent* based on other concerns, such as product quality and purity If my view is correct, this is a far cry from the statement in the 2017 Risk-MaPP that "The only criteria necessary for a robust cleaning process are the health-based, ADE derived limit, a validated analytical method with a sensitivity below the acceptance limit, that is visually clean.

The answer to Question #6 then goes on to talk about "historically used cleaning limits" for *existing* products. It states quite clearly that those limits "should be retained" and that those cleaning limits can be used as *alert* limits to "provide sufficient assurance that excursions above the HBEL will be prevented." That is, it assumed that the historically used limit will be at least as stringent as the HBEL. Now for a clarification from me. The historically used limits (called the traditional limits of 0.001 dose and 10 ppm in the draft Q&A) have only been applicable for products where the therapeutic effect of the actives is the point of departure for establishing limits; in most cases for highly hazardous actives the HBEL will be more stringent.

Okay, enough of my aside; let's get back to the EMA document. The statement in the answer to Question #6 about the historically used limits and using them to assure that the HBELs will not be exceeded is followed by this statement: "A similar process should be adopted when establishing cleaning alert levels for products introduced into a facility for the first-time." This seems to imply that the historically used limits may be used for *new* products in a facility in the *same way* as for existing products. It certainly is not clear to me what the EMA is trying to say; at times I feel, like I am trying to "read tea leaves" to find out what they are really suggesting. However, my take is that the statements in the draft Q&A are a better approach for a clarifying Q&A document. Essentially what the draft document implied was that for *all* actives, you should determine the limits based on a HBEL, 0.001 dose and 10 ppm, and use the most stringent of those three calculated limits. Note that that the draft document did not explicitly say to use that for *all* actives. But in reading what is recommended for highly hazardous actives and for non-highly hazardous actives, that conclusion is the ultimate result. My take is that for most *highly hazardous actives* either the HBEL or the 10 ppm criterion will be the most stringent, while for most *non-highly hazardous actives* either the 0.001 dose or the 10 ppm criterion will be the most stringent. That approach is one I have recommended for several years because of my concern that HBELs only consider patient safety in setting limits, and ignore other concerns related to product quality.

I think what this means is that if you want to implement the EMA guideline, you should carefully read and understand this new Q&A document, and consider all comments (mine as well as comments from others) about what is *really* states and *really* means. My disappointment in the EMA is that they had the opportunity to clarify their guideline, but only ended up obfuscating issues relating to limits in what has become a highly political atmosphere in the scientific world.

Next month's Cleaning Memo will address additional issues in the EMA 2018 Q&A document.