Cleaning Memo for January 2020
EMA vs. ISPE on Cleaning Limits?

You might be mystified at this title. What is Mr. LeBlanc getting at? Well, what I will discuss this month is the difference (or conflict?) between the EMA and ISPE on setting limits for cleaning validation. For the EMA “position”, I will refer both to the 2014 “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities” and the 2018 “questions and answers” on implementation of that 2014 guideline. For the ISPE “position”, I will primarily refer to the 2017 revision of “Risk-Based Manufacture of Pharmaceutical Products” (Risk-MaPP). For clarification, when I refer to the EMA position, I am not implying that everyone in the EMA supports this position; nor when I refer to the ISPE position, I am not implying that everyone in the ISPE supports that position. [Clearly, I am a member of the ISPE and do not fully support its position.]

I’ve set the stage. Now, what are the different positions, and what aspect of limits am I referring to? What I’m referring to are adequate and sufficient approaches and rationales for setting limits for actives (APIs) in drug products. Many of you should be aware of the general approach used before 2010. That approach, popularized by Lilly scientists in a 1993 publication, involved setting limits based on 0.001 of a minimum daily dose of the cleaned active in a maximum daily dose of the next drug product. In addition, if that calculation resulted in a concentration of more than 10 ppm in the next product, then 10 ppm was utilized in place of the value calculated by the 0.001 dose criteria. Also, the equipment was required to be visually clean.

Furthermore, while not specifically mentioned in the original publication by the Lilly scientists, that approach was applicable to situations where the primary patient safety concern was the therapeutic effect of the active. For situations where other toxicity effects (such effects as mutagenicity, reproductive hazards and cytotoxicity) of the active were critical (I typically refer to these actives as “highly hazardous actives”), the approach was not clear except that making the products in dedicated equipment was certainly an option. Another option listed in the PIC/S PI 006-3 document was to make those products in shared facilities but with a cleaning validation limit of non-detectability by the best available analytical technique (which is somewhat questionable in that, in the absence of setting appropriate limits for the active, the best available analytical technique may not adequately protect patients).

In 2010 and then in a 2017 revision, ISPE’s Risk-MaPP presented a newer approach (which had been presented before in various industry forums). Focusing on the 2017 document, Risk-MaPP states that “The only criteria necessary for a robust cleaning process are the health based, ADE derived limit, a validated analytical method with sensitivity below the acceptance limit that is visually clean.” The second criterion of having an analytical method that can actually quantify residues at the acceptance limit is nothing new, but only common sense. Clearly the third criterion of visually clean was also nothing new. So that the main point in that assertion from Risk-MaPP (and the focus
of this Cleaning Memo) is the element of setting limits solely based on an ADE (or PDE) value, that is, a focus on patient safety from a toxicological perspective.

Now, what is the EMA position? In its 2014 guideline, the approach is not so much setting cleaning validation limits, but rather to specific methods for setting health based exposure limits (HBELs). Now you might be thinking, aren’t “health based exposure limits” the same as “cleaning validation limits”? Hold on for a minute, and I’ll let the EMA clarify the difference. In that 2014 document examples of setting health based exposure limits are PDEs and TTC. But that document also states that in certain situations HBELs based on PDEs are not “appropriate”, such as for biotech manufacture where the protein actives are degraded by cleaning with hot, aqueous alkaline cleaning solutions. Another example given is for actives where the most relevant data is not animal studies but rather human clinical data. Unfortunately there is no guidance given in that document on how to set HBELs in those two cases.

Then, in 2018 the EMA clarified its position for setting cleaning validation limits in its “Questions and Answers on Limits for Shared Facilities”. In that Q&A document, in answer to Question #6 (which is “How can limits for cleaning purposes be established?”), the EMA states “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.” Whoa!!! What is this saying? As I read it, there is a distinction between a HBEL and a cleaning validation limit. What is that difference? 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.”

Even though the 2018 document does not state explicitly what those historically used cleaning limits are, they can only be what are called the “traditional limits” of 0.001 of a dose and 10 ppm as given in the EMA’s 2016 draft Q&A document. Okay, the EMA clarifies that those historically used cleaning limits should be used for existing products. What then about new products; certainly HBELs alone should be used? Not so fast. The EMA continues in its answer in Question #6 that “A similar process should be adopted when establishing cleaning alert levels for products introduced into a facility for the first-time.”[Emphasis added] Now what is meant by a “similar process”? The context would seem to make it clear that the use of “historically used limits” is also applicable for new products.

Now we can argue about the difference between the terms “cleaning limits” and “cleaning alert levels”, but my experience has always been that an alert level should be more stringent than a cleaning validation limit. So if I am correct, the cleaning validation limit should never be higher than the HBEL, but that in some cases it may be lower (that is, more stringent). And if “historically used cleaning limits” are still applicable in combination with HBELs, on what basis can the ISPE in its Risk-MaPP document assert that “The only criteria necessary for a robust cleaning process are the healthbased, ADE derived limit, a validated analytical method with a sensitivity below the acceptance limit,
that is visually clean.” Clearly there is a conflict, or at least a major difference of opinion, between these two approaches to setting limits for pharmaceutical cleaning validation.

Why Risk-MaPP states what it does is inexplicable to me. While the EMA Q&A document may be confusing in its use of “cleaning validation limits” and “alert limits”, I believe its approach has a more logical and more scientific basis for setting cleaning validation limits. From a scientific perspective, the EMA approach seems to be based on potential adverse effects on both patient safety and product quality (and thus is consistent with the approach of the FDA in the 2015 Question #7 of the FDA’s “Questions and Answers on Current Good Manufacturing Practices – Equipment”), while the ISPE approach seems to focus only on patient safety. The bigger question that the pharmaceutical cleaning validation and toxicological communities should address is how did we ever get into this murky situation? If my experience is any guide, that is a question that will never be openly addressed.