Cleaning Memo for December 2017
What's at Stake with HBELs

As you are hopefully aware, the EMA in December 2016 issued a draft "Q&A" clarifying some issues in its 2014 guidance on limits in shared facilities (see the July and August 2017 Cleaning Memos). I for one thought it was a "breath of fresh air". In June 2017 the EMA had a stakeholders' meeting where a variety of scientists from regulatory agencies and industry were invited to present their views on the Q&A document. The presentations at that meeting included the expected ones objecting to the EMA "backtracking" (my term) by allowing for the traditional approach of 0.001 of a dose for products that were not highly hazardous, as well as ones describing the uncertainties and confusion that has occurred as a result of the 2014 guideline. The EMA has indicated they intend to issue a clarified Q&A by the end of the year. As of this writing, that has not happened. What is at stake if the EMA truly back-pedals on the use of the dose criterion for non-highly hazardous product?

Before I get to what's at stake, I would like to suggest why the EMA 2016 Q&A document is *not inconsistent* with the 2014 guideline. Everyone (okay, that's an exaggeration) appears to focus on the requirement in the 2014 guideline that PDEs (Permitted Daily Exposures) be used as a health-based exposure limit (HBEL). As I have previously pointed out (see the Cleaning Memos of March, April and May 2015), the 2014 guideline (in Section 4.2) has the following statement about products where the clinical data (not animal studies) are the primary basis for evaluating patient safety:

> "If the most critical effect identified to determine a health-based exposure limit is based on pharmacological and/or toxicological effects observed in humans rather than animals, the use of the PDE formula may be inappropriate and a substance-specific assessment of the clinical data may be used for this purpose."

Now there might be different ways of interpreting this statement and applying relevant clinical data, but at least one way is the approach specified in 2016 Q&A draft, that for products that are not highly hazardous, the use of the "traditional" approach of 0.001 of a dose and 10 ppm is adequately protective of patients and constitutes a HBE for those products that are not highly hazardous.

Note that there is another section in the 2014 guideline where PDE *may* not be appropriate. In Section 5.3 is the following statement relating to biotech manufacture:

> "Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of health based exposure limits using PDE limits of the active and intact product may not be required."

Obviously in this situation the use of the 0.001 dose criterion of the native active doesn't necessarily fit. Approaches such as using estimated PDE values of the degraded/inactivated fragments (see the Cleaning Memo of February 2017) could be used (although the EMA was silent on what approaches might be used).

A final note on this issue in the 2014 guideline involves investigational medicinal products (IMPs) where there is *inadequate* information to establish a PDE (see section 5.5). In this section the EMA provides options of using a "one size fits all" type of approach using something like a TTC, where there are "fixed" acceptable values based on a toxicologist's determination of the level of hazard.

So far, what I have said is just an introduction to point out that what is given in the 2016 Q&A is *not inconsistent* with what was in the 2014 guideline. Now to my point as to what's at stake.

What is at stake is the difference between a HBEL and a cleaning validation limit (CVL). That is, a HBEL should be considered in setting a CVL; the CVL should be at least as stringent as the HBEL. However, a CVL should also consider *other* effects, such as effect on the quality of the next product. In other words, in addition to patient safety when a residue is carried over into a subsequent product, firms should also consider other possible effects of the residue. This idea of considering effects on quality is not something new. The 2015 FDA Q&A on CGMP (a rewrite of a 2001 Human Drug CGMP Note) states the following:

> "Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues."

It is possible to go back even further and find the statement below from a 1992 publication by toxicologists from Abbott published in *Quality Assurance: Good Practice, Regulation, and the Law (*Vol. 1, No. 3 June 1992, pp. 171-180):

> "In practice, the actual allowable residue concentration in a pharmaceutical should be based upon both health and product quality concerns. Thus, the residue limit(s) derived from this procedure may not always be the binding constraint on an allowable residue concentration for a residue in a pharmaceutical. For example, if a residue limit were 1 mg per day and the maximum daily dose of the pharmaceutical were 10 mg per day, the residue could potentially make up a significant fraction of a daily dose without harming the patient. Obviously, a residue present at such concentrations would not be acceptable. In these cases, the allowable residue concentration should be controlled by product specifications, good manufacturing practices, or other quality-based requirements, and not by the health-based residue limit, so long as the health-based residual limit is always met."

In other words, there may be issues other than patient safety that should be considered in setting cleaning validation limits, provided that the patient safety issues are adequately addressed.

Now, if we only set limits based on a HBEL, how can we determine what additional factors may make the limits more stringent to deal with any detrimental effects on product quality? Do we have to start doing studies that look at effects of residues on product stability or on active bioavailability? If we insist only on HBELs, this is certainly something that we should consider, and something where regulators could ask for rationales and/or data to address those other product quality concerns that may not be addressed by a toxicology assessment. I hope we don't go down this road. My view on the 10 ppm of residue (in the next product) as an alternative limit to use *if it is more stringent* than the 0.001 dose criteria (as given in the 1993 Fourman and Mullen publication) is that the 10 ppm alternative should, in most cases, address other quality effects. For clarification, this is not the rationale given in the Fourman and Mullen paper, but is my view as to its *true* significance. Note that in the 2016 EMA draft Q&A this 10 ppm is also a requirement for highly hazardous actives (that is, highly hazardous products have to meet the PDE requirement, but should also meet the traditional criteria of 0.001 of a dose and 10 ppm.

So, this discussion of setting limits is not just a matter of what's right (although my opinion is that for the most part the 2016 draft Q&A got it right). It is also a matter of what the impact of any change might be.

Let me also clarify that the 2016 EMA draft Q&A still leaves the toxicologists and pharmacologists in the driver's seat for setting HBELs. They are the ones to determine if the active is highly hazardous, *and* whether the traditional approach provides adequate patient protection for those that are not highly hazardous.

Finally, while I make a distinction between patient safety and product quality issues, realize that product quality issues *may* affect patient safety and/or health. For example, if a residue shortens the shelf life of a drug product, the patient might not obtain the beneficial outcome expected from use of the drug product.

I'm hoping this will be my last Cleaning Memo on this subject (I probably would have retired several years ago if this controversy had not continued this long). I will have to wait and see what steps the EMA takes.