June 2013
Are Health-Based Limits Enough?

Both the RiskMaPP ADE (Acceptable Daily Exposure) and the EMA's PDE (Permitted Daily Exposure) are attempts to set cleaning validation limits based on a toxicological evaluation, primarily using either a NOAEL (for an ADE) or NOEL (for a PDE) value as the fundamental basis for a limit. That NOAEL or NOEL value is then adjusted using information related to how that NOAEL/NOEL value was determined, including factors for interspecies differences, intraspecies differences and the like. These values are generally called "health-based" values for setting limits for cleaning validation purposes.

While the public database for making the following statements in this paragraph is limited, I believe it effectively captures what will happen when limits are set on either one of these two methods. For actives where the main concern is safety due to the *therapeutic effect* (I generally call these "conventional actives"), limits will be higher than the corresponding limit determined based on a 0.001 dose criterion. How much higher that limit will be will depend on the specific situation, because the 0.001 dose criterion is a "one size fits all" criterion for these types of actives. For some actives, limits may be raised by a factor of two or three, while for others limits may be raised by factors of ten or twenty. For actives that are *highly hazardous* (such as for mutagenic or teratogenic actives), a safe level will be established such that products containing the highly hazardous active no longer must be made in *dedicated* equipment, but will be able to be made on *shared* equipment.

Now this brings us to the primary issue in this Cleaning Memo: Are health-based limits *alone* appropriate for cleaning validation limits? I will answer that question in two parts, with one answer addressing conventional actives and one answer for highly hazardous actives. Let's take the conventional actives first. Remember that in Risk-MaPP, values such as 10 ppm in the next product are considered "arbitrary" and "non-scientific". My answer is that such values are valuable in cleaning validation programs. The rationale is based partly on what is written in an FDA *Human Drug CGMP Note* of the 2nd Quarter 2001. In reply to the question "Should equipment be as clean as the best possible method of residue detection or quantification?", the FDA states:

> No …. The CGMPs require that equipment be cleaned to prevent contamination that "would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 211.67(a)). The preamble indicates that this phrase was added to account for the fact that absolute cleanliness is neither valuable nor feasible in many circumstances for multi-use equipment. The answer to the question "how clean is clean?" cannot, therefore, be "it depends on the method of detection." If the method of detection determined levels of contamination, advances in the sensitivity of detection methods would necessitate correspondingly ever-lower limits and ever-increasing wash cycles. So, how clean should equipment be? It should be as clean as can reasonably be achieved, to a residue limit that is medically safe and that causes no product quality concerns (other than the fact of the contaminant's presence), and that leaves no visible residues. Reasonably avoidable and removable contamination is never acceptable.

Perhaps it can be argued that this document is twelve years old, and that it doesn't apply any more. However, the 1993 FDA Cleaning Validation Guidance is twenty years old, and it still applies (although clearly the *Human Drug CGMP Note* is a lower level guidance from the FDA).

As I read the *Human Drug CGMP Note*, it appears that there are four criteria for effective cleaning given in the last two sentences of the FDA quote:

a. As clean as can be *reasonably achieved*
b. To a residue limit that is *medically safe*
c. To a residue limit that cause *no product quality concerns*
d. To a level that is *visually clean*

So, if we just base limits on a toxicological evaluation, we are just addressing the "medically safe" criterion. Now don't get me wrong. I believe most cleaning validation experts would clearly add the visually clean criterion as a minimum criterion. Furthermore, as I have pointed out repeatedly, Risk-MaPP calls for cleaning equipment to as low a level as possible (Section 7.1 of Risk-MaPP reads "It is important that the residue data is as far away from the STV as possible"; STV for Risk-MaPP is the "Safe Threshold Value"). [Note: this section of Risk-MaPP is seldom covered in various discussions of implementing Risk-MaPP.]

But neither Risk-MaPP nor the EMA draft document addresses the issue of other "product quality concerns". In other words, if Risk-MaPP examples are to be believed, the safe level for conventional actives may be as high as 1/20 (or 0.05) of a dose; depending on the manufacturing parameters, this may results in a limit in the next product as high as 2% (that's not 2% of a dose, that 2% of the active in the next drug product). I think most of us would agree that while that level might be medically safe, it is not an acceptable level from a CGMP perspective, nor from other quality concerns such as changing product stability, bioavailability, and/or physical properties (dissolution, for example). I believe this might be one reason the Lilly scientists selected a "default" value for the limit in the next drug product of 10 ppm (although admittedly that value is somewhat arbitrary, in that higher or lower values could have been selected based on professional judgment).

How do I address these concerns for highly hazardous actives? Remember, in this case the situation is that with a health-based limit, I am moving from dedicated equipment to multiproduct equipment. In that case, the limits I calculate are generally going to be much more stringent than the 0.001 dose criterion, and in most situations will be more stringent than a criterion of either visually clean or 10 ppm in the next product. Therefore, the issue of "other product quality concerns" is reduced significantly. Therefore, using health-based limits alone is more likely to be the case for highly hazardous actives (although I would still prefer to specify a default requirement of 10 ppm active in the next drug product and a requirement for visually clean if those criteria are more stringent than the health-based limit).

Another issue with using the health-based limit alone is that that calculation assumes that by taking the next drug product, a patient will get a no more than a safe amount (the ADE or PDE). What happens if a patient is taking ten different drug products. Should not there be concern about cumulative residues from multiple drug products having an additive effect? I addressed this is a general way (although not in the context of Risk-MaPP) in the April 2011 Cleaning Memo. At least one way to address this is to consider the real world, where actual residues values are considerably below calculated limits, and where limits such as 0.001 are overprotective if one solely considers residues from only one drug product.

Let me reiterate that health-based limits correctly determined should be adequate for *highly hazardous actives*. My two concerns for this situation are consistency in terms of how professional judgment is applied for determining an ADE or PDE value (including the lack of published studies where the detail of such calculations is illustrated for actives) *and* the difference between the Risk-MaPP determination of an ADE and the EMA determination (from ICH Q3C) of a PDE.

For *conventional* actives, either the 0.001 dose or ADE/PDE limit can be used, provided that there are still requirements for a default value (such as 10 ppm in the next drug product) and a visually clean criterion. Although not popular with Risk-MaPP advocates, one possibility is to determine both the ADE/PDE value and the 0.001 dose value, and use the more stringent of the two. However, there are situations where the ADE/PDE approach may be preferred. One is where the 0.001 dose limit results in a value that is not measureable by practical analytical methods. In that case, the ADE/PDE will give a higher limit and the analytical methodology may be suitable. A second case is where the active is degraded in the cleaning process (as is typically the case in biotech manufacture); in that situation setting limits based on the ADE/PDE of the degradants provides a more logical approach.

It is ironic that one of the main arguments that Risk-MaPP advocates use against the 0.001 dose criterion is that it was "non-scientific", because I find myself in the situation of making the assertion that health-based limits applied *alone* are "non-scientific".

Let me also clarify that in the *broad sense* of what a health-based limit is, I consider the 0.001 dose criterion a "health-based limit". It was designed to protect the health of patients, but unlike the ADE/PDE determination, is a "one-size fit all" determination (and as Risk-MaPP advocates like to point out, is overprotective for many actives). Finally, I should clarify that contrary to what I hear some people saying, an ADE or PDE is not a replacement for a MACO (maximum allowable carryover) determination. With an ADE or PDE, one still has to do a carryover calculation. The only difference is that in place of using 0.001 dose as the safe daily amount, the ADE or PDE amount is utilized. It is still necessary to include data such as the dosing of the next product, the shared surface area, the batch size of the next product and the sampling parameters to adequately determine acceptance criteria in a cleaning validation protocol.

The purpose of this Cleaning Memo is to further discuss issues in appropriately setting limits for actives in cleaning validation protocols. For previous critiques of Risk-MaPP the reader should go to www.risk-mapp-gate.com .