

May 2014 - Addendum Shortcomings of ADE/PDE Values for Cleaning Validation

Let's cut to the chase (as they would say when making old movies). The reason that ADE/PDE values alone should not be adopted for cleaning validation is that those values only address one of the concerns in setting limits. Toxicity to the patient is only one of the concerns in setting limits. Risk-MaPP states that setting limits based on 0.001 of a dose is unscientific, and Risk-MaPP advocates have stated consistently that we should be using "good science". My contention is that it is the ADE/PDE advocates who are not using "good science". Why do I say that? Do I need to repeat myself? Toxicity to the patient is not the only concern in setting limits for cleaning validation.

Let me also be clear that ADE/PDE advocates are correct in saying that a PDE/ADE is a more accurate way of assessing toxicity to the patient. However, I believe that except for what I call "highly hazardous actives" (call them "highly toxic actives" if you prefer that terminology), 0.001 dose is adequately protective (or as suggested by many ADE/PDE advocates, is overly protective).

"Highly hazardous actives" include those actives that have significant toxicity apart from the therapeutic effect. This would include products with toxicity related to reproduction, genotoxicity, and cytotoxicity. These are the actives that previously were considered to be candidates for dedicated equipment. And I agree that setting limits based on PDE/ADE values for these actives is valid as part of an overall risk assessment.

But, let's get back to the main difference between what I consider "good science" and what the ADE/PDE advocates want. The reason ADE/PDE values alone are not enough for cleaning validation limits is related to what the FDA (at one time) said about limits. In answer to the question "Should equipment be as clean as the best possible method of residue detection or quantification?", the FDA answer in a Human Drug GCMP Note of 2001 was:

"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."

In their words, in addition to "medically safe", the limits must be based on not causing "product quality concerns", as well as preventing contamination from residues that are "reasonably avoidable and removable". Product quality concerns were not further elaborated in that Human Drug CGMP Note, but could reasonably include effects on product stability, physical properties (such as tablet strength and dissolution), and/or bioavailability. Now I would doubt that most companies have specific studies directly addressing these concerns. But most have data suggesting that what has been used for limits for the past 20 years has not caused such quality concerns. So, my question is, does it make more sense to continue with limits for non-highly

hazardous actives based on a proven track record, or do we start setting limits 10 or 20 fold higher and either do studies to confirm no quality affects or pray that such higher limits present no actual effects on product quality?

This issue of concerns other than toxicity for addressing residues in drug products was also addressed in a paper co-authored by one of the co-leaders of Risk-MaPP. Dr. Bruce Naumann, a toxicologist currently with Merck, was with Abbott at the time he co-authored the paper “Setting Health-Based Limits for Contamination in Pharmaceuticals and Medical Devices”, by David L. Conine et al, published in *Quality Assurance: Good Practice, Regulation, and the Law*, Vol. 1, No. 3 June 1992, pp. 171-180. This article includes setting ADI values based on values such as subchronic and acute toxicity data. In a section on “Application to Pharmaceuticals” is the statement:

“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.”

Now my question, which has not been addressed by Dr. Naumann or other ADE/PDE advocates, is “What has changed since 1992? Has the science changed? Or what?”

Besides saying that ADE/PDE values are “good science”, those ADE/PDE advocates maintain that moving to ADE/PDE values for limits will be more cost effective. What constitutes cost effectiveness has been presented as less stringent cleaning or as better compliance (fewer deviations because limits are higher). It has also strangely been presented as the need not to test equipment for residues on a continuing basis, because the calculated limit in many cases will be above what is visually clean. This latter argument misses the point in that most companies do not measure residues on a continuing basis after completion of validation protocols. However, cost effectiveness is not part of an argument as to whether something is “good science” or not. [I would also argue that if companies are looking to be more cost effective in their cleaning validation programs, they could do many other things (other than significantly raising limits to make their cleaning programs less robust) to make their programs more cost effective.]

This is probably my last Cleaning Memo on this subject, unless something radically changes. The reason is that PDE’s are being written into draft Annex 15 of the EU GMPs. If that is the case, it will be difficult for companies to be in compliance with the EU unless they adopt that toxicity determination (it is unclear to me whether an ADE determination would be considered equivalent to a PDE determination). I have previously offered one piece of advice to the industry in terms of adopting “health-based limits” (see my December 2013 Cleaning Memo). I will offer another option. That is, consider adopting limits that are the more stringent of 0.001 of a dose and a PDE value. The reason for this is that one formulation of limits could be used for both the highly hazardous and non-highly hazardous actives. Furthermore, such a limit definition would address the product quality concerns that have been adequately addressed by the 0.001 formulation. Now I clearly expect

that for non-highly hazardous actives, the 0.001 dose criterion will be lower, and that for highly hazardous actives, the PDE value will be lower. A final word on why I would go with a PDE rather than an ADE. The reason is that ADE is defined in an industry publication, while a PDE is specified (or will be specified) by a regulatory agency. Furthermore, many other regulatory bodies still have a requirement for the dose-based calculation. Using the more stringent of the two (dose-based and PDE) will thus cause fewer compliance headaches internationally.