

## **June 2011 Addendum Where Risk-MaPP Got It Wrong**

Hopefully anybody reading this knows that I have major concerns about some sections in ISPE's Risk-MaPP document. In this special Cleaning Memo, I will try to focus on where Risk-MaPP went astray. But before I do that, I want to make sure that all understand that I agree with the basic approach of Risk-MaPP in terms of dealing with highly hazardous drug actives. Highly hazardous drug actives are not those that are "potent". While Risk-MaPP tries to get away from the use of the term "potent", that term does have a common usage in the pharmaceutical industry as an active which has a therapeutic dose of no more than 10 mg per day. Unfortunately the term has been expanded by some to include highly hazardous actives, such as those that are cytotoxic, those that have reproductive hazards, those that are mutagenic, etc. It is this latter category that should have been the primary concern of Risk-MaPP. The approach that Risk-MaPP takes for these highly hazardous actives is to recommend that limits be established based on a toxicity consideration related to the property that causes the active to be highly hazardous. For example, if the drug active has reproductive hazards, then the cleaning validation limit should not be set based on 0.001 of a therapeutic dose. Rather the limit should be set on a toxicological evaluation related to the reproductive hazard. This emphasis is not unique to Risk-MaPP. It is something that has been in my training seminars for a long time.

What appears to be the Risk-MaPP emphasis is that the health-based limit of highly hazardous actives is a better approach (and more "scientific") than the 0.001 therapeutic dose criterion. While I have seen some companies use the 0.001 dose criterion for highly hazardous actives, it is clearly not appropriate. In regulatory documents such as the PIC/S PI 006-03, when dealing with these highly hazardous actives, the recommendation is that the equipment be dedicated or that cleaning validation be done with limits for the highly hazardous active being set as non-detectable by the best available analytical technique. The specific language of the PIC/S document in 7.11.3(d) is:

For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

There are also sections in the ANVISA regulations dealing with dedicated equipment for hormones.

It is clear that regulations specifying dedicated equipment or non-detectability may be appropriate in some cases, but not all. It is for this reason that the Risk-MaPP recommendations for a toxicological evaluation of highly hazardous actives are appropriate; there may be certain situations where restrictions such as dedicated equipment are not required. Now the funny thing is that the Risk-MaPP team started off with an objective of identifying "highly hazardous drugs", but somewhere along the way it changed into dealing with cross-contamination of any drug. It leaves behind a focus on highly hazardous actives, and focuses on the use of a toxicological evaluation for all actives because the 0.001 dose criterion is judged not scientific (or is overly-restrictive for non-highly-hazardous drugs, but not restrictive enough for highly hazardous drugs). For emphasis, let me state again that Risk-MaPP goes one step further and maintains that for *all* actives (highly hazardous or not), a toxicological evaluation should be used in place of the 0.001 dose criterion.

So the first point in terms of "where Risk-MaPP got it wrong" is that the emphasis should have stayed focused on highly hazardous actives, and that for highly hazardous actives the toxicological evaluation was a better

option than an automatic requirement for either dedicated equipment or for limits based on non-detectability. Why Risk-MaPP ventured off into limits for non-highly-hazardous actives, I can only speculate. However, it was not necessary and only detracts from what should have been the primary emphasis.

Which bring us to the second point in terms of “where Risk-MaPP got it wrong”, which is in requiring a toxicological evaluation for non-highly hazardous drugs. The document includes examples of non-highly hazardous actives, and gives data on an ADE (Acceptable Daily Exposure based on a toxicological evaluation) and a daily dose. While the document does not calculate the 0.001 daily dose value, it is an easy thing to multiple the daily dose value by 0.001 to come up with a value equaling 0.001 of a dose for these non-highly hazardous actives. The result is that in some cases, the ADE value is only 1/20 (that’s 0.05) of a daily dose. Now I’m not a toxicologist, but I find it hard to believe that this is really an acceptable amount for setting limits for cleaning validation purposes. Leaving aside the toxicological issues, it is possible to take this ADE value and arrive at a possible residue level in the next product of approximately 2% (See my November 2010 Cleaning Memo). One can take that further and arrive at surface area limits for typical manufacturing situations significantly above what is generally considered visually clean. In other words, assuming that the toxicologist actually got the right answer, no one would clean equipment only to that level, which is why the criterion of 10 ppm in the next product and visually clean are also included in typical cleaning validation criteria for non-highly hazardous actives.

In answer to the question “Should equipment be as clean as the best possible method of residue detection or quantification?”, the FDA’s answer in a Human Drug CGMP Note (Second Quarter, 2001) is:

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.

The FDA list four criteria: (1) what can be reasonably achieved, (2) what is medically safe, (3) what causes no product quality concerns, and (4) what is visually clean. The Risk-MaPP document focuses only on what is medically safe. Even if 1/20 of a therapeutic dose is safe (which I find hard to believe except for an active like calcium carbonate), the other concerns are not addressed by setting limits for non-highly hazardous actives solely on an ADE.

I suspect one reason that the Risk-MaPP focuses on patient safety was that the authors were composed mostly of toxicologists and experts in occupational exposure. The only person on the team with significant

involvement in cleaning validation was Andy Walsh of Stevens Institute. In fact, in searching for cleaning validation publications for the various team members, I found very few. There have been publication by team members following the issuance of Risk-MaPP, but they sometimes demonstrate the lack of knowledge of basic cleaning validation issues. For example, in a paper in the March 2011 Contract Pharma entitled “Risk-MaPP and Multi-Use Facilities”, one of the Risk-MaPP authors states that “In essence the ADE value would replace the 1/1000th of a low clinical dose (LCD) or the 10 ppm in rinse water to calculate cleaning limits.” Well, the conventional formulation for “10 ppm” as given in the 1993 Fourman/Mullen paper and in various regulatory documents is not “10 ppm in rinse water”, but rather “10 ppm in the next manufactured product”.

A possible response of the Risk-MaPP defenders is that the Risk-MaPP document just states that limits should be set on ADE principles, and another section of the document recommends that actual residue values should be much lower than the ADE limits. For example, in Section 5.4 of Risk-MaPP is the statement that “Evaluation of the cleaning validation data is the only way to ensure that any residuals after cleaning are *as low as possible below* the health-based criteria and the risk of crosscontamination is minimized. It should be emphasized that the ADE should not be seen as a “limit” in the true sense, but as a reference point for determining the level of “risk” presented by the residue data.” [Emphasis added] In Section 7.1 of Risk-MaPP is the statement “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”. In other words, limits are set based on an ADE, but the actual residue values should be as far away as possible below those limits set on ADE values.

What concerns me about that possible response is that the Risk-MaPP authors seem to maintain that setting limits for non-highly hazardous active using 0.001 of a dose is overkill requiring extra effort (it is “overprotective”), but that if you use the ADE approach you should also have significant overkill in your program. There seems to be an inconsistency here.

I have quoted from Risk-MaPP several times. I will probably be accused of taking things out of context, so I would refer you the document itself to see if I have misrepresented what is in the Risk-MaPP document. [Of course, in one sense any critic who quotes a portion of a document is taking it “out of context”; the only way to present it “in context” is to quote the entire document. The real question is not whether I am taking things out of context, but rather whether I am accurately portraying the inconsistencies in the Risk-MaPP document.]

I want to clarify at this time what I am looking for in changes in the document. What I would like to see (and what I think would be technically correct) is to remove all references to “non-highly hazardous” actives from the document, and that the emphasis be on setting limits based on ADE principles for highly hazardous actives. That would seem like a relatively simple thing to do (in fact, if ISPE would provide me with a Word version of the document, I would propose possible revisions to them.)

Do I think this is likely to happen? In a word, “No”. Why? So far the ISPE has basically ignored me. They claim to want an open dialogue, but they are surprisingly silent, and when they do respond, I hear that either

my comments are not accurate or that I have not expressed myself adequately. A second reason why I don't think there will be a change is because of image. I suspect the ISPE might consider it an embarrassment if they had to significantly modify the Risk-MaPP document. Thirdly, there are a number of prominent pharmaceutical firms that contributed to this document. Those firms include Merck, Roche, Astra-Zeneca, J&J, GSK, and Sanofi-Aventis. I suspect it would not be allowed that scientists from those companies write a critique of the Risk-MaPP document. I think this is why I hear verbal or email support from a number of people, while I seem to be the only one raising significant objections in print.

So, let's revisit the original question, "Where Risk-MaPP got it wrong?". I have two basic answers. My first answer is that they did not limit the ADE evaluation to highly hazardous active. My second answer is that they only considered patient safety, and did not consider effects of residues on product quality.

I'll wait and see if ISPE can admit problems in the document and make appropriate changes. However, I will continue writing and publishing articles critiquing what I see as major concerns in the document.

Note: This Cleaning Memo is a special addendum as part of the June 2011 Cleaning Memo.