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The Good, the Bad and the Inexplicable of Risk-MaPP

Your mom told you the same thing my mom told me, "Always say something positive about something before you say something negative". Well, I've said enough negative things about Risk-MaPP, so it's time I said something positive (don't worry, I will also fulfill the second half of her admonition later in this Cleaning Memo). The positive thing about Risk-MaPP is that it does put the manufacture of highly hazardous actives on a sounder, risk-based footing. I believe the original mandate of the Risk-MaPP team was to deal with a risk approach for highly hazardous actives. By highly hazardous actives, I mean those actives with toxic properties like cytotoxicity, mutagenicity, genotoxicity, sensitization, teratogenicty, reproductive hazards, and the like. These are properties that are inherent in the molecular structures, but generally are not part of the desired therapeutic effect.

It has been generally recognized that setting limits for these highly hazardous actives based on a typical calculation of 0.001 of a dose being a safe level is not appropriate. The reason for that is clear – the hazard is not due to the therapeutic effect, but rather to that *other* toxic property. The response of some regulatory bodies has been to set rather stringent criteria for manufacture of these highly hazardous actives. For example, PIC/ S PI006-03 in section 7.6.2 states "Dedicated equipment should be used … for products with a high safety risk…." Furthermore, in Section 7.11.3(d) is the paragraph "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." In other words, for these highly hazardous products, if cleaning validation is done, limits for the active must be below the LOD of the best available analytical method, and if that is not possible, the manufacture of a given product should be in dedicated equipment or a dedicated facility. [Note: please don't tell me that PIC/S is not a regulatory body; I know that. But for a practical matter, its publications have the force of regulatory guidance documents.]

What Risk-MaPP does is say is something like, "Whoa, let's take a look at the science behind these types of restrictions." Using the principle that "it's the dose that makes the poison", Risk-MaPP suggests that a toxicological evaluation should be made for these highly hazardous actives based on a specific toxicological end point of concern (called the "critical effect" in Risk-MaPP). If the level for carryover of the highly hazardous active is below a safe level as determined by a toxicological evaluation (called the Acceptable Daily Exposure, or ADE), then those limits may be used in cleaning validation protocols to allow manufacture of those highly hazardous active in a multiproduct facility. Just for clarification, it is not just adequate cleaning validation using the ADE limits that should be considered in establishment of multiproduct manufacture. Other considerations, such as airborne transfer, transfer from operator actions, and transfer due to mix-ups should also be addressed. Furthermore, practices to protect workers from occupational exposure are also required.

Okay, this is the good part of Risk-MaPP, providing a consistent path forward and one supported by a risk analysis, for dealing with highly hazardous actives on multiproduct manufacturing equipment. And it is a very good approach.

Now for the bad. Risk-MaPP makes a variety of statements suggesting or stating that current methods of setting limits (such as the 0.001 of a dose criterion) are "arbitrary" and "not scientifically justified". While

using 0.001 of a dose to set limits for a highly hazardous active is certainly not scientifically (or logically) justified, it is unclear in what way that criterion is not appropriate for non-highly hazardous actives. After all, the data presented by Risk-MaPP for non-highly hazardous actives would indicate that the 0.001 of a dose criterion does provide adequate patient protection for non-highly hazardous actives. We must realize, however, when we have a "one size fits all" safety factor to convert a dose to a safe level, in some cases the level of overkill will be greater than in others (for clarification, the "one" size is a safety factor for non-highly hazardous actives).

One response to my objection is "How do you know that 0.001 of a dose is a safe level for a non-highly hazardous active unless you perform a toxicological evaluation?" Well, the answer is partly in the data presented in Risk-MaPP, where in each case where an ADE determination is done for a non-highly hazardous active, it is less stringent than a 0.001 dose calculation. The other supporting rationale for this is that the 0.001 dose criterion has been widely used for non-highly hazardous actives, and is cited in most guidance documents.

The other thing that we must realize is that when something is called "arbitrary", it sounds negative and bad (which I suspect is the intention of the RiskMaPP in calling the 0.001 dose criterion arbitrary). However, we use "arbitrary" values like this all the time in science. We consider a 3-log reduction significant for endotoxin reduction studies. Why not 2.5 logs or 3.2 logs? We consider 10^{-6} an appropriate factor for sterility assurance. Why not $2X10^{-6}$ or $8X10^{-7}$? We set criterion for %RSD at certain values like ±15% for cleaning validation methods. Why not 12% or why not 20%? In other words, the statement that the 0.001 dose criterion is "arbitrary" is a nonsensical statement just to connote the idea that it is "bad". Values such as these are chosen because we have to "draw a line in the sand" somewhere, and it is generally based on a consensus judgment of the scientific community.

Furthermore, the same argument of arbitrariness can be used for the various factors (such as factors from 1-10) that toxicologists would use to convert a NOAEL or NOEL value to an ADE value. However, that "arbitrariness" doesn't make those factors "non-scientific". I should probably point out here that the EMA in its recent "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" (20 October 2011) states that it is seeking an approach for setting exposure limits for multiproduct equipment/facilities that "should be scientifically based and aim to limit variability in deriving acceptable exposure limits thereby ensuring consistency." [emphasis added] It may be unclear exactly what is meant by this, but at least one interpretation is that EMA wants to get away from situation where adjustments factors for ADE values are strictly based on the *judgment* of the toxicologist, and that more careful delineation of rules should be established so that one toxicologist's judgment is not significantly different from another toxicologist's judgment.

And now for the inexplicable. There will be two main issues that I will cover under the category of "inexplicable". The first deals with the rationale given in Risk-MaPP for their approach to dealing with highly hazardous actives. The main argument (in Risk-MaPP) for using ADE values for highly hazardous actives is that conventional "unscientific" approaches such as 0.001 of a dose do not adequately address the hazard of those highly hazardous actives. This is true. But that's not and should not be the main thrust of arguing for ADE limits for highly hazardous actives. It is generally not the case that in the pharma industry that people have been manufacturing highly hazardous actives on non-dedicated equipment using the 0.001 of a dose carryover criterion. No, what has been generally done is to follow the recommendations in PIC/S PI006-03

about making those products on dedicated equipment or else doing cleaning validation with a criterion of non-detectable by the best available analytical technique. Amazingly, there is nothing in Risk-MaPP to suggest that the PIC/S recommendations are overkill. Yes, Risk-MaPP does talk about using ADE in cleaning validation protocols to avoid dedication, but there is nothing specifically to single out those sections in PI006-03 that seem to be the unreasonable constraints on the manufacture of highly hazardous actives. Instead, Risk-MaPP goes out of its way to criticize conventional ways of setting limits for actives that are not highly hazardous. So the inexplicable thing is this: Why did the Risk-MaPP authors not even cite the relevant chapter and verse in PIC/S document in trying to explain why the ADE approach was a better approach (in fact, PI006-03 is not referenced anywhere in the Risk-MaPP document). Instead, the Risk-MaPP authors apparently found it easier to set up a "straw man" (or "straw person") in the guise of the conventional 0.001 dose calculation for non-highly hazardous actives to show why the ADE approach is more scientific and more risk based.

The second inexplicable thing in Risk-MaPP is that one of the main rationales presented for using ADE calculations for non-highly hazardous actives is that the traditional 0.001 dose calculation results in significant overkill, causing pharma companies to have to use significant overkill in cleaning processes, thus wasting time, effort and money (without adding any value). So after arguing that cleaning limits and cleaning processes can be made *less stringent*, what do the Risk-MaPP authors do? They state that when pharmaceutical companies perform cleaning processes, they should be designed to produce residues *as low as possible*. To me this is baffling. If I believe that I can set limits for non-highly hazardous actives at a much higher level, why can't I clean to be consistently below that higher limit, as opposed to being as low as possible? Am I missing something? If a pharmaceutical company has been cleaning a product with the active limit based on 0.001 of a dose, and it is able to consistently meet that limit, then wouldn't that level be part of the "clean to as low a residue level as possible". In other words, shouldn't the company continue to clean at that level even though the ADE limit is higher by a factor of, for example, 10.

Some of you have written me to suggest (politely) that I am too hard on Risk-MaPP. My viewpoint is that the industry and ISPE have been too easy on themselves. While the majority of the Risk-MaPP document (that part that deals with limits for highly hazardous active) is basically a good document, there are some side issues that make it a flawed document. And, the Risk-MaPP authors (for the most part) and ISPE have refused to even engage me in a discussion of my critiques. I should add that there has been one Risk-MaPP author who has contacted me informally to discuss my concerns. But for the most part, it has been like talking to a wall to see what data was used to generate the examples given in the Risk-MaPP document.