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Does Risk-MaPP Offer More Patient Protection?

A key concern for cleaning validation is patient protection – to prevent consumers of drug products from getting unacceptable amounts of actives or other residues that may transfer to a product from cleaned equipment. We'll cover the question of patient protection from the use of Risk-MaPP ADE values in two situations: for the manufacture of a drug product with a highly hazardous active (HHA), and secondly for the manufacture of a drug product with a non-highly hazardous active (NHHA).

The traditional way of protecting patients from HHA's (those actives with significant toxic properties, including such properties as teratogenicity, mutagenicity, and cytotoxicity, generally unrelated to the therapeutic effect) has been to make those products in dedicated equipment/facilities. The risk from cross-contamination due to the cleaning process of that highly hazardous active into a different drug product is virtually eliminated (note that there still may be concerns about contamination from mix-ups and/or from other modes of contamination, such as airborne due to an improper air handling system).

The Risk-MaPP approach allows for setting a quantified residue limit (called an ADE, or Acceptable Daily Exposure) based on a toxicological evaluation of the target effect. This allows for the possibility that products with HHA's could be made in shared equipment with appropriate cleaning validation. Note that this includes manufacture of multiple HHA's in the same equipment as well as manufacture of HHA's and NHHA's in the same equipment. The question then is which provides better protection for the patient, the traditional approach of dedicated equipment, or the Risk-MaPP approach of cleaning validation with an ADE value used for calculating a limit for cleaning of the HHA. Note that we are just considering the difference due to cross-contamination due to residues from the cleaning process.

One approach is that patients are equally protected. Yes, with the Risk-MaPP approach there is some level of possible exposure due to residues of the active left on surfaces potentially transferring to a different product. However, those residues are at an acceptable risk level. This approach is not unlike the approach of saying that for a limit set on the 0.001 dose criterion for NHHA's, there is no difference in patient protection between actual residue levels of 0.0001 of a dose and 0.0003 of a dose (both values are below the acceptable risk level of 0.001 of a dose).

The objection to this approach is the possibility of no residue being less of a risk as compared to a low, but acceptable value as determined by the toxicological evaluation.

However, the more important issue is not the risk to patients based on successful cleaning validation protocols. The more important thing is what could happen to patients if something happened to the cleaning process after successful cleaning validation protocols. That is, does the company have appropriate practices set up for routine monitoring of each cleaning process as part of what the FDA calls "continued process verification" (in its process validation guidance)? Based on the relative risk to patients if something bad happens in the cleaning process, it is prudent to have more routine monitoring for cleaning of HHA's as compared to cleaning of NHHA's. This might include a specific analytical method for the HHA on samples from the rinse water of equipment cleaned by a CIP process. If equipment is manually cleaned, there are more concerns about consistency; it would be prudent to perform more extensive swab sampling (or other direct surface techniques)

in such cases. These concerns of doing more routine monitoring for HHA's applies even if there is included in the cleaning process a step to deactivate (by chemical degradation) the HHA.

I think a reasonable risk analysis would suggest also that if I were adopting the ADE approach so that HHA's could be made in shared equipment, then it is prudent to do more routine monitoring of the cleaning process once validation protocols are performed. This helps provide an assurance that the risk to patients is acceptable. This issue of more extensive routine monitoring for cleaning of HHA's is consistent with the relative risk (compared to cleaning of NHHA's).

What about the second situation, where I am cleaning NHHA's? Does the Risk-MaPP approach of setting limits provide more patient protection as compared to a situation where the limit is based on a 0.001 dose criterion? Well, the answer there might depend on what part of Risk-MaPP is utilized. If the appeal is only based on setting an ADE based on a toxicologist's evaluation (and if the assertions and examples in Risk-MaPP are to be believed), then significantly higher residue values might be acceptable as compared to the 0.001 dose criterion. The examples given in Risk-MaPP suggest that values of 1/20 (0.05) to 1/40 (0.025) of a dose would be acceptable for determining carryover limits of a NHHA. [I should make it clear that I am not a toxicologist, but that I am highly skeptical that numbers such as 0.025 dose for NHHA's are based on sound toxicological judgments. See my March 2012 Cleaning Memo entitled "How Are ADE's Determined for Non-Highly Hazardous Actives?" for more on this issue.]

The question then arises again for this situation, which is better for patient protection, 0.001 dose or 0.025 dose? The argument can then be made (by those who advocate the ADE approach) that if 0.025 dose is an acceptable value, then there is no significant difference in patient protection (although there is some wording in Risk-MaPP that might suggest the opposite).

The Risk-MaPP also presents a concept of "margin of safety", which it defines as the difference between the actual values achieved by a cleaning process and the acceptance limit. Assuming the cleaning process is the same (regardless of whether the limit is based on an ADE or a 0.001 dose criterion) and the same actual residue values are obtained, then by definition the margin of safety is going to be greater with the Risk-MaPP limit than with the 0.001 dose limit. Now let's be clear what that margin of safety is. That margin of safety is not related to the level of patient protection. What it is related to is the "margin of safety" of meeting the calculated limit; that is, a manufacturer is more likely (has a greater "margin of safety") to meet its acceptance limit if the acceptance limit is higher.

I said the issue for NHHA's depends on what section of Risk-MaPP is applied. While most of the publications dealing with Risk-MaPP promote the ADE-based limit, there is another section of Risk-MaPP (in Section 5.4) that states that manufacturers should actually achieve values "as low as possible" below the limit based on an ADE value. This section is not discussed prominently by various scientists who promote Risk-MaPP. However, if "as low as possible" means as low as a company is currently achieving using the 0.001 of a dose criterion, then it is clear that with this approach the level of protection to the patient is the same (even though the "margin of safety", as defined in Risk-MaPP, is greater with the ADE limit.)

Where does that leave us? First, let's all admit that the "margin of safety" concept as used in Risk-MaPP is not

offering additional patient protection. As defined in Risk-MaPP, this concept strictly relates to the relative “safety” of a manufacturer meeting its acceptance limit (make the limit higher, and of course it is easier to meet that limit).

This discussion is centered on the concept of patient protection under the traditional approach for limits and the Risk-MaPP approach to limits. Note that I still have significant concerns about how limits are set in the ADE approach, specifically around what values are used for the uncertainty factor as applied to a NOAEL (for both HHA’s and NHHA’s), as well as how a NOAEL is determined for NHHA’s. The December 2012 EMA draft publication “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities” did some to help this situation by using the ICH Q3C PDE (Permissible Daily Exposure) approach for residual solvents, in which for some cases there are guidelines for the selection of modifying factors. Whereas the EMA concept paper of October 2011 (“Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities”) started that one objective was to “limit variability” for ADE values (note that the EMA did not use the term ADE), the December 2012 EMA publication does not go far enough to deal with the issue of limiting variability of toxicological evaluations.