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A Way Forward for "Health-based" Limits

Last month I critiqued the EMA document on "dedicated" facilities, which takes an approach not unlike Risk-MaPP to set limits for all actives (drug substances or APIs) for cleaning validation purposes based on a comprehensive toxicological evaluation. As most of you know I am not a big fan of such an approach for all actives. I believe that the current criterion which has been used for the past 20 years is more than adequate to protect patients and maintain product quality for actives where the primary safety concern is the therapeutic effect. That criterion, cited in almost every regulatory guidance, is based on a safe level of no more than 0.001 of a minimum therapeutic dose of an active in a maximum therapeutic dose of the subsequent drug product (for now, I will limit my discussion to drug product cleaning validation). While both Risk-MaPP and the EMA point out that such a level is not protective enough for "certain" drug actives, what they fail to point out is that the criterion of 0.001 of a minimum dose is not considered the appropriate criterion for those "certain" drug that have highly hazardous properties such as reproductive hazards, mutagenicity, carcinogenicity, genotoxicity, and sensitization.

The approach that has been used for those drug products with are highly hazardous has been either to make the drug products in dedicated equipment (and/or facilities), or to provide cleaning validation with limits set at the limit of detection of the best available analytical technique. This is explicit in the PIC/S PI-003 recommendations on cleaning validation. As a sidenote, I have generally added a caveat to the second criterion (non-detectability), and the caveat has been that a toxicological evaluation should be done to confirm that a value at the limit of detection is a safe level (just in case the "best available" analytical technique is not good enough). In fact, as I have indicated in last month's Cleaning Memo, the initial impetus of both the Risk-MaPP and EMA groups was to address the question of setting appropriate limits for such highly hazardous actives so that they could be made in non-dedicated equipment/facilities.

So, where do I think we should go? First of all, I am in favor of saying we should have health-based limits. However, as I have suggested, the 0.001 dose criterion is adequate for non-highly hazardous actives, and can be considered a "heath-based" limit. What can be done is to require for any active an evaluation by a toxicologist to determine that either (a) the therapeutic effect is the primary concern, or (b) there are additional safety concerns that require additional evaluation. In other words, if in the toxicologist's opinion, the primary concern is the therapeutic effect, then that active falls into a category where the 0.001 dose criterion may be used. Otherwise there should be a more detailed toxicological evaluation. Note that this detailed toxicological evaluation may be an extensive evaluation such as in the Risk-MaPP ADE or the EMA PDE. It may also be an appeal to the TTC concept for actives with limited toxicological data (such as clinical trial materials).

If for whatever reason the firm could, but does not want to, utilize the 0.001 criterion for actives where the primary concern is the therapeutic effect, then that firm could perform a toxicological evaluation to set a PDE or ADE value that would be less stringent than a limit based on the 0.001 dose criterion. The reasons for this might be varied. Some companies might find that the available analytical technique is not able to accurately measure residues at the calculated level. Therefore, an ADE or PDE will result in a higher limit, which may be measureable by the analytical technique.

Some consultants urge the adoption on ADE values for non-highly hazardous actives because cleaning could

be less stringent and the firm might save money. This may be true, but if it is true, let the firms decide whether they want to spend the money on the ADE determinations and the costs related to process changes, but possibly save money on cleaning processes, or whether it is more cost effective to continue with their existing cleaning limits and cleaning processes. If the financial issue is the driving force, then let the "free market" decide which approach is better. That said, is it really an option to change a cleaning process, which a firm has demonstrated that it can consistently meet for the last 10 or 20 years, to a less stringent cleaning process.

One additional concern about wholesale conversion to ADE or PDE values is that the effect on the patient is only one of the reasons for having a relatively low carryover. There may be other reasons, such as possible effects on stability profile of a subsequently manufactured drug product, or possible effects on the bioavailability of the subsequently manufactured drug product. This is one reason that even with the 0.001 dose criterion, a "default" limit of 10 ppm of the cleaned active in the next drug product is utilized if that default value produces a limit lower than that determined by the 0.001 dose criterion.

If the toxicologist's opinion is that there are significant effects in addition to the therapeutic effect, then a comprehensive toxicological evaluation should be done, along the lines of the Risk-MaPP's ADE or the EMA's PDE.

Now, this is just one of the criteria for a true "risk-based" approach as to whether highly hazardous actives can be manufactured in shared equipment/facilities. Other concerns, including those brought up by Risk-MaPP, are:

1. Are there adequate procedures in place to prevent mix-ups?

2. Are there adequate procedures in place to deal with potential mechanical transfer from environmental surfaces and operators?

3. Are there adequate procedures in place to deal with potential airborne transfer?

4. Are there adequate routine monitoring techniques to detect excursions (deviations) in carrying out the cleaning process such that those excursions could be readily detected?

The last point is primarily a concern for manual cleaning processes. For automated cleaning processes, such as CIP cleaning, there are generally adequate routine monitoring data (times, temperatures, pressures, flow, cleaning agent concentration, final rinse conductivity) to detect problems with execution of the cleaning cycle. With manual cleaning, that may not necessarily be the case. Note that I omitted the routine monitoring technique of visual inspection; the reason is that with the low limits likely with highly hazardous actives, it is likely that the active may be present at unacceptable levels and still be visually clean. Of course, for manual cleaning, this issue may be addressed by performing cleaning verification rather then cleaning validation. In cleaning verification, the acceptability of the cleaning process is determined by appropriate sampling and measurement of residues of the active for each and every cleaning event. This reiterates my belief that determination of acceptability of processing highly hazardous actives in shared equipment/facilities is not just a toxicological evaluation, but a more holistic approach to protection of patients.

One final comment on moving forward. As much as practical, the ADE and/or PDE values should be established on an industry consensus, rather than determination by one toxicologist or one toxicology group/