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More on ISPE's Risk-MaPP

As stated in my November 2010 Cleaning Memo, I have serious problems with the ISPE document "Risk-Based Manufacture of Pharmaceutical Products" (Risk-MaPP). My primary objection is not related to using a health-based limit for highly hazardous actives; that is something I also teach. My primary objection is to "collateral" statements made in the document related to how cleaning validation limits have been set in the past (and in the present). Those statements to the effect that current methods of setting limits for actives are "nonscientific" and arbitrary lack support, and are misleading and wrong.

Furthermore, the effort of the Risk-MaPP team should not have been to critique current methods of setting limits for actives in general, but they should have focused their critique on current methods of setting limits for "highly hazardous" actives. Current methods for highly hazardous actives are best summarized by the PIC/S PI 06-003 recommendations, in which case those actives should be made in dedicated equipment/ facilities or cleaning validation should be performed with limits set as non-detectable by the best available analytical technique.

In addition to this major concern, there are other concerns that I have about the document. Some are simple issues and some more complex. Below is a discussion of some of those issues

Use of TOC as an analytical technique

In section 7.2 is the statement "Recovery studies utilizing Total Organic Carbon (TOC) analysis can be performed with the final determination of the suitability of the existing cleaning procedures augmented by TOC analysis after the initial cleaning". I seriously doubt whether TOC is an appropriate analytical technique for measuring residues of highly hazardous actives. The reason is that limits for such highly hazardous actives, based on "health-based calculations", will generally be extremely low. After all, isn't one of the main points in the Risk-MaPP document that such limits (for highly hazardous actives) are generally going to be well below the 0.001 dose criterion? If that is the case, TOC will generally not be useful because, as a practical matter, the quantitation limit of TOC in a cleaning validation protocol will be 100 ppb or 200 ppb at the best (dues to the fact that you always have to subtract out the background or blank). As a practical matter, a specific analytical technique, such as HPLC or UPLC, will most likely be preferred for measuring these highly hazardous actives.

Furthermore, TOC as an analytical method represents a worst-case in that it picks up all sources of organic carbon (including excipients and cleaning agents). If I am dealing with a highly hazardous active, then I should prefer to know as accurately as possible how much of the that active is present. Extraneous carbon from other sources may provide a misleading (and perhaps) unacceptable value. [Note: Please don't get me wrong here; TOC may be a perfectly acceptable analytical technique in other situations, but for determining acceptable levels of highly hazardous actives in a cleaning validation protocol, it probably is not acceptable.]

Risk for cleaning agents

In section 1.3 is a statement that a "scientifically based risk assessment should be performed on the cleaning agent, which should pose the least risk to patient safety." Is it really appropriate to state that the risk from the cleaning agent should be the "least" risk? Isn't the whole point of Risk-MaPP that risks

should be acceptable risks? If I were to choose cleaning agents with the least patient risk, I would probably choose water alone. Clearly this statement in Risk-MaPP is an inappropriate statement.

Route of exposure considerations

In section 5.3 is the statement "The ADE represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime." Does this mean that an ADE is applicable for any route of exposure? Wouldn't a better statement be "The ADE represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by a specified route of exposure, at or below this dose every day for a lifetime." If I base an ADE on an oral route, and the next product is given by an oral route, I have determined an acceptable ADE for that situation. If the ADE for a active is established based on an oral route, and the next product is given as an injectable (as might be the case for API manufacture), then I'm not sure (but as a non-toxicologist, I doubt) that I should automatically assume that an ADE based on data from an oral route is also applicable for an injectable route. This issue is addressed somewhat in section 5.5 with the statement that "Adjustments may be necessary to address route-to-route extrapolation, even if the same critical effect is used. For example, an OEL derived from the ADE may need to be adjusted for differences in bioavailability between the route used to identify the critical effect (e.g., oral) and the anticipated route of exposure (e.g., inhalation)." This statement would suggest that a better wording for section 5.3 would be specifying "by a specified route of exposure". [Note that this concern about routes of exposure is also something that is an issue in the TTC (Threshold of Toxicological Concern) approach in the EMEA document on genotoxic impurities, something I have written on previously.]

LD50 data for limits

In section 5.4.1 is a discussion of using a fraction of the LD_{50} data for setting limits. Unfortunately two different factors are used for converting an LD_{50} value to a safe level. Those values are 0.5×10^{-4} (in the fourth paragraph in this section) and 5×10^{-4} (in the fifth paragraph). This is probably a result of inadequate proofreading. However, the latter value (the less stringent value by a factor of 10) is used to illustrate (in the example of morphine sulfate) why LD_{50} is inadequate. However, based on my experience most companies will use a factor of 10^{-5} or 10^{-6}. Using the less conservative value of 10^{-5} results in a calculated safe value of morphine sulfate of 0.27 mg, significantly less than the 14 mg calculated in Risk-MaPP. Now, that is still more than 0.001 of a low dose of morphine sulfate. But, this just illustrates that if a dose is known for a product, a better approach is a calculation based on a fraction of the dose, as compared to a calculation based on a fraction of the LD_{50}. In other words, the appropriate use of an LD_{50} calculation is if there is no dosing information for materials that are not actives.

Again, it seems to me easy from a scientific point of view to edit the Risk-MaPP document and take out the "extraneous" comments about cleaning validation in general, and focus only on cleaning validation for highly hazardous actives. I await the results of the independent review of the Risk-MaPP document to address my concerns as well as the concerns of others.