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A Critique of Cleaning Validation Issues in ISPE's RiskMaPP

ISPE has issued the document "Risk-Based Manufacture of Pharmaceutical Products" (Volume 7 of their Baseline Guides, September 2010). As I understand it, the effort to write this guide started with concerns over regulatory bodies tending to require dedicated equipment and/or facilities for certain highly hazardous drug actives, such as potent drugs, hormones, genotoxic compounds, and cytotoxic compounds. The major rationale for this ISPE guide was to counteract this approach by providing for an analysis of safety/toxicity data of these "highly hazardous" drug actives to determine a level that might be a negligible (but acceptable) risk in other drug products (thus allowing, with appropriate controls, the ability to manufacture in non-dedicated equipment/facilities).

This effort involved setting limits for these "highly hazardous" actives based on what is called a "health based limit", that is, a limit based on a toxicological evaluation of the relevant safety data (typically a No Observable Adverse Effect Level or NOAEL). This health-based limit is called ADE, or Acceptable Daily Exposure, in the ISPE guide. This effort for setting limits for cleaning purposes for these highly hazardous actives is to be applauded.

Unfortunately, the guide goes beyond that basic focus to discuss cleaning validation in general, and to imply that this method for cleaning validation is appropriate in all cases, including what I will call "conventional" actives that don't have these highly hazardous concerns. Specifically, the guide states that current methods of setting limits such as "1/1,000th of the lowest clinical dose or 10 ppm in a batch" are "arbitrary limits". (page 42) Furthermore, "the use of arbitrary non-health-based limits is not scientifically justified" if data exists to calculate a health-based limit. (page 45) Additionally, "Another non-science-based approach for setting cleaning limits is the use of the '10 ppm' specification" (page 46), and "if default factors of 10 [ppm] are used arbitrarily to set allowable residue limits, they may be lower than they need to be from a health perspective" (page 45). It further states that using such values ignores toxicological data and can be "too restrictive or not sufficiently restrictive". (page 42)

In other words, according to this guide, current methods of setting limits for cleaning validation purposes (which have been used for at least the last 17 years) are "arbitrary" and "not science-based". I do not find those assertions to be factually correct, nor is there anything in the guide to support those assertions.

Part of the issue is that the ISPE guide sets up a "straw man" in terms of how limits are currently set. Criteria such as 1/1,000th dose or 10 ppm are critiqued individually. As used by manufacturers, the current method (note that this is what I consider the best approach; I am not suggesting that all pharmaceutical companies use this approach) involves setting limits based on the most stringent of these three criteria:

- 1/1,000th of a dose of an active in a dose of the next drug product
- 10 ppm of the active in a dose of the next drug product
- Equipment surfaces are visually clean

In other words, these are not considered independently. Now, this works well for most drug actives. Does it work well for a teratogenic drug active? Of course not, and nobody with any significant experience in cleaning

validation would state that limits are set on 1/1,000th of a dose for a teratogenic drug active. The relevant safety concern for the teratogenic drug active is not the pharmacologic effect; therefore the cleaning validation residue level is not set based on a fraction of the drug dosage. The general approach based on the PIC/S recommendations for cleaning validation is that the equipment either be dedicated or that a residue level be established as “non-detectable” by the best available analytical technique. [Note here that my recommendation for this “non-detectable” requirement has been to have a toxicologist confirm that the non-detectable level is an acceptable risk; this addresses “best available techniques” that aren’t good enough.]

It is this latter concern (of dedicating equipment or establishing limits as non-detectable) that I would think that the ISPE guide would want to counteract by offering the idea of a toxicological evaluation to set an acceptable limit. I don’t see the value (or rationale) for the ISPE guide stating that current methods of setting limits are “arbitrary” and “non-scientific”.

Some of the statements made in the ISPE guide about the current way of setting are true. If limits are set at 1/1,000th of a dose, with some conventional drug actives the level of protection will be more than is necessarily required from a patient safety concern. This is to be expected with a “one size fits all” approach (but don’t get me wrong; this one size fits all doesn’t apply to active where the hazard is not related to the therapeutic effect). However, this does not mean that limits are set in a non-scientific way.

In the training session introducing the guide, one of the speakers stated that there is a degree of judgment in establishing appropriate factors for calculating health-based limits. Does that mean that the limits are non-scientific? Of course not! What it means is that different toxicologists may come up with different numbers for the health-based limits, one being more stringent than the other. An analogous situation exists with the 1/1,000th calculation; it is more stringent than it needs to be for some actives, but for all conventional actives it provides a safe limit.

If the health-based criterion is applied to conventional actives, the acceptable levels given in some examples in the ISPE guide are extremely high, such that there might be other concerns other than patient safety. Those concerns might include stability, production efficiency, and interference with the bioavailability of the next active. For example, an ADE of an unspecified NSAID active is given as 40 mg/day. A daily dose of this NSAID is given as 800 mg. (page 101) The implication here is that 1/20th of the daily dose is a safe level to have in a daily dose of a subsequent product. If this ADE were present in a subsequently manufactured drug product involving 250 mg tablets given eight tablets per day, the acceptable concentration of that active in that next product would be 20,000 ppm (2%). Would anyone really consider allowing any drug active to be in a subsequent drug product at that level? It just wouldn’t be CGMP. In case you might think I am overstating the case, there is another example given for an “antisense” active, where the ADE is 0.5 mg/day and the daily dose is 10 mg. (page 102) The implication here is 1/20th of a dose of the antisense active is a safe level. Again, this might be safe from a toxicologist viewpoint, but I doubt if most companies would (or should) allow or permit such levels.

Furthermore, at those high levels, it is likely that residue on equipment surfaces (those that could be observed) would be visually dirty. Does it make sense to set limits to allow such a situation (unless for conventional

drugs we really want to only require “visually clean” for surfaces which are readily observable)?

The reply to my objection might be given that I have not read the entire document, and that just because these are limits, it doesn't mean that manufacturers want to allow residue nearing those levels. The concept of “Margin of Safety” is presented in the ISPE document (page 42). The “Margin of Safety” is not to be confused with so-called “safety factors” that are used in setting limits based on a fraction of the dose. The “Margin of Safety”, as defined in the ISPE guide, is the difference or “distance” between the established limit and the actual residue data obtained in a cleaning validation protocol. The argument might be made that while the safe limit (as determined by the ADE) is relatively high, the actual data is much below that ADE-based limit, so the situations I discussed are not likely to happen.

My response to that reply is that those situations are allowed if the limit is that high. Yes, under either ADE limits or 1/1,000th limits, I would like my residue data in protocols to be significantly below my established limit. In other words, I want a robust cleaning process. But this is where the ISPE guide and I differ. The ISPE guide states 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...” [emphasis added] (page 43) It sounds like the guide, while arguing that limits in some cases are more stringent than they need to be, suggests that manufacturers should still clean to residue levels as low as possible. So that you don't think I am taking this out of context, the guide also states that “Efforts should be made to ensure that cleaning procedures provide as large a safety margin as possible.” (page 45) In other words, the guide seems to be saying that for conventional actives, limits can be looser (that is, higher), but you should still clean to the same low level so that the “Margin of Safety” is as great as possible.

There are other concerns I have about the document. However, the main concern I have is the way the document inappropriately “trashes” current methods of setting limits as arbitrary and non-scientific. I think an easy fix could be made to the document by revising it to what I think is its original focus. That is, take out all general references to how limits are set, and focus on the main issue, which is that health-based limits are appropriate for dealing with drug actives that have considerable hazard concerns unrelated to the therapeutic effect. Those actives include hormones, potent steroids, and actives that are genotoxic, cytotoxic, or have reproductive hazards. The rationale for this suggested change is that the purpose of the ISPE guide seems to be having a science-based method for avoiding manufacture of such compounds in dedicated facilities/equipment. Supposedly there is in development another ISPE guide on cleaning validation. It would seem that that cleaning validation guide should be the one to specifically address the issue of whether limits for “conventional” actives should be changed.

Some of you might want to know why I am voicing my objections now. After all, the guide has been in development for five years. In the fall of 2007, I contacted ISPE about obtaining the draft document to provide

comments, but found out that the comment period had just closed. However, I voiced my objections (essentially the same objections expressed here) back in 2008. These concerns were not specifically about the draft of the document at that time, but were based on presentations made by Andy Walsh (a RiskMaPP task force member) at an ISPE meeting in Washington DC in the summer of 2008. I gave a webinar entitled “Are we Setting Limits Correctly?” in August 2008 and wrote a Cleaning Memo with the same title in October 2008. However, whatever happened in the past, it should be clear that the published guide needs correction.

For clarification, I am not concerned about the guide’s approach to setting limits for highly hazardous actives. The approach of a toxicological evaluation based on those hazards is appropriate. If those evaluations result in making products in non-dedicated facilities/equipment, then that is a needed step forward. Note that this approach is consistent with the December 2009 EMA document EMA/INS/GMP/809387/2009, “Update on revision of Chapters 3 and 5 of the GMP Guide: Dedicated facilities”.