Cleaning Memo for January 2018
A Look at the Revised Risk-MaPP

In 2017 ISPE released a revised and updated version of its 2010 Risk-MaPP document. The reasons for the revisions given in the document's preface and in section 1.3 were to address new EU GMP requirements, the EMA guideline on shared facilities, and ICH M7, as well as to provide "additional information for cleaning, HVAC, and examples to assist the reader". This Cleaning Memo will focus exclusively on the changes (and the lack of changes) related to setting limits for cleaning validation purposes.

Some partially "good" news

Unlike the 2010 Risk-MaPP, the 2017 document does not call the 0.001 dose criterion "not science-based". It merely refers to the dose criterion as the "traditional" approach (reflecting the same terminology given by the EMA in its recent draft Q&A). However, it still is not the "preferred" strategy (section 6.3.2.3). (Note: I guess it is possible to interpret this as meaning it is an acceptable strategy, just not preferred. However, that is not explicit in the updated document. If ISPE views the dose criterion as an acceptable, but not preferred strategy, then it would be helpful if it clearly stated that it is only an acceptable strategy for non-highly hazardous actives, much like what is stated in the draft EMA Q&A.) That is a step in the right direction. That said, the revised Risk-MaPP still refers to the ADE approach as the "science-based" approach, in contrast to the traditional approach. What I don't quite seem to understand is why the "traditional" approach is not considered a science-based approach. After all, in the draft EMA Q&A the traditional approach is considered a HBEL for products that are not highly hazardous. Are we to conclude that the EMA is advocating something that is not science-based? Finally, in discussing the traditional approach, ISPE fails to clarify that the traditional approach utilizes the *more stringent* of the 0.001 dose criterion and 10 ppm in the next product. Note that this failure to *fully* describe the traditional approach is also present in EMA draft Q&A. It baffles me why so fundamental a fact is not accurately portrayed.

In either this revised Risk-MaPP or in the 2010 edition, there is no reason given to explain what about the dose criterion prevents it from being called "science-based". I suspect that the objection to the dose criterion is that it is not as specific to the variations that are present in the different drug products. In this sense, a detailed calculation like given for ADEs and PDEs has the appearance of being more "scientific" as compared to the one size fits all approach with the dose-based calculation. (Note that when I refer to the traditional dose calculation as being "one size fits all", I mean that the 0.001 dose and 10 ppm criterion is applicable to all products where the primary safety/health concern is the therapeutic effect.)

It seems inconsistent for the Risk-MaPP authors to be concerned about a "one size fits all" approach for cleaning limits, but apparently welcomes it in toxicological evaluations. For example, in its Table 5.2 on adjustment factors both Risk-MaPP and the EMA list a factor of 10 as the intraspecies adjustment factor, a "one size fits all" factor. Is it not possible that the intraspecies factor might vary based on the chemical species, the nature

of the critical effect, and the nature of the relevant population or sub-population? Now, as has pointed out to me, I am not a toxicologist, but I assume that this adjustment factor is appropriate based on the judgment of qualified toxicologists. But, my point is that this is *not conceptually different* from the 0.001 dose criteria being applicable to a certain class of products (namely those that where the primary safety concern is the therapeutic effect).

Another example of this inconsistency is the reference to the Dolan *et al* journal article (section 5.3.5.3) for setting limits with limited tox data. That article lists a three tiered approach to selecting ADE values (1 µg for products likely to be carcinogens, 10 µg for products likely to be toxic or potent, and 100 µg for others not in the first two categories). Obviously, the Risk-MaPP authors don't consider this to be unscientific and see it as an acceptable strategy.

A second reason that the dose criterion is not preferred for non-highly hazardous products may be that in most cases (probably in almost all cases for non-highly hazardous products) the use of an ADE results in a higher (that is, *less stringent*) limit. This revolves around what Risk-MaPP calls the "Margin of Safety" and the ability to set higher limits. This issue will be discussed in more detail in next month's Cleaning Memo. However, it should be noted (and should be common sense in setting cleaning validation limits) that patient safety is not the sole criterion for setting limits. Other effects on product quality should also be considered (see the December 2017 Cleaning Memo for more on that issue). ISPE seems to ignore other quality concerns in its statement in section 6.3.2.3 that the "only criteria necessary for a robust cleaning process are the health-based, ADE derived limit, a validated analytical method with a sensitivity below the acceptance limit, that is visually clean."

What's new or different
Sections 3.2.1.4 and 6.3.2.2 discuss compounds that are denatured, degraded and/or deactivated during the cleaning process. In this situation an ADE should be developed for the resultant residues.

In section 5.2 is a discussion of using OEL and OEB values to estimate ADE values, mainly for the purpose of "prioritization in risk assessments".

In section 5.3.1 is a description of a "qualified toxicologist". Note that this was a question side-stepped to a large extent by the EMA in question #9 in its draft Q&A document.

In section 5.3.5 the use of the term "uncertainty factors" in ADE calculations has been modified in favor of calling them "adjustment factors". Table 5.2 gives a comparison of adjustment factors in Risk-MaPP and in the 2014 EMA guidance

In section 5.3.5 is that statement "Ideally, the ADE is based on the route that it will be applied to in the evaluation." This issue is further addressed in section 5.3.5.1, and seems to be saying that if only one route (such as oral) is probable, then ADE values could be adjusted but should be done in a "later step in the risk assessment process". This sounds like it might mean that ADEs can be developed as route specific, but that a formal ADE

by any/all routes of administration should be first determined, and then at a later step an adjustment can be made to consider only one route. That is, if the cleaning validation evaluation (I assume that is what the word "evaluation" applies to) is for an oral route, then an oral ADE can be developed. This emphasis on the primacy of "any/all" routes appears to be based on the description of an ADE in section 2.5.1 as well as the definition of an ADE in section 16.2, which refers to a value that is adequately protective by "any route" and by "all routes".

Section 5.3.5.5 discusses beta lactams. While pointing out that most regulatory agencies have strict requirements for making these in dedicated facilities, ISPE seems to suggest that in jurisdictions where beta lactams can be "co-manufactured" with other products, ADE values should be developed for risk assessments and for setting limits.

Section 5.5 outlines a format for documenting the determination of an ADE.

Section 6.3.2.1 refers to the fact that swab limits based on an ADE may "actually permit the equipment to look dirty ... so therefore the acceptance criteria would be set to visually clean". It is unclear (at least to me) whether the intent here is that a high calculated acceptance limit means that a visual clean criterion could be the *only* criterion for a cleaning validation protocol. Section 6.3.2.3 refers to the use of ADE limits allowing for visual detection for monitoring as part of routine operations (after completing protocols). Note that visually clean is also discussed in section 6.3.2.10.

Section 6.3.2.1 seems to call for establishing microbial limits based on a "very similar procedure" as done for chemical species. No further elaboration or detail is given on how this is actually done.

Sections 6.3.2.7, 6.3.2.8 and 6.3.2.9 deal in more detail (as compared to the 2010 version) with introducing new products and small scale cleanability studies.

Sections 6.5.2 and 6.5.3 deal with addressing non-product contact surfaces. An example is given of performing a risk assessment by sampling walls and determining the worst case potential transfer to the next product. Unfortunately, the example given addresses contamination *only* from room walls, and does not address the *cumulative* potential transfer of residues from walls *and* from equipment product contact surfaces.

The comments here do not cover all the changes relating to limits, but cover the significant ones for my purposes except for a discussion of the "Margin of Safety" issue, which will be covered in more detail next month.

While I believe the 2017 Risk-MaPP (like the 2010 original document) is *deeply* flawed, for those wanting to implement it for cleaning validation limits, I highly recommend that it be carefully reviewed (as well as reviewing critiques of it) to address its possible implementation.