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Another Critique of Risk-MaPP

As many of you know, I like Risk-MaPP when it discusses using a toxicological evaluation to deal with highly hazardous actives (those with properties such as reproductive hazards, genotoxicity, etc.). It is a sound approach to use as an alternative to dedicating equipment, or to performing cleaning validation with limits of non-detectability, for such actives. I still have some questions, however, as to how those toxicological evaluations are done to assure accuracy and consistency of the ADE (Acceptable Daily Exposure) values.

I also see value in other situations for non-highly hazardous actives. One example is where the active is degraded during cleaning (and this includes biotech manufacture), and the residues left after cleaning are degradants of the active. In this case, it does seem reasonable to perform a toxicological evaluation of the degradants and set limits for cleaning validation based on those values. A second situation involves cases where I have set limits based on a typical 0.001 dose calculation, and my analytical method cannot measure at the corresponding level of active found in a swab or rinse sample. In that case, I might do an ADE determination on the assumption that the ADE value would be much higher than the limit based on the 0.001 dose calculation (and therefore my analytical method might be adequate).

That is just an introduction to delve into another publication by two of the authors of Risk-MaPP. That publication is "The Use of Acceptable Daily Exposures (ADEs) for Managing the Risk of Cross Contamination in Pharmaceutical Manufacturing", by Stephanie Wilkins and Julian Wilkins, published in the July/August 2012 Pharmaceutical Engineering. That article repeats a number of assertions similar to what is in Risk-MaPP, but also adds some interesting twists. Furthermore, while the authors present positives about the ADE approach, they fail to address any of the critiques of the Risk-MaPP approach, including the numerous ones I have made.

One of the main differences about this new article is that, even though the original purpose of Risk-MaPP was to address highly hazardous actives, there is no mention of that term, or anything relating to actives with highly hazardous properties. In other words, the aim of this article appears to be to present ADEs as the only way to set limits for pharmaceutical cleaning validation. The authors still make statements about 0.001 of a dose being non-scientific. For example, this is one statement: "Using a safety factor of 1000 has not been scientifically proven to equate to a no adverse level for all compounds." And guess what? That statement is true!! But, the 0.001 dose criterion, as it is currently used, is not appropriate for all compounds. It is well recognized in the literature (including many of my publications, and my training slides for the FDA) that the 0.001 dose criterion is not applicable to highly hazardous actives where the major safety concern is an effect other than the therapeutic effect.

The article also has some misleading examples. For example, there is a statement regarding the temptation to set limits based on the most stringent of ADE, a 0.001 therapeutic dose, 10 ppm in the rinse water, and LD50. The authors state that this will not lead to "safer, better cleaning" (that is, if one uses the 0.001 dose criterion rather than the ADE), but to increased failures. First, the "10 ppm" criterion as used by the industry generally refers to 10 ppm in the next product, not 10 ppm in rinse water. Secondly, use of the ADE for non-highly hazardous actives will result in higher limits. The authors consider this an advantage because of a peculiar definition (also given in Risk-MaPP) of what a "margin of safety" is. However, with ADE-based limits for non-highly hazardous actives being more than 10 times higher (using the examples given in Risk-MaPP), it is

unclear where patient safety is improved. The only improved "margin of safety" is that a manufacturer is more likely to pass protocols with the higher limits.

Which brings me to the next point. The authors state "In all cases where the ADE value is higher than the more traditional methods, the visual detection threshold will actually override and become the acceptance limit." While not explicitly stated by the authors, the "in all cases" seems to refer to non-highly hazardous actives. That is, for these cases, the ADE-based limit will be higher than what is visually clean. This consequence of using ADE-based limits is something that is pointed out in my Cleaning Memo Addendum of June 2011. While the authors state that "visually clean would become the overriding acceptance value", it is unclear whether the authors believe that visually clean is only to be used for routine monitoring of a process after validation runs are completed, or whether they believe visually clean can be the acceptance criterion in the validation protocol itself.

My last point is that the authors selectively quote regulatory documents to support the ADE approach. For example, they quote the EMA 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" as follows:

> "Currently toxicological data are not always used in establishing limits for cross-contamination. In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall Quality Risk Management in shared facilities."

It seems like this means the EMA likes the Risk-MaPP approach. However, following that statement is the following statement in the section on "Recommendations":

> "The Safety Working Party recommends drafting new guidance on toxicological assessment to be used in the risk identification stage of the Quality Risk Management process in determining whether a medicinal product should be manufactured in dedicated facilities. More specifically the agreed approach should be scientifically based and aim to limit variability in deriving acceptable exposure limits thereby ensuring consistency."

As I read this, the EMA seems to be concerned about highly hazardous actives (thus, the statement about whether products should be manufactured in dedicated facilities). Furthermore, even though this EMA document came out about a year after the formal launch of Risk-MaPP, apparently the Risk-MaPP document does not provide adequate detail to "limit variability in deriving acceptance exposure limits", and thus is not "ensuring consistency". Note that I was present at the Risk-MaPP launch in Washington DC in October 2010. On the final day of that meeting, a representative from a European regulatory agency made a comment to the effect that he was not entirely comfortable with the manner in which ADEs are determined in Risk-MaPP (if ISPE has a recording of that meeting, that comment can be confirmed). The level of professional judgment allowed by the Risk-MaPP ADE determination is a concern that I have previously expressed.

Some of you might be concerned that my critiques are damaging the reputation of Risk-MaPP and the ADE approach. My opinion is different. I am out to position Risk-MaPP for applications where fits, such as for highly hazardous actives. My opinion is that there is a core of scientists who are Risk-MaPP advocates, who choose not to engage in discussions or debates about Risk-MaPP, and who are thus giving Risk-MaPP a bad