

**November 2013**  
**Comments on the EMA Guideline on Dedicated Facilities**

I am writing this Cleaning Memo with some hesitation, because the EMA draft guideline is currently undergoing a review and probable revision. Just in case (my pessimism is coming through), but also because it has some very good aspects (as compared to ISPE's Risk-MaPP), I am venturing with this critique.

First, here are some of the good things about the EMA draft guideline.

1. The EMA (in this document at least) has avoided calling current methods of setting limits for actives that are not highly hazardous (the 0.001 dose criterion) "arbitrary" and "unscientific".
2. The way limits are set based on a PDE are subject to less subjectivity as compared to the Risk-MaPP ADE. In specific, while there is some degree of judgment in selecting the various F factors (applied to adjust a NOEL to a safe level), there is no term like MF in Risk-MaPP's ADE which is a "Modifying Factor" used "if there is a need to address residual uncertainties not covered by the other factors".
3. The EMA draft guideline includes a discussion of determining a PDE for a substance where the main concern is the "pharmacodynamic effect" (I understand this to mean the drug's therapeutic effect). For such actives, the NOEL is set at the lowest clinical dose that is "non-efficacious". For clarification, the NOEL term in this case is not a safe level for the subsequent product; the various F factors still have to be applied to that NOEL value to produce a PDE. However, I would assume that since the NOEL is based on human clinical data for this situation, the factor related to interspecies variability is minimized.
4. The EMA includes the TTC (Threshold of Toxicological Concern) concept for actives where there is no established threshold value (I understand the threshold value to mean a PDE based on a NOEL). I'll comment later on the TTC value the EMA selected.
5. The EMA recommends that a TTC value be established for reproductive hazards for application to active where there is inadequate data to establish a NOEL for this critical effect. They recommend that this be done by an industry group based on substances with known reproductive hazards, and that the results be published.

Okay, that's the good stuff, and is a significant advancement over Risk-MaPP. Here are my concerns about the EMA draft guidance.

1. Like the Risk-MaPP group, EMA started off in 2005 with an objective of addressing setting residue limits for "certain" highly hazardous actives, so that manufacturers could decide whether appropriate controls could be put into place such that the substances should be made in dedicated facilities/equipment, or could be made in multi-product equipment/facilities. However, like Risk-MaPP somehow that effort morphed in an approach to set residue limits for all actives (those that were highly hazardous and those that were not). This does not reflect the fact (and I believe it to be a fact) that for conventional actives (those that are not highly hazardous, or viewed another way, those where the main hazard is from the therapeutic effect of the active) the traditional approach of using 0.001 of a minimum dose is generally a safe level in another drug product. Yes, it is a "one size fits all" criterion for conventional actives. And yes, it is a reasonable overkill

for some conventional actives and a significant overkill in other cases (but what else is new for pharmaceutical manufacturing)? Perhaps a ADE or PDE determination would allow much higher residue levels following cleaning of conventional actives, but as suggested by some Risk-MaPP authors (and also by me) this will most likely result in visually clean being the default acceptance criterion. [Furthermore, with all those lawyers waiting to sue at the drop of a hat, I don't see most pharmaceutical manufacturers, much less regulatory authorities, would want to make limits significantly more lenient.]

2. The EMA suggests a TTC value for genotoxic residues of 0.15 µg/day. The rationale for that level is based on the TTC level of 1.5 µg/day in EMA's "Guideline on the Limits of Genotoxic Impurities" is for manufacturing impurities. The EMA argues that residues following cleaning are "avoidable", as compared to impurities from a manufacturing process. This is a very weak argument. Yes, residues from a cleaning process can be reduced by improving the cleaning process; however, impurities from a manufacturing process can also be further reduced by additional purification processes. The argument about "avoidability" doesn't make sense. There is no reason why a TTC value of 1.5 µg/day that is applied to manufacturing "impurities" should also not be applied to cleaning "residues". A chemical is a chemical is a chemical, and its hazard (and its risk) should be independent of how it got into a drug product. [Note that I am also concerned about applying the TTC value independent of the route of administration. That value of 1.5 µg/day is based on the level that the FDA recommended for certain food packaging additives, suggesting an oral application. An adjustment should be considered for other routes of administration, such as given in Section 4.1.2 "Extrapolation to other routes of administration".]
3. In Section 4.1.5 the EMA covers "Therapeutic macromolecules and polypeptides" (which I assume includes biotech actives) by stating that the primary concern is the "pharmacodynamic" effect (again, my interpretation is that this is the therapeutic effect). This may be a valid argument if the intact macromolecules and polypeptides were the residues left after a typical cleaning process in a biotech manufacturing facility. However, since those cleaning processes typically involve hot aqueous alkaline solutions, this means that protein actives are almost universally degraded into smaller fragments, and the residues that exist after a cleaning process are those degraded fragments. And if immunotoxicity is the main concern, then smaller proteins have less concern with immunotoxicity as compared to larger proteins. These essential facts should be considered in setting limits for biotech actives.
4. The EMA guideline bases the PDE on the "critical effect(s)". However, while examples of critical effects are given, there is no definition per se of "critical effect". Note that this issue is one that is also true of Risk-MaPP. While I recognize the formulation of a definition for "critical effect" is not easy to clearly state, it would be very helpful to have such a definition for a concept that is critical for determining a PDE.
5. The PDE value is to be based on "all relevant literature". It is assumed that this is not limited to published data, but also includes unpublished studies. Particularly for investigational drug products (clinical trial products), unpublished data may be critical. Furthermore, there may be significant data gaps for such products. Perhaps a concept like the TTC concept for genotoxic materials can be applied to other concerns. An example is the TTC approach suggested by the EMA for dealing with products that don't have adequate information to assess that hazard.

These are my major concerns with the EMA draft guideline. It shares some of the same shortfalls as "Risk-

MaPP”; however, it does represent a significant improvement over Risk-MaPP. Furthermore, it a more concise presentation of the basic issues (but I must add that Risk-MaPP concerns itself with more than just setting residue limits for cleaning, in that it addresses other routes of contamination, such as mechanical transfer and mix-ups).

I should also note that I was mildly concerned that the EMA document did not mention or reference Risk-MaPP. Risk-MaPP was released in November 2010, well before the release of the EMA guideline (December 2012). I don’t know the reason for this omission, but I hope it was not “territorial” (USA vs. EU, or industry technical group vs. regulators).

This Cleaning Memo addresses good aspects and my main concerns about the EMA draft guideline. Next month’s Cleaning Memo will present what I see as the way forward with the issue of “health-based” limits.