Cleaning Memo for April 2015
EMA on Limits for Shared Facilities – Part 2

This is the second in series of Cleaning Memos discussing the finalized version of EMA's "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities". It discusses additional specific issues in the November 2014 *finalized* version.

TTC

One issue relates to a change in the value used for a TTC (Threshold of Toxicological Concern) for genotoxic materials (or potentially genotoxic materials). The value used by the FDA and the EMA's "Guideline on the Limits for Genotoxic Impurities" is 1.5 µg/person/day. In the November draft guideline, the EMA proposed using a value of 0.15 µg/person/day, ostensibly the EMA stated because residues from the cleaning process should be held to a more stringent standard as compared to impurities resulting from a manufacturing process. Well, that has changed. Somehow a light bulb clicked on and the EMA realized that an effect of a chemical compound in a drug product is the same regardless of where it came from (a manufacturing impurity or a cleaning residue). The value in this finalized document is 1.5 µg/person/day.

Note that the use of a TTC value as a safe threshold value is for genotoxic materials where there is *no established threshold value*. I believe this means that in testing, there is *no* NOAEL from which to determine a PDE. For genotoxic materials with "sufficient evidence of a threshold related mechanism", the safe threshold value is established using the PDE calculations. Under this category of "genotoxic potential", the EMA adds a third category of actives with sufficient *carcinogenicity* data; for these actives a "compound specific risk assessment" should be used (and not the TTC value).

For actives for human patients, the EMA assume a weight of 50 kg for an adult. The TTC value can thus be expressed as 0.03 µg/kg bw/day (meaning micrograms per kilogram of body weight per day). This impacts veterinary products, where the drug product may be given to animal that might be in a human food chain. For animals *not* in the human food chain (called "food producing animals" in this guideline), a TTC value specific to the animal (based on weight) could be used. For animals which are in the human food chain, TTC values must be calculated based on the specific animal safety and on the safe value for humans assuming some worst case calculations of what might be present in food from that animal. [Note: The EMA is silent on the question of how this might apply to animals which are food products for *other* animals, although I assume similar principles can be used in that situation.]

Sensitizers

The EMA does not provide any clarification on this issue. It merely repeats the criteria listed in Chapter 3, paragraph 3.6 of the EU GMPs. Those criteria (which are not specific to sensitizers) are as follows (this quote is from the GMP, not this guideline):

"Dedicated facilities are required for manufacturing when a medicinal product presents a risk:

a) Which cannot be adequately controlled by operational and/ or technical measures or

b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

c) Threshold values derived from the toxicological evaluation are below the levels of detection"

In determining a safe threshold value for an active with sensitizing potential, one should consider the frequency of sensitization in humans, the probability of sensitizing in humans based on animal or other "validated" tests, and the severity of these reactions. In other words (my words), it depends on the professional judgment of the toxicologist(s). I would assume that the basis for this professional judgment should be captured in a document (to be discussed next month in Part 3) similar to what is required for a PDE determination.

Veterinary Products

In the section on PDE determination, the EMA expands slightly what is said about health-based limits for veterinary products. While the draft guideline emphasizes the potential of humans being exposed to residues from consuming animals exposed to those residues, the finalized guideline more clearly calls for a determination of a PDE based on humans (for human safety if the animal provides food for humans) and a PDE based on safety to that specific animal. If the veterinary drug is *not* dosed on a "mg/kw bw" basis, then as a worst case the animal is assumed (as a worst case) to have a body weight of 1 kg.

The EMA is silent on the issue of determining the distribution of residues from the cleaning process in the animal organs, and then how much of those organs is typically consumed by a human as a worst case. However, presumably that will be part of the evaluation by the toxicologist.

Routes of administration

This section, an excellent point, survives word-for-word from the draft document. It basically states for a PDE determination that extrapolation from route of administration to another (from the route used for the animal species in the NOAEL determination) to a different route of exposure for the final drug product (in humans, for example), a correction factor may be applied based on the ratio of availability of the drug active for the two routes of exposure. If the drug active has systemic availability of 40% by the oral route, and if the NOAEL is based on an oral route, then a correction factor of 0.40 should be applied to derive a PDE based on respirable absorption (assuming 100% availability of an inhalant). On the other hand, for cases where the availability in route of exposure in the animal study is expected to be greater than the availability for the route of final drug product use, then as a worst case it may be possible to forgo an adjustment factor (that use of an adjustment factor would make the PDE higher).

While this is definitely a good distinction, the EMA fails to apply it to the TTC concept. The TTC concept was originally developed for additives to food packaging, where the route of possible exposure was oral. It is unclear why a lower value should not be selected for injectable actives based on a possible difference in availability via the two routes. [Note: This may have been addressed in the past by qualified toxicologists; I am open to clarification on why this is not a valid issue to bring up.]

Campaigns

There is not a separate section in the EMA guideline on campaigns, but there is a statement in Section 5.1 (the TTC approach) that use of a TTC value of 1.5 µg/person/day is conservative because "in practice, levels of residual active substance carryover can be expected to diminish on a batch by batch basis". I think (but may be wrong) that this is a reference to a campaign, where after cleaning a given product with a certain active (Active A), the residues of that active would be highest in the first lot of a subsequent campaign of a different product with a different active, whereas following lots in that campaign of the subsequent product would have much lower residues (if any measurable amounts) of Active A. The assumption is that over a lifetime, a person taking the subsequent product is not likely to always use lots with higher residues of Active A, or that the person might use product from lots of the subsequent product made following a different product (with Active B, for example). While this is a mitigating factor in most cases, it is also possible to argue that some (one in a thousand?) might get always get the lots with the maximum amount of the previous residue. If arguments of this type are to be made, it is probably better to evaluate the additional safety based on the fact that most manufacturers, when they design cleaning processes, try to develop processes which produce actual values at least 50%, and preferably 20% of the calculated residue limits.

Part 3 in May will hopefully be the last Cleaning Memo in this series on the EMA guideline.