Cleaning Memo for August 2018
Other Issues in EMA's Q&A

This is the third Cleaning Memo discussing issues in EMA's Q&A on limits in shared facilities (April 19, 2018). It is also the least important of the three, so if you have more important things to do, you may be tempted to skip reading this one (of course, how will you know whether something else is "more important" until you have actually read this). So I think you are trapped into reading this Cleaning Memo that covers these other significant issues.

Question 4 (Q4) answers the question as to what *competencies* are needed for people developing a HBEL. In the draft version of this Q&A, the answer for the equivalent question (given in Question 9) was simply looking at the person's "experience and qualification". In the finalized version, the answer is threefold. The person should have (a) "expertise and experience in toxicology/pharmacology", (b) "familiarity with pharmaceuticals", and (c) experience in the development of HBELs (such as OELs or PDEs). Furthermore, when outside experts are contracted for developing HBELs there should be a contractual agreement consistent with Chapter 7 of the EU GMPs. That Chapter 7 agreement is one dealing with "Outsourced Activities". Finally, in answer to this Q4, the EMA comments about "purchasing" HBEL monographs, with the statement that if those assessments are purchased there must be a "recording" of the "suitability of the provider (including the specific technical expert) as a qualified contractor". Although not specifically addressed by the EMA, it is probably appropriate for assessments done by in-house toxicologists/pharmacologists that their suitability (that is, based on the threefold qualifications stated above) be confirmed.

Question 5 (Q5) deals with HBELs for contract manufacturers. The answer states that the *contract giver* should either (a) provide a "full HBEL assessment" to the contract manufacturers, or (b) provide data to allow the contract manufacturer to perform that assessment. I assume that the reason in "a" for requiring that the "*full*" assessment (and not just the HBEL value) be provided is that the contract manufacturer is responsible for making sure that the HBEL is appropriately determined, since that HBEL is of more concern for determining effects on *other products* (as opposed to effects on the safety of the product the HBEL is associated with) that perhaps are from a *different* contract giver.. Furthermore, I would assume that for "b" if the HBEL is developed or contracted out by the CMO, that that assessment should be provided by the CMO to the contract giver, because from a GMP perspective the contract giver is ultimately responsible for cleaning validation of its product.

Question 12 (Q12) deals with HBELs for veterinary products in facilities that make products for different species. The first part of answer is that carryover limits should "generally" be based on the human HBEL. While not specifically stated in the Q&A, consistent with section 4.1 of the 2014 EMA Guideline the human HBEL should be utilized for veterinary products not as a mass value but rather as a mass/body weight value (then the body weight of the species taking the *next product* can be used; this helps

address the large difference in body weight between a cat and a horse. The second part of the answer deals with specific "known susceptibility" for a species; rather than try to summarize it, the full answer given is "However, in cases where there is concern relating to known susceptibility of a particular species (e.g. monensin in horses) the HBEL approach should take into account knowledge of specific animal toxicity when evaluating products manufactured in shared facilities/equipment."

Well, if you got this far, you are either thinking "Man, did he waste my time!!" or else "Wow, this was really helpful. I think I will take another look at the EMA Q&A document". If your response is the first, don't say that I didn't warn you.

Next month we will start again with Cleaning Memos that I had previously prepared that were displaced by this series on the EMA Q&A document.