Cleaning Memo for September 2018
What If the *Next* Product is the *Same* Product?

In performing carryover calculations, we usually talk about limits for the active of Product A if Product B is the next product. Can carryover calculations be done if Product A is cleaned and then Product A is the next product? For clarification, this generally comes up in the context of there being two or more products made on the same equipment. So, this is *not necessarily* a situation of equipment dedicated to one product (although what follows could be applied to that situation). And, it is *not* the situation of cleaning in a campaign where minor cleaning is done between batches of the same product, and where a validated cleaning is done at the end of that campaign.

So, what can be done? The key is deciding what to do for the L1 calculation, where L1 is the limit in the *next* product. For review, what is typically done for this type of calculation using (for illustration purposes) a dose-based limits is as follows. The L1 limit is expressed as 0.001 of a minimum daily dose of the active of the *cleaned* product A divided by the maximum daily dose of the *next* drug product B. This is expressed mathematically as:

$$L1 = (0.001)\ (MinD_{ActA}) / (MaxD_{ProdB}) \qquad \text{[Equation I]}$$

Where:
$MinD_{ActA}$ = Minimum daily dose of the active of drug product A
$MaxD_{ProdB}$ = Maximum daily dose of drug product B

So, the question arises, what if the cleaned product is A and the next product is *also* A? Do I follow the same equation with a minimum dose of the active in A in a maximum dose of the product A itself? While it is possible to do so, it is not required logically or from a scientific perspective. Why is that the case? And what is the alternative if that calculation is not required?

If firms want to use the same type of carryover equation for a L1 value for the A→A situation, the recommendation I usually have is to require an L1 of 0.001 of the product active concentration. Expressed mathematically, this is:

$$L1 = (0.001)\ (Conc_{ActA}) \qquad \text{[Equation II]}$$

Where:
$Conc_{ActA}$ = Concentration of the active in drug product A

Note that dosing (minimum or maximum) doesn't come into play here. So this type of formulation for A→A could also be used for highly hazardous actives or any situation where ADE/PDE values are used for the typical L1 equation.

For the situation with two *different* products, the reason that we specify the minimum for A and the maximum for B in Equation I is that we don't know what the appropriate dose for Product A would be for a specific patient taking the maximum dose of Product B. So we use as a worst case the lowest dose of A. But, if both products are the same, then it doesn't matter whether the patient is taking the minimum dose or the maximum dose; the 0.001 factor provides the "equivalent" protection in terms of patient safety. But the main concern in this situation is *not* patient safety. Where the cleaned product and the next product are the same, the *real effect* of carrying over the *same* active into the next batch is to change the concentration of the active in that second batch. [Of course, there are exceptions, such as when the active degrades during the cleaning process. In that case I may consider a toxicity limit based on that specific degradant.]

Back to the main case, here is an example of setting limits where the active in not degraded. If the concentration of active in a tablet is 5% (for example, 20 mg active in a 400 mg tablet), then the L1 would be one one-thousandth of that, or 50 ppm. So, the second batch containing not 5% active but rather 5.005% active would *not* be a significant patient safety concern or a significant product quality concern. In fact, it probably would be well with the normal potency specification for that product.

Now, when I go back and read my explanation I'm not sure it is entirely clear to me. So let me give an *analogy* that might help with the logic. Let's say I am dealing with two *different* products (A and B) each of which are dosed differently for adults and for children, and where the child dose is *always smaller* than the adult dose. For the cleaning of A, do I need to set limits based on the *minimum child* daily dose of the active in A divided by the *maximum adult* daily dose of drug product B? The answer is I could, and it would be safe in the situation discussed (just for clarification, it would not be if the dose for children was *greater* than the dose for adults). However, it should *not* be required. Why? Because in that situation the relevant safe dose of the active of A in Product B (where product B is taken by an adult) is the *adult* dose the active of A. So in this situation, I recommend that firms consider calculating the child-to-child dose and also the adult-to-adult dose, and use the *more stringent* (lower) of the two L1 values for subsequent calculations. Note that in this analogy, I am not going from A to A, but from A to B, so the analogy is not perfect. [As an aside, if I were using a HBEL calculation in this situation, I might consider a child's HBEL of the active of A in a maximum child dose of the product B, and similarly for the adult situation.]

Let's back to the situation of A to A limits. For clarification, this formulation of A → A cleaning in Equation II is not necessarily required. It still *may* be appropriate to only require visually clean as a limit for the active (while still measuring bioburden and cleaning agent in the protocol). I could also see the possibility that some firms *might* have a rationale to use a less stringent safety factor (such as 0.01). Furthermore, since the context of where Equation II is usually done is in a situation where I am making multiple products on the same equipment, I still do calculations for A→A, A→B, A→C, and so on to eventually arrive at an L3 value (limit per surface area) for each situation. Then I compare the different L3 values for the cleaning of A, and use the lowest (the most stringent) to set acceptance criteria for my protocol for the cleaning of A.

This sounds like a lot on a topic that might not commonly come up. However, it always helps to understand the rationale for what is done if we choose to do it.