Cleaning Memo for March 2018
Carryover Calculation Errors to Avoid

Carryover calculation are easy to execute, particularly with a software program (like eResidue) or with an Excel spreadsheet. The critical element is making sure the calculations are correct, giving you valid results. This Cleaning Memo will explore different way that the design of that calculation can go wrong.

First let me give a typical carryover calculation for a limit of what I typically call L4b (see the Cleaning Memo of September 2012 for a presentation of my L0, L1, L2, etc. shorthand for expressing limits) of an active in an extracted swab sample for drug product manufacture:

$$L4b = \frac{(SDA)\,(BS)\,(SA)}{(MDD)\,(SSA)\,(SEA)}$$

Where:
SDA is the safe daily amount of the active (in mass units like micrograms or milligrams)
BS is the batch size of the next product (in mass units, such as grams or kilograms)
SA is the swabbed area (in area units, such as cm^2)
MDD is the maximum daily dose of the next drug product (in mass units, such as grams)
SSA is the shared surface area for the two products (in area units, such as cm^2)
SEA is the solvent extraction amount (in either mass (grams) or volume (mL) units)

In this equation I am assuming the desired output is a L4b concentration in terms of mass/mass (such as micrograms per gram) or mass/volume (such as micrograms per mL).

So, let's start with simple things like making sure the units are correct. That is, when I enter the values, do the units "cancel out" mathematically so that my desired output is in the correct units? If a term is added or omitted that causes the output to be just micrograms, then something is wrong. I should try to find out what is missing, or what needs to added, or what needs to be changed. However, if things are not right, don't just add or subtract a term to make the units correct; make sure that the changes you make not only are correct in terms of the units output, but also technically and logically correct in terms of giving the correct limit. I prefer to do this exercise with pencil and paper rather than with a spreadsheet, so that I am clearly seeing what is cancelling (or maybe it's because I have misplaced my slate and slate pencils). [Note here that if the equation is designed to report out mass per swab, then my expected output could be just grams, and not a concentration.]

Related to this issue is making sure the unit "cancel" appropriately. For example, if I were to enter BS in kilograms and the MDD in grams, I will not get the correct answer unless I included a units conversion factor in the equation. In this example, a units conversion factor could be to convert the kilograms in the numerator to grams, or to convert the grams in the denominator to kilograms. Another example would be making

the sure the SEA units are correct. If I want a concentration in mcg/g, then the SEA units should be in grams (ppm); if I want a concentration in mcg/mL, then the SEA units should be in milliliters (realizing that for dilute aqueous solutions with a specific gravity of 1.00, mcg/mL can be considered ppm.

We can take this units issue ones step further and make sure that, where appropriate, the units refer to the same thing. The main issue here is that the mass units for BS and for MDD both refer to mass units of the *next* drug product. This should make it clear that the batch size to be entered is not the batch size of the cleaned product, but the batch size of the *next* drug product made in the cleaned equipment. Furthermore, while the SDA is an amount (mass) of the active in the cleaned drug product, the MDD is the maximum dose of the next *drug product* and not of the *active* in the next drug product.

Leaving the units behind, another potential error is assuming that if I move from a dose-based limit to an ADE or PDE limit, that I still apply a factor such as 0.001 to the ADE/PDE value. The so-called "safety factor" applied to a minimum daily dose of the cleaned active should *not* be used for the ADE/PDE; the ADE/PDE value is a safe daily amount, and there is no need to apply an additional safety factor. For clarification, you might apply a factor for units conversion of 0.001 to an ADE/PDE value expressed in micrograms, so that the SDA is expressed as milligrams, but that is a different use of the 0.001 factor.

Still another potential error is not in the carryover equation itself, but in how the SSA is determined. The SSA is the *total (or cumulative) shared surface area* between the two products. It is not correct to perform separate calculations for each equipment item in an equipment train. Doing separate calculations by allowing a SDA in each equipment item in a train essentially allows a multiple of the SDA by cumulative transfer of residue from each equipment item into the next batch.

There may be variations of the basic equation that individual facilities use which might modify how you make sure the calculations are correct. For example, some firms multiply the calculated limit by the sampling recovery factor expressed as a decimal. That change does not basically change any of the items brought up so far. Another option is where companies use "dose units" (for example, tablets) to express both the minimum batch size and maximum daily dose of the *next* product; if you use that option, make sure you carefully define what a "dose unit" is, since it is easy to get confused.

While I earlier said that you can do carryover calculations for equipment items in a train separately, one exception to that is the use of "stratified sampling" (see the March, April and May Cleaning Memos of 2009). In stratified sampling is it possible to divide the L2 value among the different equipment items (either arbitrarily or based on such factors as the surface area), as long as the *total* carryover is no more than the L2 value.

As in other things in cleaning validation, design is important. So make sure your carryover equations are correct for your situation; otherwise erroneous limit values will carry over into you cleaning validation protocols.