Cleaning Memo for October 2016
Limits for Products with Multiple Actives

If I have a drug product with multiple (two or more) actives, do I have to set limits for and measure *all* actives in my cleaning validation protocols? Or, is there a rationale for perhaps focusing only on one active as a representative active? That is, just like grouping of *different products* together and selecting one product for performing my validation protocol, is it possible to group together *different actives* in the *same* product to simplify my cleaning validation work? Well, the good news is that it may be possible. I'll go through several examples depending on how limits are set so that the relevant parameters in each situation are clear. The three situations I'll cover are limits set on 0.001 of a dose, limits set on an ADE/PDE, and finally limits set on 10 ppm default (used if it is more stringent than either a dose-based or health-based calculation).

In all cases, I will cover a simple example of a drug product with only two actives, one at a relatively high level and one at a relatively low level in the drug product. The example I'll use is a tablet with Active P (ActP) at 20 mg and with Active Q (ActQ) at 2 mg. Furthermore, let's suppose that the minimum daily dose of this drug product is one tablet. If I set limits based on 0.001 of a dose, the limit for ActP will 10 times larger than the limit for ActQ. Certainly one option is to measure *both* actives in my cleaning validation protocol. But, a second option is to determine if it is possible to only select one active for measuring analytically in my protocol. Is there a rationale for doing that?

Example with dose-based limits
One approach is to utilize a grouping (matrixing) approach for the two actives. In a grouping approach for *multiple drug products* on the same equipment, the typical approach is to select the most difficult to clean product and set limits for that active at the lowest limit of any product in the group. How does that translate to grouping two actives *within* one product? Well, first I might argue that with both actives in the same excipient formulation, the excipients do not contribute to the relative difference in cleanability of those two actives. Therefore, it may be that the relative solubility of the two actives in the cleaning solution would distinguish the difficulty of cleaning between the two actives. If that is the case (and there may be factors which might affect this conclusion, such as different actives in each layer of a bilayer tablet that has different excipients in each layer), then I can conclude that the active with the lowest solubility is a worst case, and is therefore the one I want to measure in my cleaning validation protocol.

So my next question is, how do I set limits for that worst case (lowest solubility) active? Do I set it as the lower of the two actives (as I would for grouping among different drug products)? My answer is "no". Why? Using the example I started with, let's say on a relative basis the safe daily amount (what I generally call the L0 value) of ActP is 0.001*20 mg = 0.020 mg and the safe daily amount of ActQ is 0.001*2 mg = 0.002 mg. If ActP has the *lower* solubility, then using *conventional* drug product grouping principles, in my cleaning validation protocol I would measure ActP at a limit equivalent to a safe daily amount of 0.002 mg, the lower of the limits for the two APIs. However,

that approach is not required if both actives are in the same product; therefore I would set the limit of ActP at a value equivalent to its safe daily amount of 0.020 mg. The rationale would be that if I could reduce ActP to a level 0.001 of its daily dose, then for ActQ, which is more soluble (less difficult to clean), it should also be below 0.001 of *its* safe daily amount.

If ActQ were the least soluble active, the same would apply – I would just measure ActQ at its limit based on a safe daily amount of 0.002 mg; this would provide assurance that ActP (*more* soluble) was below *its* safe daily amount.

Note that in this approach (using dose-based limits where both actives use the same safety factor applied to the minimum dose), the general principle is to measure only the least soluble active at its limit.

Example with ADE/PDE limits
If I am setting limits based on ADE/PDE values, there has to be a slight wrinkle. I am still going to determine the least soluble active and only measure that in my protocol. Let's assume in this case that ActP is still the *least* soluble active, and it is the active I will measure in my protocol. In this situation, if I set my limit based on the limit of ActP I will *not necessarily* clean ActQ to a level that would be safe based on its ADE/PDE value. Here is an example. Let's suppose the ADE/PDE of ActP is 0.050 mg and the ADE/PDE of ActQ is 0.003 mg. If my cleaning reduces ActP to a level below a limit equivalent to 0.05 mg (a reduction by a factor of 0.0025), then if I get the *same* reduction with ActQ, I would have a value equivalent to an ADE/PDE value of 0.005 mg. But my ADE/PDE value of 0.003 mg is *lower*, and I would not have an assurance that I would meet my acceptance criterion for ActQ.

Here is where the wrinkle comes in (you could call it a "wrinkle just in time"). What I would do in this situation is to calculate the reduction required by ActQ. In this case the required reduction based on a concentration of 2 mg and an ADE/PDE value of 0.003 for ActQ would be 0.003/2 = 0.0015. Therefore I would apply that reduction factor to ActP, where the "adjusted ADE/PDE" would be 20*0.0015 = 0.03 mg. Note that this is *lower* than the values determined by my qualified toxicologist. But, measuring ActP down to a level equivalent to an ADE/PDE of 0.030 mg would provide assurance that ActQ (which is more soluble) would be below its ADE/PDE value of 0.003 mg.

Of course, if the situation was reversed *in this example*, and ActQ was the *less* soluble of the two actives, then no adjustment in the PDE of ActQ would be required. Furthermore, setting a limit based on an ADE/PDE of 0.003 mg for ActQ would provide assurance that ActP (more soluble) would be below its limit based in an ADE/PDE of 0.05 mg.

Example with 10 ppm limit
Let's say I have my limits set up so that I would use a 10 ppm level of each active provided that a 10 ppm value was *below* the limit in the next product using a dose-based or ADE/PDE value. The approach I would use in this situation is still to determine the least soluble active. However, I face a similar quandary as in the previous ADE/PDE

situation. Let me illustrate with same two actives, again supposing that ActP was the least soluble. In this case, I would argue that if I can reduce ActP (at a level of 20 mg in the tablet) down to a level *in the next product* of 10 ppm, then ActQ, which starts off at a *lower* level and is *more* soluble), should also be reduced to a level below 10 ppm in the next product. So, I would just measure ActP using a limit of 10 ppm in the next product.

Let's reverse the situation and assume that ActQ was *least* soluble. Using similar logic for the case where ActQ was reduced to 10 ppm in the next product, I would *not necessarily* conclude that Act P would also be reduced to at least 10 ppm. That is, if ActQ (present at 2 mg in the tablet) was reduced to 10 ppm in the next product, I *cannot* conclude that ActP (present at 20 mg in the tablet) would also be reduced to 10 ppm in the next product. It may very well be that it is reduced to that level based on its greater solubility, but I cannot just assume that it *must* be the case. In this latter situation, I could conceivably just measure both actives in my protocol. Or, I could set my limit for ActQ at a lower level (for example, concluding that if the limit for ActQ were set at a level of 1 ppm in the next product, I could expect that expect that ActP would be at a level no higher than 10 ppm in the next product).

Of course, in cases of multiple actives, it is always an option to measure residues of *each* of the actives in my cleaning validation protocol. However, it may be possible in some cases (such as illustrated here) to provide a rationale for only focusing on one of the actives. If this approach is utilized, it should be described in appropriate cleaning validation documents.