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**Limits for Rinse "Grab" Samples**

Limits for rinse samples in finished drug manufacture have always been a problem area for pharmaceutical cleaning validation. How does one justify limits on a scientific basis, much like is ordinarily done for swab sampling? I have answered this in part in a May 1998 Pharmaceutical Technology magazine publication. However, I have gone one step further in many of my seminars over the last few years to better establish a justified limit for rinse sampling for *grab samples of the final rinse* at the end of a CIP cleaning process.

When determining the limit for a grab sample, other limits, such as the limit in the next product, the maximum allowable carryover, and the limit per surface area, are unchanged. I generally call these L1, L2 and L3 respectively, with L4 then being the limit in the analyzed sample. (In my book published in 2000 I used slightly different terminology; this newer, slightly modified terminology, is what I have been using for at least the last three years.)

For rinse sampling, an L4 value is calculated as:

$$L4 = \frac{0.001 \text{ X A X C X E}}{\text{B X D X F}}$$

Where A = minimum dose of the active of the cleaned product
B = maximum dose of the next drug product
C = minimum batch size of the next drug product
D = total shared surface area between the two products
E = sampled equipment surface area
F = volume of rinsing sample

In this equation, 0.001 represents the "safety factor".
The only critical issue for this discussion is finding values for E and F. If a separate sampling rinse is used (after the final process rinse), then the values for E and F are straightforward (E is the surface area rinsed and F is the volume of the separate sampling rinse). Note that this applies whether the separate rinse is a CIP rinse or a "dump and fill" (also called "agitated immersion") rinse.

If a sample is taken of the final process rinse in a "dump and fill" cleaning process, then the values for E and F are also straightforward; E is the surface area and F is the volume of the final process rinse.

Now for the case that is of critical concern for this Cleaning Memo. How does one determine the limit for a grab sample of the final process rinse in a CIP process? Remember that the values for A, B, C and D are independent of the sampling method; it is the values for E and F that need to be addressed. The value for E is easy enough – it is the total surface area rinsed by the CIP process. Note that this value may or may not be the same as the value for D. For example, if the equipment I am sampling is part of an equipment train for manufacture of the drug product, then the value for D is the total shared surface area, while the value for E is the surface area of the equipment item(s) rinsed.

How does one determine the value F for a grab sample of the final CIP rinse? Well, one way is to say, "Let's suppose I continued the final process rinse for an additional time (or volume) of rinse that would be equivalent

to a separate sampling rinse." That additional volume of rinse solution would be an appropriate value for F if I were doing a separate rinse. But I am actually taking a grab sample at the end of the final process rinse. How do these fit together? Well, the way they fit together is that the value of residue *concentration* measured in the grab sample of the final process rinse will be no greater than the concentration value calculated for the residue limit if I were to continue with a separate sampling rinse. In other words, I set my limit as if I were doing a separate process rinse, but actually measure the residue in the worst case, which is the grab sample at the end of the process rinse.

If that is the case, how do I determine the value for F? There are at least three possibilities. One is to use the actual value of the final process rinse. This can be appropriate if there are discrete rinse bursts that are defined, and if I am confident that the volume of the final burst is adequate to cover all equipment surfaces. A second possibility is to use the volume of solution used for riboflavin coverage testing for the equipment item. This can be appropriate if the equipment cleaned is the same as the equipment tested for riboflavin coverage. Remember that if the equipment sampled includes the process vessel and significant process piping, the volume of rinse used for riboflavin coverage may not be adequate to contact all surfaces of the process vessel *and* the process piping. A third option is to use some arbitrary, but reasonable, volume which is a percentage of the total equipment volume. A value typically used is 5-10% of the equipment volume for CIP applications. If this option is selected, it is important to remember that this 5-10% figure applies to equipment cleaned by CIP spray devices. If associated piping is included in the equipment actually sampled, be sure to add in a volume which represents the volume for a final rinse of the process piping. This additional value can typically be equal to the actual volume of the piping itself.

Is it necessary to consider each of these three options and then select the worst case (for limits calculations, the worst case is the highest value for F, since this will give the lowest limit value)? The answer is clearly "No". Each of these three estimates alone provides a worst-case situation for setting limits when I am taking a grab sample of the final process rinse. While taking the worst case of the three values for F is acceptable, it is not necessary from a scientific or compliance perspective.

One final issue on setting limits for a grab sample of the final process rinse is to clarify that the volume of the actual sample taken is immaterial for setting the residue limit. I may take a 50 mL sample or I may take a 500 mL sample. In either case, my calculation of the limit is the same, and has nothing to do with the volume of the actual sample taken.

This Cleaning Memo is designed to clarify issues with setting limits when you take a grab sample of the final process rinse, and is limited to those situations where limits are calculated by a 0.001 dose criterion (or a maximum allowable carryover criterion). It does not apply in situation such as bulk active manufacture in biotech, where limits are usually established in another manner.