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More on "Stratified Sampling"

Last month I covered the basics of "stratified sampling". While "sampling" is part of the name, stratified sampling is not primarily a way to sample (although that is part of it), so much as a way to determine whether measured residues are in compliance with a calculated total carryover limit.

Last month we covered the example of applying stratified sampling to segments within a given piece of equipment. For this month, I will cover an example where it is used for a series of equipment items in a manufacturing equipment train (for finished drug product manufacture). Let's assume for simplicity that there are three equipment items used for manufacture of the drug product. I'll call them P, Q and R. I'm cleaning Product A, and Product B is the next manufactured product. Let's assume the surface area of the three equipment items are as follows:

Equipment P: 100,000 cm^2
Equipment Q: 85,000 cm^2
Equipment R: 15,000 cm^2

In a typical carryover calculation, I would calculate my limit using the total surface area of the equipment train to arrive at a surface area limit. Let's say that result (based on the dose of the active in Product A, the dose of the drug product Product B, the total shared surface area, and the batch size of Product B) is a L3 value (limit per surface area) of 1.0 µg/cm^2. I would then require in my protocol that *each* swab sample meet that limit of 1.0 µg/cm^2. If I were doing a separate sampling rinse for Equipment Q, and if I used a sampling rinse volume of 50 L, I would set a rinse limit for that equipment item based on conventional rinse calculation:

$$L4 = \frac{(L3)\,(\text{Surface area sampled})}{(\text{Rinse volume})} = \frac{(1.0\ \mu g/cm^2)\,(85{,}000\ cm^2)}{(50{,}000\ mL)} = 1.7\ \mu g/mL$$

I would then expect my rinse sample to meet that L4 limit. And those determinations are perfectly acceptable (and commonplace) ways of determining that I meet my acceptance criterion.

But, I can also use stratified sampling to determine compliance with my calculated L2 limit (the total carryover). Remember that there are conditions to utilizing stratified sampling in this way. The primary concern is that the residues carried over from equipment surfaces are uniformly distributed in the next manufactured product.

Continuing with the example I started with, the equipment train is stratified by the individual equipment items in that train. Then during my protocol, I want to make sure I sample all the worst-case locations in each equipment item. Note that this sampling is essentially the same sampling (locations and number of samples) as if I were not doing stratified sampling. I then measure residues in all samples. The next step is to multiply the highest value of any swab sample for any swabbed site within a given equipment item by the surface area of that equipment item. This gives me a maximum possible actual carryover for that equipment item. Let's assume the measurements below are the highest values obtained for a given equipment item. The maximum actual carryover for each equipment item is calculated by multiplying that value by the total surface area for

that equipment item.

Equipment P: 0.15 μg/cm^2 X 100,000 cm^2 = 15,000 μg
Equipment Q: 0.20 μg/cm^2 X 85,000 cm^2 = 17,000 μg
Equipment R: 1.20 μg/cm^2 X 15,000 cm^2 = 18,000 μg

The total possible carryover under this scenario would be the sum of all equipment items, or 50,000 μg (50 mg, for those of you used to seeing smaller numbers). Going back to my original calculation of a total carryover limit, if my average L3 was 1.0 μg/cm^2 and if the total surface area were 200,000 cm^2, my total L2 limit would be 200,000 μg. Since my actual maximum residue value as determined by stratified sampling was 50,000 μg, my cleaning was effective because it was under the residue limit.

The value of this approach is seen in that (with the example used) I would have failed the protocol (at least for Equipment R) with this data, with at least one location in Equipment R being above the calculated L3 limit of 1.0 μg/cm^2. But using a stratified sampling approach, I still have a scientific and logical rationale for saying the carryover is less than the calculated total amount. Yes I would be happier to see all data points meeting the one L3 limit of 1.0 μg/cm^2. But, I would also be happier if all my data points were below the limit of detection (LOD) by the best available analytical technique. But at least for most situations, that is not required.

Some of you may question the use of this technique, never having seen it before. Frankly, when I started as a consultant, I had not seen this "stratified sampling" approach. When I saw it, my response was something like "It's not the typical method most pharmaceutical companies use, but it does have a scientific and logical basis for use." Particularly with all the talk about wanting to be on a sounder scientific rationale, there should be no serious objection to this technique provided it is used correctly and in appropriate situations.

Realize that this technique offers an advantage to a manufacturer mainly when a smaller equipment item has a larger residue value. However, it also offers some advantages when the larger equipment item has the higher swab residue values. Reversing the highest swab values for P and Q in the example previously given results in the following carryover values:

Equipment P: 1.20 μg/cm^2 X 100,000 cm^2 = 120,000 μg
Equipment Q: 0.20 μg/cm^2 X 85,000 cm^2 = 17,000 μg
Equipment R: 0.15 μg/cm^2 X 15,000 cm^2 = 2,250 μg

In this case, the total carry is 139,250 μg, which is still below the acceptance limit of 200,000 μg. However, it is possible to carry this approach only so far. Here is a third case:

Equipment P: 0.15 μg/cm^2 X 100,000 cm^2 = 15,000 μg
Equipment Q: 0.20 μg/cm^2 X 85,000 cm^2 = 17,000 μg
Equipment R: 5.20 μg/cm^2 X 15,000 cm^2 = 78,000 μg

I can total the carryover to get a value of 110,000 μg, and it looks like I will pass my total carryover acceptance limit of 200,000 μg. However, in this case it is likely that I will fail my visually clean criterion (with a swab value of 5.20 μg/cm^2). In other words, the use of this technique is not completely elastic.