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Differing Ways to Express Limits

In this Cleaning Memo, I will discuss the conventional way limits are set for finished drug manufacture. This discussion will not cover *fundamentally different* basic calculations; it's just how those basic principles are expressed that is different. I will illustrate the different ways (again, with the same scientific basis) using limits for the active ingredient. A basic principle is that of allowing no more than 0.001 of a minimum daily dose of the active of the cleaned product in a maximum daily dose of the next drug product made in that same equipment (note that this is not the only factor in limits of actives; concerns about properties such as genotoxicity are an additional consideration).

I will start with the variation that I usually teach. That method defines four limits (in all cases, limits for the cleaned active):

L1 – the maximum *concentration* in the next product (in µg/g or µg/mL)
L2 – the maximum *total amount* of carryover to the next product batch (in mg)
L3 – the maximum *amount per surface area* (in µg/cm^2)
L4 – the maximum *amount per swab* (in µg), or the *maximum concentration* in a desorbed swab sample or a rinse sample (in µg/g or µg/mL)

For clarification, the units given are examples only; L2 could be expressed in any suitable mass units, such as µg, mg or g. Also, for simplicity, I will only use a swab example (although my basic presentation and the variations also can be applied to rinse samples).

The variables that are inputted are as follows:

DoseA: Minimum dose of *active* of the cleaned drug product
DoseB: Maximum dose of the next *drug product*
BS: Batch size of the next drug product
SSA: Shared surface area between the two products
SA: Swabbed area
SDA: Solvent desorption amount

I usually recommend that all four limits (L1, L2, L3 and L4) be calculated. The reason is that different expressions may be useful for different purposes (for example, in determining spiked amounts for sampling recovery studies, L3 can be the most useful number to consider). Here is how the calculations are performed:

$$L1 = \frac{(0.001)(DoseA)}{(DoseB)}$$

L2 = (L1) (BS) [Also called the Maximum Allowable Carryover, or MAC]

$$L3 = \frac{L2}{SSA}$$

$L4 = (L3)\,(SA)$ [for the limit per swab]

$$\text{OR } L4 = \frac{(L3)\,(SA)}{(SDA)}$$ [for the limit in the desorbed swab sample]

The thing I like about doing it this way is that I have all four values in case I need them. Also, by calculating L4 as the limit per desorbed swab sample, when I measure the concentration of residue in the analytical sample, I can compare that value to my L4 limit for the desorbed swab sample to directly to my L4 limit (of course, I will include my sampling recovery factor to "correct" either the L4 limit or the measured analytical value for the sample; this recovery factor will also need to be considered in variations covered later, but will not be discussed further).

Now we'll discuss some variations on this. One variation is to stop the limit calculation at the L2 value. Then, when I determine my desorbed swab sample concentration (which I will call SC), I work "backward" to determine what the SC would correspond to as a MAC. Here is a mathematical determination of the equivalent MAC:

Then the calculated actual MAC (based on the analytical sample result) is compared to the calculated L2 limit previously determined. In principle, the result of this calculation (in terms of pass/fail) will be the same as for the previous calculation.

Another variation is to calculate the L2 value using 0.001 of DoseA and multiplying it by a derived value that is an expression of the "minimum dose units" of the next drug product (which I will call MDU). By MDU, I don't mean something like how many grams per daily dose. The MDU is calculated by dividing the minimum batch size of the next drug product by the maximum daily dose amount of the next product (with both the batch size and maximum daily dose amounts being in the same units). I will illustrate what I mean by using tablets. Suppose the maximum daily dose is two tablets, and that one tablet is 250 mg (or 0.25 g). If the minimum batch size is 10,000 grams (10 kg), then the "minimum dose units" is (10,000 g)/(2 X 0.25 g) = 20,000 dose units. Some companies use this "dose units" concept, and there is nothing wrong with it. It gives the same value for L2 as the previously given calculation. Why I don't prefer it is that it uses a derived value (the "minimum dose units") rather than what I consider the "fundamental" values (the maximum daily dose and the minimum batch size). Using the fundamental values avoids a separate calculation, as well as clearly illustrates the effects of the dose and batch size of the next product.

There are certainly other variations that could be used. For example, I could stop my limit calculation at L3, and then convert my analytical sample value to a value per surface area. The important thing to note is that despite various ways (discussed here) of expressing limits and determining compliance of the analytical sample with that limit, they are all based on the same scientific principles. Any variation can be used, preferably as long as it is used consistently by a given facility or company.