September 2012
My Revised Shorthand for Expressing Limits

Over the last decade I have used a shorthand method for expressing limits for cleaning process validation protocols. It originally started out with three categories (L1, L2, L3), and was revised several years ago to four categories (L1, L2, L3 and L4, with three subcategories for L4). Last year I made a further change because of the ISPE Risk- MaPP emphasis on an ADE (Acceptable Daily Exposure). So now I am at five categories (adding L0, or "L Zero"). All of these are useful in discussing limits for different purposes. Below are the shorthand "abbreviations" I now use.

L0 The safe amount of residue that can be administered to a person on a daily basis for a long time period. The units for this are mass units, such as µg or mg. Note that L0 values for a given residue may be different depending on the route of administration (e.g., oral, injectable, topical). Furthermore, L0 may be adjusted based on a limited time of potential exposure. L0 may be calculated by formulas such as 0.001 of minimum daily dose of an active, by the Risk-MaPP Acceptable Daily Intake (ADE) determination, or by an LD50 determination (for cleaning agents).

L1 This is the safe concentration of residue in the next manufactured product. This is typically in units such as ppm, µg/g, or µg/mL. This, of course, makes certain assumptions about the route of administration and time frame of exposure in determining the L0 amount. For finished drug product manufacture, it is calculated by dividing the L0 value by the maximum daily dose of the next drug product. Note that for those of you who use a "default' value of 10 ppm in your carryover calculations, that 10 ppm value is typically used as the L1 value whenever it is more stringent than the calculated L1 value.

L2 This is the total amount of residue allowed in a batch of the next product, and therefore the total amount allowed on shared product-contact surfaces of the equipment train. This is typically in mass units, such as µg, mg or g. It is calculated by multiplying the L1 value by the minimum batch size of the next manufactured product.

L3 This is the amount of residue allowed per surface area of product contact surfaces. This is typically in units of mass per surface area, such as µg/cm2 or µg/in2. It is calculated by dividing L2 by the total product-contact surface area of the equipment train.

L4 There are several variations here, depending on how sampling is done. L4a is the amount of residue per swab (for swab sampling). It is in mass units, typically µg or mg. L4a is calculated by multiplying the L3 value by the area swabbed (typically about 25 cm2 or 100 cm2). For clarification, if two swabs (for example, one wet and one dry) are used, L4a is not the amount per swab, but the amount for two swabs.

[Note that the L4a limit can be increased by swabbing a larger surface area.]

L4b is the concentration limit in the liquid (such as water or solvent) the swab is extracted into. This is typically in units such as ppm, µg/g, or µg/mL. It is calculated by dividing the L4a limit by the amount of liquid used to extract the swab. [Note that the L4b limit can be increased by extracting the swab in a smaller volume of liquid.]

L4c is the concentration limit in the liquid (such as water or solvent) that is used for rinse sampling. This is

typically in units such as ppm, µg/g, or µg/mL. If the entire equipment train is rinsed as a unit, L4c can be calculated by dividing L2 by the amount (or volume) of liquid used to sample the equipment in the rinse sampling process. If items in the equipment train are sampled independently of each other, then L4c is calculated by multiplying L3 by surface area of the equipment sampled, and then dividing that result by the amount (or volume) of liquid used to sample the equipment sampled in the rinse sampling process. [Note that the L4c limit can be increased by performing the rinse sampling with a smaller volume of liquid.]

Note that other terms can and have been used in the industry. However, the terms L0, L1, L2, L3, and L4 have no significant connotations (except that they are associated with me), so that is one reason I prefer them. A second reason for using them is that terms like MAC (originally Maximum Allowable Carryover, referring to the total amount of residue that can be carried over from the cleaned equipment to the next manufactured product) have been used in so many different ways by different companies that it seems futile to try to have people in the industry use the term in the same way (incidentally, MAC as originally defined is the same as my L2 value).

One reason I utilize these different shorthand expressions is that which limit is useful will depend on what I am doing. For example, if I am doing sampling recovery studies, I find it useful to refer to the L3 limit, because this limit is what I want to use for my one spiking level in my recovery study. On the other hand, if I am doing a product grouping (matrixing) I want to perform a protocol with the most difficult to clean product evaluated at the lowest limit of any product in the group. A comparison of L3 values will most easily determine the lowest limit in a product group. As mentioned, if I want to use a 10 ppm default value when it more stringent than my carryover calculation, I compare the 10 ppm to my L1 value (and not my L4b value). If I am using "stratified sampling" (see my Cleaning Memos of March, April and May 2010), then my L2 limit is critical. Note that in some cases, alternatives can be easily used; companies using swab sampling can express that limit as either L4a or L4b; which is chosen is usually a matter of past practice.

There is certainly no requirement that these shorthand expressions be used. However, they may have value. The main downside is changing your documentation to reflect this. Based on available resources, it may be a low priority to do so.