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Limits for Topicals

This Cleaning Memo addresses cleaning validation limits for topical dermatological finished drug products. Since the typical dose-based (or carryover) calculation involves the dose of the cleaning product active as well as the dose of the next manufactured product, the key question is how those doses are defined, specifically if the two drug products can be applied to either a very small surface area or a very large surface area of the skin. Let's first exclude some cases which can be handled without any special concerns. First is the case where the drug product is applied topically, but the drug effect is systemic (due to the fact that the drug is absorbed through the skin and is available systemically). A good example of this is a nicotine patch. In that specific case, there is no special change in terms of the limit calculation. Note that the only exception here is that if there is evidence that the drug active residue carrying over to the next product is not systemically available because a different carrier or excipients is used in the next formulation; however, even in this case it is probably best (because the data supporting lack of systemic availability in the next formulation may be somewhat weak) to perform a standard carryover calculation.

Another exception may be where the only intended drug effect is a topical effect, but the drug active may be systemically absorbed because of application conditions of the next manufactured product. An example of this may be an antibiotic ointment used on non-intact skin (such as for burn victims). In this case, a carryover calculation can be used, but the "dose" of the residual active (from the previous product) should be based on the systemic effect of that drug active, not necessarily on the topical dose.

Let's get back to the basic case (of primary interest here) where both topical drug products (the product cleaned and the next manufactured product) may be applied to either a small body surface area or a large body surface area. Do we perform a carryover calculation using the minimum dose of the first product covering only small surface area (such as 5 square centimeters) and a maximum dose of the next product covering the entire skin surface (1.8 square meters)? If we do that type of calculation we drive the limit extremely low (in many cases impractically low). Under what conditions does that type of calculation not make sense? Well, it doesn't make sense in cases where the skin is intact (and is non-mucosal skin), and where the drug active is not systemically absorbed. In other words, if the pharmacologic effect is limited solely to the skin that the product is applied to, then the limit calculation should take that into account. For example, the dose equivalent to 5 cm2 application, if present in the next product, would only present a dose in the next product if it were also applied to only 5 cm2. Furthermore, if residue of the cleaned active were present in the next product to produce a topical effect when applied to 5 cm2 of intact skin, it would produce that topical effect when applied to any 5 cm2 surface of intact skin. The conclusion is that (under these specified conditions) the concentration limit of the cleaned active in the next product is the same whether that next product is applied to a large or small body surface area.

How does this work out in practice? Here is the typical dose-based calculation for the limit in the next product (what I typically call L1):

$$\text{(I)}\quad L1 = \frac{\text{(minimum dose cleaned drug active)} \times 0.001}{\text{(maximum dose of next drug product)}}$$

Since (minimum dose cleaned drug active) = (conc. of active) X (amount applied),
and since (maximum dose of the next drug product) = (amount applied),
then since the "amount applied" is the same in each case, this L1 equation simplifies to:

(II) L1 = (conc. of active) X 0.001

In other words, if the relevant amount applied is the same for both products (and this is reasonable in cases where the pharmacologic effects limited to the skin the product is applied to), then L1 (that is, the concentration of the cleaned active allowed in the next drug product) is simply 0.001 of the concentration of the active in the cleaned product. For example, suppose I have a dermatological product with an active concentration of 12% (120,000 ppm or µg/g). Provided the restrictions discussed apply, then the limit of the cleaned active in the next product would be

(III)L1 = (120,000 µg/g) X 0.001 = 120 µg/g

Of course, if my policy was to use a default value of 10 ppm if that default were lower than my calculated L1, then I would default down to 10 ppm (or 10 µg/g). Once L1 was determined, L2, L3 and L4 would be calculated as usual (based on the batch size of the next product, the shared surface area, and the sampling parameters).

There are some considerations that would require that I change the calculation slightly. One concerns the frequency of application. In other words, if both products are applied once daily, then no change is required. However, if the cleaned product is applied once daily and the next product is applied twice daily, then the L1 calculation should be modified by multiplying by the frequency of application of the cleaned product and then dividing by the frequency of application of the next product. In example calculation above (Equation III), if the first product were applied once daily and the second product twice daily, then;

$$\text{(IV)}\quad L1 = \frac{(120{,}000\ \mu g/g) \times 0.001 \times 1}{2} = 60\ \mu g/g$$

Note that in considering frequency of application, if both products can be applied an "unlimited" number of times daily (that is, the instructions are "apply as needed"), there is no need to correct for frequency. However, if the cleaned product is applied at a fixed frequency (for example, only once per day) and the next product is applied "as needed", then some reasonable estimate needs to be made of what that maximum application frequency might be. On the other hand, if the cleaned product is applied "as needed" and the next product is applied only once, it would be prudent to consider both products as being applied only once daily.

A second consideration is the amount of product applied. The amount applied should be the amount applied per surface area (such as g/cm2), which I will call "application coverage". If both products are applied at roughly the same application coverage, then no correction is needed. However, if it is clear that one product is applied at a significantly different application coverage, then an adjustment needs to be made. It should be recognized that application coverage is highly dependent on the person applying it, so whether the difference is significant will be a matter of professional judgment. In an adjustment similar to that of application frequency,

if there is a difference in application coverage, then the L1 value is adjusted by multiplying by the application coverage of the first product and dividing by the application coverage of the second product. Note that as I have discussed it, application coverage only is the amount applied in one application (and not how many times per day it is applied). For example, if the cleaned product is applied at a coverage of 2 grams per 100 cm2 and the next product is applied at a coverage of 3 grams per 100 cm2, then in the previous example (Equation III), L1 would be modified accordingly:

$$\text{(V)} \quad L1 = \frac{(120{,}000\ \mu g/g) \times 0.001 \times 2 = 80\ \mu g/g}{3}$$

Note that inmost cases, where the limitation of no systemic absorption applies, if the concentration of active in the cleaned product is 5% or more, regardless of the application frequency and application coverage effects, the calculated L1 value will be above the default value of 10 ppm. However, it should be remembered that the issue of "no systemic absorption" also applies to the active of the cleaned product if it were present in the vehicle (excipients) of the next product.