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The Use of Safety Factors in Limits Calculations

Safety factors are a commonly used part of the usual dose-based calculations for cleaning validation residue limits. In the traditional formulation, “one one-thousandth of a minimum dose of the active in the maximum dose of the next drug product”, “one one-thousandth”, or 0.001, represents the “safety” factor. This Cleaning Memo will cover the significance of the safety factor as well as possible variations in safety factors used.

In one sense the so-called “safety” factor is not a true safety factor. In general, the use of a safety factor is an extra factor that provides protection over and above what a scientific calculation shows could be safely used. It is an additional factor applied to what is considered a safe level. In a dose-based calculation, the dose (of the active) itself is not a safe level. Therefore the safety factor is not truly 0.001. There are numerous stories about where the factor of 0.001 comes from. One is that a three log-reduction is somehow a “significant” reduction in scientific circles. However, the explanation given by one of the formulators of the dose-based calculations is that the 0.001 factor comes from two sources. One is a factor of 0.01 to take a dose from a therapeutic level to a safe level, and that a factor of 0.1 is the true “safety” factor (applied to the “safe” level) to provide additional assurance. Regardless of how it came about, this factor applied to the therapeutic dose will probably always be called a safety factor. However, it may be important to understand what it really signifies. Sometimes people will assert that it is not necessary to be so stringent in cleaning validation because of the safety factor of 0.001 in residue calculations. If the above analysis is valid, then the true “safety” factor in a residue limit calculation is significant (0.1), but not as great as 0.001.

While the initial formulation of a safety factor focused on the use of 0.001 as the factor, some companies will use different safety factors depending on the route of administration of the drugs. For example, one scheme involves the use of the following safety factors:

Parenteral	0.0001
Oral	0.001
Topical	0.01

The rationale is apparently that parenteral products require more safety and topicals require less. While this may sometimes be the case, it is not necessarily always the case. Certainly there is no objection (from the scientific viewpoint) if one chooses a safety factor greater than 0.001. However, is it justified to pick a less stringent factor for topicals? Since the presumed safety of a topical is that it is solely on the skin and not systemically absorbed, one must consider the fact that a changed vehicle for a topical active can significantly affect the systemic absorption of that active. If a given active is manufactured in a vehicle that provides low systemic absorption, and yet the subsequently manufactured product (in the same equipment) involves a vehicle that would provide a significantly greater systemic absorption of the active that potentially could be a residue, then using a less stringent safety factor may not be appropriate.

It should be realized that a safety factor is an arbitrary factor. [Note: some will assert that in a safety factor of 0.001, 0.1 due to one factor, 0.1 to another factor, and 0.1 to a third factor. In such a case, the arbitrary nature of the factor is just transferred to each of those three factors.] The 0.001 factor is widely accepted now; in the future, that may change. If one chooses to use a factor more stringent than 0.001, there should be no scientific or regulatory objection. However, if one chooses to use a factor less stringent than 0.001, a careful justification should be expected.

One should also consider that a dose-based calculation is not the only consideration in determining residue limits. In many cases it is the starting point, but other consideration such as allergenic, reproductive, or cytotoxic effects may have to be considered.

This Cleaning Memo is designed to stimulate thought about the use of “safety” factors in dose-based calculations. It does not proscribe nor prescribe any safety factors, but rather is meant to assist manufacturers as they consider the appropriate residue limits for their individual situations.