March 2013
Using Safety Factors Less Stringent than 0.001 of a Dose

The traditional approach for limits for actives that are not highly hazardous (that is, do not possess properties such as mutagenicity and teratogenicty) is to set limits based on 0.001 of a minimum daily dose in the maximum daily dose of the next drug product. Are there situations where factors less stringent than 0.001 could be used?

The answer is clearly "yes". The 0.001 factor was designed to deal with situations where the next drug product was administered for a lifetime (thus resulting in the residue from the previously cleaned drug product being administered over that lifetime). There may be situations where the next drug product is only administered for a short period, such as for several weeks. Examples might be cough syrups and antibiotics. In such cases, based on the input from a qualified pharmacologist and/or toxicologist, this may result in a safety factor less stringent, such as 0.01 of a dose. Clearly, there may be modifications to the situation. While a subsequent drug product may be taken for only a week, it may be taken for a week several times a year; that should also be considered.

Another example where a less stringent safety factor may be appropriate is in plasma fractionation, where the drug actives are normally present at high levels in the human body. For example, residues of albumin or Factor VIII getting into another fractionation product at a low level may present less of a concern, particularly if that active is already present in the subsequent product produced by plasma fractionation. This may also be a case where the products are not administered for a lifetime, but for a relatively short period of time. This should be balanced by the fact that the residues after cleaning may not be the various components in plasma, but rather degraded fragments of those components (due to cleaning with hot, aqueous alkaline cleaning solutions).

A third situation is where the active is degraded during the cleaning process. In that situation, a typical approach in the past has been to measure degradants by a non-specific technique such as TOC, and then express that TOC as if it were the undegraded active. This is done on the assumption that toxicity and/or safety concerns of the degraded fragments are not more stringent than the safety/toxicity concerns of the undegraded active. This may also be a case where a safety factor of less than 0.001 may be appropriate, based on input from a qualified pharmacologist and/or toxicologist. For example, if the degradants do not possess structural elements known to be important for the therapeutic effect of the drug active, this may lessen the concern with the degraded fragments. (Note that if there are known degradants with significant and/or unusual toxicity concerns, those should be targeted with a toxicity evaluation to set limits).

Some of you may be wondering why I am not including topical drug products in this category where less stringent factors may be used. There are two reasons. First, if the topical drug product is applied topically but passes through the skin and is available systemically, then the concerns for setting limit are not fundamentally different from oral or injectable drugs which are available systemically. There is no rationale for a less stringent factor here just based on the fact that it is topically applied (although note that the frequency of administration issue discussed above may be relevant). The second reason is that for topical drug products where the therapeutic effect is limited to the skin it is applied to, there are problems in using the typical carryover calculation (0.001 of a minimum dose of the cleaned active in the maximum dose of the next drug

product). Because the effects are limited to the skin surface it is applied to, minimum dose is not a few square centimeters of skin and maximum dose is more than a square meter of skin. As discussed in the Cleaning Memo of November 2008, the more typical approach here is to allow 0.001 of the concentration of active from the cleaned topical in the next topical product. Such a calculation will generally result in limits that are readily achievable for most topical products (that are not systemically available in the next drug product).

Of course, the other option to allow less than 0.001 of a dose for non-highly hazardous drug actives is to use the ISPE Risk-MaPP approach of providing a toxicological evaluation to arrive at a safe level. Such an approach will generally result in a safe amount less stringent than 0.001 of a dose, and it is clearly an option. This is based on the fact that the 0.001 dose criterion was designed to be a "one size fits all" approach, which was a significant overkill in most situations. Of course, this approach is not one of using a less stringent safety factor as applied to a dose, but rather of providing a toxicological evaluation to arrive at a safe level.

The purpose of this Cleaning Memo is not to specify safety factors, but to provide suggestions on where safety factors less stringent than 0.001 might be applicable.