Cleaning Memo for August 2015
Route Specific Health-based Limit Values

Can ADE and/or PDE values for cleaning validation purposes be determined and used for a specific route of administration based on the possibility of residues only being transferred to a specific limited class of products (such as solid oral drug products)? The answer could be "Yes", based on sound scientific principles. If my facility is only manufacturing oral dose products, then why shouldn't I be able to set limits based on the effects of that next product when that next product is administered only orally?

What do the ISPE and EMA say about this issue?

ISPE's Risk-MaPP defines an ADE (Acceptable Daily Exposure) as:

> A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime. By definition the ADE is protective of all populations by all routes of administration.

That sounds like an ADE should be protective for any (all?) routes of exposure. However, following that (and included as part of the definition of ADE is the statement:

> Normally, the ADE should be based on studies using the same route that it will be applied to evaluate. When this is not possible, and an ADE is required, proper professionals should be engaged (toxicologists) to provide a sound scientific rationale to support application to a different route. Only then can the ADE be adjusted to extrapolate between routes which may result in a lower or higher value.

I have always been confused by this latter part of the definition. Is the ISPE really saying that I can establish an oral ADE (different from a parenteral ADE)? Or is it saying that if I have only toxicity data from the oral route, I can utilize that to determine a safe level for parenteral exposure, which will give me a "true" ADE value for "any route"?

It's obvious that my hang-up is the phrase "by any route" in the ADE definition. When Risk-MaPP was introduced, I suggested to the ISPE that the definition be changed from "by any route" to "by a specified route", but the ISPE stuck with their definition.

The EMA defines a PDE (Permitted Daily Exposure) as:

> The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

The issue of "by any route" is missing. Later in its guideline, the EMA states:

"While the PDE value derived for an active substance (contaminant) generally is based on studies applying the intended clinical route of administration, a different route of administration may be applied for the active substance or medicinal product subsequently produced in the shared facility. Changing the route of administration may change the bioavailability; hence correction factors for route-to-route extrapolation should be applied if there are clear differences (e.g. > 40%) in route-specific bioavailability."

This suggests that route specific PDE values are possible (although I still believe this issue should be clarified by the EMA).

Note that if, as suggested by the EMA, ADE and PDE are synonymous terms, then this issue definitely should be clarified. I believe a clear path has been set by the recent ICH Q3D (limits of elements in drugs products). In that document, PDE values are presented for a variety of elements (both metals and non-metals). Those PDE values are given for three different routes of administration: oral, parenteral, and inhalation. The clear conclusion is that at least for that ICH body, PDE values (at least for these elements) can be route specific. In fact, this guide also includes a statement related to other routes of administration:

When PDEs are necessary for other routes of administration, the concepts described in this guideline may be used to derive PDEs.

Once caveat in route specific PDE/ADE values is that while an approach is clearly possible for a facility making drug products, it may not be possible for manufacturers of APIs (drug substances) where one API is for an oral route and another API is for a parenteral route. If the order of manufacture cannot be controlled, it is likely that PDE values should be based on a worst case route of administration of the next API. Needless to say, if I am only producing API's for oral administration, then PDE/ADE values for oral administration should be acceptable.

For those of you who might think I have "thrown in the towel" and advocate setting limits solely on ADE/PDE values, that is not the case. I still think other quality and purity considerations need to be addressed. Last month I gave an example of a published ADE value for NaOH, and presented why that was not appropriate as a "safe" value in a pharmaceutical product. Here is another example, from that same publication dealing with cleaning agent limits, where an ADE value of sodium dodecylbenzne sulfonate (an anionic surfactant) is given as 63 mg/day. Let's assume that value is correct, meaning I can give patients that amount on a daily basis for the rest of their lives. However, it is one thing to say that I can give that amount on a daily basis in water alone (for example). However, could it make a different if that amount were present in a drug product? It might not be a toxicological concern, but should I be concerned about any ionic interactions such that the bioavailability of a drug active was changed? Or should I have any concerns about the stability of a drug product containing that amount of an anionic surfactant? The answer is, of course I should. (For now I'm ignoring the issue of having 63 mg of *any* foreign material in a

500 mg tablet). This is why an ADE/PDE value should only be a starting point for cleaning validation limits. This is consistent with the general principle of not affecting or altering the "safety, identity, strength, quality, or purity" of a drug product. This would mean that cleaning validation limits should be set with inputs from toxicologists, pharmacologists and formulation chemists (among others).

Next month, we'll discuss the issue of adjusting limits based on the duration of exposure of the next product.