Cleaning Memo for July 2016
Should 10 PPM be Used for Limits?

A recent publication ("Cleaning Limits – Why the 10-ppm Criterion Should be Abandoned", by Michel Crevoisier et al, *PharmTech*, Volume 40, Issue 1, pp 52-56) advocated abandoning the 10-ppm criterion for pharmaceutical cleaning validation limits. The authors point to the EMA document on health-based exposure limits, as well as the lack of any regulatory guidance documents *requiring* the use of a 10-ppm criterion. They state that a 10-ppm limit is not consistent with the generally recognized toxicological principle that "the dose makes the poison". They then state quite clearly (and accurately) that setting a limit at 10-ppm in the next product does not provide a distinction between those actives that are more highly hazardous and those actives that are less hazardous.

So, is this a good analysis of the situation with a 10-ppm criterion? It depends what you are looking for. In one sense the authors are technically correct: when you compare the use of 10-ppm *alone* to the use of a PDE *alone*, the PDE value is a better estimate of toxicological hazard to the patient. In another sense, the authors reflect a misunderstanding (or lack of knowledge) of how the 10-ppm criterion is (or should be used) by the pharmaceutical industry for process equipment cleaning validation. The general approach in the past (before ADEs and PDEs) has been to use 10-ppm of the cleaned active in the next drug product as an alternative to be used *only* if it provides a lower limit than the limit calculated by a dose-based criterion (such as 0.001 of a minimum daily dose). That is, the choice is not "10-ppm or 0.001 of a dose, *choose whichever you want*"; it has been to calculate a limit in the next product using the 0.001 dose criterion, compare that to 10-ppm in the next product, and then *use the more stringent (lower) of the two values* to determine the limit per surface area and the limit in the analytical sample. Why the authors glossed over this *proper* usage of the 10-ppm criterion, I have no idea.

Why is the 10-ppm criterion used in this way (if it is the more stringent of the two criteria)? One reason is that a carryover (MAC or MACO) calculation can result in very high limit. In some cases calculated limits result in values above what is considered visually soiled (typically given as 1-4 $\mu g/cm^2$). A visually clean criterion is also a "check" on exceedingly high calculated limits. A second reason is that toxicological safety is not the only criterion that is appropriate for setting cleaning validation limits. The FDA "Q&A on CGMP" (the section on Equipment, question/answer #7, dated 6/8/2015, states:

> "Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues. Contamination that is reasonably avoidable and removable is never considered acceptable."

There are at least three (and perhaps four) criteria listed there. The first is that the residue and residue level is safe. Note that in an earlier version of this question/answer (Human

Drug CGMP Notes, Second Quarter 2001), the FDA statement was that it must be "*medically* safe" [emphasis added], which is the toxicological evaluation. The second criterion listed by the FDA is that the residue causes no product quality concerns. What does that mean? Well the FDA is not specific, but I assume it can be things like effect on the subsequent product stability, effect on the bioavailability of the active in the subsequent product, effect on physical properties such as breaking strength or dissolution of a tablet, and perhaps effects on lyophilization such that reconstitution with water were affected. In looking at effects on product quality, it may be helpful to look at another Q&A on CGMP dealing with *objectionable organisms* (the section on "Production and Process Controls, question/answer #20), which states:

> "The meaning of the term *objectionable* needs to be evaluated on a case-by-case basis by each drug manufacturer. The primary meaning relates to microbial contaminants that, based on microbial species, numbers of organisms, dosage form, intended use, patient population, and route of administration, would adversely affect product safety. Microorganisms may be objectionable for several reasons; for example, they:
>
> - Are a known human pathogen
> - Adversely affect product stability
> - React with, or potentially damage the integrity of, the container closure system (for example, fermentation that creates gaseous pressures sufficient to rupture a product container/closure)
> - Interfere with analytical methods or active ingredient bioavailability"

For clarification, these possible effects are given *as examples*. However, it may be appropriate to, at a minimum, consider these same possible effects (treating human pathogenicity as toxicological safety) for cleaning validation purposes. That may have has been one of the reasons for establishing a reasonable check on a dose-based calculation. [I should note here there that another check that has also been used is to establish an alterative limit of either 1 µg/cm^2 or 4 µg/cm^2, if that limit is lower than the dose-based limit. Those values are based on the typical values given for what is visually clean.]

So, if that is how the 10-ppm criterion has really been used, do we still need to use it if we are using health-based limits, such as PDEs or ADEs? My answer is a definite yes, if concerns other than toxicological safety should be considered. In analyzing the data presented in Tables II and III in the authors' publication, eight of the eleven actives where the 10-ppm criterion was used to determine the limit per surface area (as given in Table III) are more stringent (sometimes by a factor of 10 or more) as compared to the surface area limits given in Table II. Two cautions are needed here. One is that the limits in Table II are calculated for *each* possible subsequent product, thus giving ten limits for each active. In Table III, the surface area limit for each product based on the 10-ppm criterion is calculated in going from the active in one product to that same product as the next product. So, in one sense a direct comparison is not fully a scientific comparison. The second caution is that surface area limits are given in mg/m^2, so if you are used to

values in µg/cm^2, you will need to divide the values reported by 10 to convert from mg/m^2 to µg/cm^2 (just to fully appreciate what is really happening).

One other point made by the authors is that based on "250 swab results" collected "over two years", high risk changeovers were identified as the ones that required a surface area limit of less than 25 mg/m^2. Okay. They have just said that 10 ppm does not distinguish a high risk from a low risk, but apparently 25 mg/m^2 does?? Does that mean that a limit of 25 mg/m^2 for acetaminophen is the same risk as 25 mg/m^2 of a potent steroid? In other words, the authors appropriately reject the 10-ppm criterion as not distinguishing toxicity risk, but apparently allow the 25 mg/m^2 criterion to separate high risk from low risk situations. Something is inconsistent here.

What concerns me most about this publication is the way a straw person is set up, and that the relevant comparison presented by the authors is a limit based on a PDE value *versus* a limit based on a 10-ppm criterion. That totally distorts how the 10-ppm criterion has been used from the time it was first *proposed by Lilly scientists in 1993* (although I am aware that some companies have tried to use the 10-ppm criterion independently of a dose-based or health-based calculation).

For clarification, I do accept that the 10-ppm criterion is somewhat arbitrary. A different value could have been chosen, such as 5-ppm or 15-ppm. That does not make it "unscientific". It is no more unscientific than (or has the same level of arbitrariness as) the F1 factor of 5 given in ICH Q3C for "extrapolation from rats to humans". Other factors could have been used, but the selected value reflects a scientific consensus.

Just to keep the record straight, the 10-ppm criterion discussed here is not the 10-ppm criterion used for upstream bulk biotech manufacture. That 10-ppm is a limit in any analytical sample, and not necessarily the limit in the next product.