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Revisiting Medically Safe Limits

The FDA states in a Human Drug CGMP Note (Second Quarter 2001) that residue limits should be established that are practically achievable, are medically safe for the next manufactured product, and don't affect the quality of the next manufactured product. For limits for drug actives in finished drug manufacture, the medically safe criteria is usually met by allowing no more than 0.001 of a minimum dose of the active of the cleaned product in the maximum dose of the next drug product. This is typically modified by utilizing a "default" limit of 10 ppm in the next product, if the dose-based calculation results in a value above 10 ppm (one might say this "default" limit somewhat addresses the FDA's product quality criteria).

For actives for which a dose is not established, such as for early clinical trial products, a calculation based on toxicity considerations is typically done. However, two recent publications by scientists at Merck and the Toxicology Center for Risk Assessment suggest an alternative approach for setting limit for actives where there is no dosing information and for which there is limited or no safety information. Those publications are Dolan et al, "Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations", Regulatory Toxicology and Pharmacology, Vol. 43 (2005) pp. 1-9, hereafter referred to as "Dolan et al", and R. Forsyth et al, "A Single Adulteration Limit for Cleaning Validation in Pharmaceutical Pilot-Plant Environment", Pharmaceutical Technology Vol. 31 (January 2007) pp.74-83, hereafter referred to as "Forsyth et al".

Let's look at Dolan et al first. The basic approach in Dolan et al is to utilize the principle of "threshold of toxicological concern" (TTC) to set ADI (Acceptable Daly Intake) values. The TTC principles were originally developed by the FDA for food additives. Dolan et al propose applying the same principles to "non-food chemicals" and for other exposure routes, such as a parenteral route.

The authors recommend different ADI values based on three categories of compounds where there is limited or no toxicity data. For compounds that may be carcinogenic, an ADI value of 1 μg/day is recommended. The potential for carcinogenicity is based on in vitro mutagenicity data or structural analogies to known carcinogens, with an in vivo confirmation. Note that there is an exception here for "five structural groups of highly potent carcinogenic chemicals,... [including] steroids, polyhalogentated dibenzo-p-dioxins and -dibenzofurans, alphatoxin-like, azoxy- and N-nitroso compounds".

For compounds that "may be potent or highly toxic", an ADI value of 10 μg/day is recommended. This category includes those compounds that "may produce pharmacologic or toxic effects at very low doses".

The third category is for "compounds that are not likely to be potent, highly toxic or carcinogenic". The recommend ADI for these compounds is 100 μg/day.

Note that these recommendations are based on chronic exposure. I don't fully understand all the background and justification for such recommendations; I would refer you to the original document for that detail. However, what is important for those involved in cleaning validation is that the authors give an example from cleaning validation to illustrate the use of their recommendations based on the TTC principles.

Furthermore, the example given for a case where the contaminant is highly potent or toxic results in a calculated residue limit for the active per swab of 3 mg (that is, 3000 µg) for a swab area of 25 cm^2. That is equivalent to a surface area limit (what I typically call a L3 limit) of over 100 µg/cm^2, which would be considerably beyond what would be expected for visually clean (as the authors themselves noted).

Forsyth et al includes these recommendations based on TTC principles in an evaluation of cleaning validation in a pilot-plant situation (certainly an example where there could be limited or no toxicity data). For this publication, the authors evaluated three criteria for setting limits, and selected the most stringent of the three. One criterion was the "health-based risk assessment", meaning the value of 100 µg/day (0.1 mg/day) as the ADI value based on the Dolan et al recommendations. The second criteria was the "adulteration based calculation", or the standard default value of 10 ppm in the next product. The third criterion was application of "visible residue limits". Essentially what was found for this application was that the visible residue limits were the most stringent of the three criteria. While the main conclusion of the authors was that a standard visible residue limit of 100 µg per 25 cm^2 (4 µg per cm^2) was more stringent in most cases than a calculation based the adulteration limit of 10 ppm, I believe it is fair to say that the data presented also supports the conclusion that the calculation based on the adulteration limit of 10 ppm is more stringent in most cases than the calculation based on the health based limit (the health-based limit is the TTC ADI value of 100 µg/day). I believe it is also fair to say that the Forsyth et al use of the TTC ADI value was for illustrative purposes only, and was not meant to be a critical evaluation of the concept.

The good news about the Dolan et al approach is that, if it is valid, it indicates that our current ways of setting limits is too conservative (that is, too stringent). What do I mean by this? Well, a typical approach for an active for which there is known dosing information is that 0.001 of a dose of the active is a safe level in a maximum daily dose of the next drug product. Let's assume a typical situation for a product that is not highly potent, not highly toxic, and not carcinogenic, thus fitting into a Dolan et al ADI value of 100 µg/day. Assume that the next product is a tablet that is 1 gram gross weight, and is dosed daily. Based on the Dolan et al approach, the limit in the next product is 100 µg per 1 gram, or 100 ppm. Based on typical approach using a default value of 10 ppm, the Dolan et al approach gives a value 10 times higher. In this example, an active would have to be classified in the second group (highly potent or toxic) to have a TTC ADI value of 10 µg/day, thus having a limit in the next product of only 10 ppm (the same as the default value).

Furthermore, a highly potent active is likely to have a dose of less than 100 mg/day. With that known dosing information, we can calculate limits as we conventionally have done. Using a dose of 100 µg/day results in a limit in the next product (again assuming the conventional "safety" factor of 0.001 and a daily dose of the next drug product of 1 gram) of 0.1 ppm. Note that even if we considered a smaller tablet mass for the next drug product, such a change would correspondingly raise both the limit based on a TTC ADI calculation and the limit based on 0.001 of a dose, but the relative difference would still be evident. What I am saying is that if traditional dose-based calculations usually result in limits much lower than limits based on TTC ADI principles, then either the traditional 0.001 dose calculation is too conservative, or the application of the TTC ADI concept to pharmaceutical cleaning validation requires further refinement.

Some may argue that it is inappropriate to compare a 0.001 dose calculation to a TTC ADI calculation, because the TTC ADI concept is supposed to apply to compounds (actives) for which there is limited or no toxicity information, and therefore assumed limited or no dosing information. While that assertion has some truth, it is not a valid objection. One would assume that one should be more conservative in setting limits in cases where information on safety or dosing is limited. However, if the TTC ADI principles result in higher limits for situations where there is known safety and dosing information, then something is wrong. As I suggested, either we (the industry) have been too conservative in setting limits, or the TTC concept as applied to cleaning validation needs further refinement.

Some possible refinements in TTC ADI limits might include setting different ADI limits for oral doses and parenteral doses. Another area to consider is whether the ADI or "permitted daily exposure" (PDE) values set by the ICH Q3C(R3) for residual solvents and by ICH Q3A(R2) for impurities in drug substances are appropriate analogies for cleaning validation ADI values. The difference is that ICH documents deal with intrinsic impurities, while cleaning validation deals with extrinsic impurities. On the other hand, is it really critical that the level of residual solvent in a drug substance be different depending on whether that solvent is used in the drug substance synthesis or in the cleaning procedure? This also requires us to decide whether the cleaning procedure is part of the manufacturing process or is something different than the manufacturing process.

Please don't get me wrong here. I am not suggesting that the TTC ADI concept be adopted, nor am I suggesting it be discarded. What I am suggesting is that people more knowledgeable than me in pharmacology and toxicology may want to reevaluate how limits are set in pharmaceutical cleaning validation. However, until that is done, it is probably best to continue setting limits as we have done in the past.