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Are We Setting Limits Correctly?

This Cleaning Memo is a shortened version of my recent (August) webinar of the same title. The way limits are currently set for cleaning validation protocols has been critiqued by Andy Walsh (of Clean6Sigma) as not risk-based, as not science-based and as arbitrary. This critique was given in presentations at an ISPE conference this summer, but parts of the critique also appear in drafts of ISPE's RISK-MaPP Baseline Guide and Cleaning Validation Baseline Guides. For example, the fact that different safety factors are used to apply to a dose to arrive at an acceptable level is used to say that the limits are inconsistent. The use of a 10 ppm default limit is used to say that limits are set arbitrarily. The use of default levels is seen as not risk-based because it can cause, in certain situations, potent and less potent drug actives to have very close to the same limits. Furthermore, it is stated that a dose calculation ignores the effect of other safety concerns, such as cytotoxicity and reproductive hazards of drug actives.

While many of the critique may appear reasonable taken in isolation, they unfortunately do not take a holistic view at how limits are currently set. Furthermore, the critique brings up differences (which are certainly appropriate in a risk-based approach) as a reason for saying they are inconsistent. The current best practice (this is my view of best practice) for the way limits are set for a drug active in finished drug manufacture is to set limits for the active based on some dose calculation (typically 0.001 of a minimum daily dose in a maximum daily dose of the next drug product). If that calculation results in a value above a default (typically 10 ppm), then the default value is used. Furthermore, the equipment must be visually clean. And, if there are significant toxicity or safety concerns other than the pharmacological desired effect, these need to be addressed. Those significant concerns include things like cytotoxicity, allergenicity, and reproductive hazards. Another significant concern is the possible interaction of the drug active of the cleaned product with the drug active of the next manufactured product.

Walsh proposes replacing the current scheme of setting limits by an ADI (Acceptable Daily Intake) type of calculation, where the ADI value is calculated from a variety of safety values, such as the NOEL or NOAEL of the drug active. While that is possible, Walsh fails to clarify whether the desired pharmacologic effect would be part of the adverse effects. In one of his slides in the June ISPE conference, he lists an ADI value for a certain active as 40 mg, while the daily dose is 80 mg. It would seem that his technique needs further refinement, because having 50% of the daily dose of one drug active in a different drug product would usually be unacceptable.

Furthermore, while critiquing the current scheme in that it may result in potent drug and non-potent drugs having the same limit (the example given is a potent drug that has a calculated dose limit of 9 ppm in the next product and a relatively non-potent drug that has a calculated limit of 1000 ppm in the next product, but whose limit is set at 10 ppm because of a default value), Walsh goes on to present an approach to cleaning where every product is cleaned to the same residue level (regardless of the limit)! In other words, under his proposal, both potent and non-potent drugs are treated the same, the exact thing that he criticizes in the current scheme.

Walsh's proposal lacks any consideration of a default value. It must be admitted that in some sense use of default value is arbitrary. However, it is not inappropriate. If a dose based calculation (or an ADI based calculation) results in a limit in the next product of 100 ppm or limit per surface area of 20 micrograms per

square centimeter, I would be concerned about having limits set at those levels, and actually having residue values of 25-50% of those limits. Of course, in one sense Walsh could avoid this criticism by saying that all products will be cleaned to the same level (providing that that same level is an appropriately low level). However, setting practical default values, which are only used if they are below the calculated limit, is reasonable. Most companies set a default limit of 10 ppm active in the next product. However, an alternative is to set a default limit based on the surface area limit, typically a default value of 4 micrograms per square centimeter (a typical value used for “visually clean”). Note that this is not the same as using a visually clean standard alone. In this case, the limit is calculated, and if it is above 4 micrograms per square centimeter, that lower default limit is used for calculating swab and rinse sample limits.

Note that this I am not saying that the current way of setting limits cannot be improved. However, what I am saying is that it is not appropriate to say that current methods are arbitrary, not science based and not risk based. Some of the things that Walsh proposes can be integrated into a holistic approach. However, it is not necessary to trash current methods of setting limits in order to recommend improvements.