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The Science Behind Limits

There has been a lot of discussion (at least in the USA) in the past months about returning science to its rightful place. What does this mean for cleaning validation limits? What is the role of *science* in setting limits? While we might all like to say that our limits are scientifically set, there is an element in which other concerns, such as economic, political and moral concerns, affect how we set limits. What do I mean by that? Well, let's look at a example of setting "limits" (or "determining what is acceptable"). It is common practice to say that an acceptable level of cancer cases from a food additive is, for example, one in a million. We can look at that and throw our hands up and say that one case is unacceptable, so we reject that certain food additive. But, with that approach, we will probably starve to death. Part of the reason why a level of "one in a million" is accepted is that there is a certain background level of cancer cases in a typical population. This makes it difficult to determine that any specific additive has a cancer rate below that background rate. And so the "scientific community" (however that is defined) agrees that a rate of one cancer in a million cases is acceptable. On this basis, we say the acceptable level is based on science. But we clearly know that there is *not a formula* that tells us "one in a million" is an acceptable rate for incidences of cancer due to a given food additive.

We can also look at how economic or social factors affect what we consider acceptable if we look at deaths due to automobile accidents. Clearly the number of deaths each year in the USA (about 37,000) is unacceptable. So, do we set strict limits on who can drive, how fast they drive, and what they can drive? The answer is no, for a variety of reason. Now we do some things to limits accidents and their effects (such as seat belt laws). But we also consider other things, like the fact that transportation by car is critical for many in the USA to travel to a place of work. Or, like the fact that large cars are safer, but we want people to drive smaller cars for other reasons. It is possible to design safer cars and safer highways (with safer rules of the road), but it not a politically or economically feasible situation to change the situation such that fatalities are even cut in half.

You might say there is a big difference between cars and food additives. And that is true. But in both cases we allow forces *other than what we know scientifically* to help determine what is acceptable.

Now, how does this apply to acceptance limits in cleaning validation? We can use the example of allowing limits of an active such that no more than one one-thousandth (0.001) of a daily dose of the active from the cleaned product is present in a daily dose of the next product manufactured in the same equipment. Why is it 0.001? Why not 0.01? Or why not 0.0001? Or why not 0.0036? Is there a scientific reason why we use 0.001? Yes we know that the effects of the active are not as significant at 0.001 of a dose as compared to a full dose. But, where does 0.001 come from? It is possible to trace it to the Fourman and Mullen 1993 *Pharm Tech* paper, but why did they choose 0.001 (and not 0.002 or 0.0005). I have heard Mike Mullen describe (I believe as a joke) that when all concerned parties (scientists, management, lawyers) at Lilly were evaluating the safety factor to use, everyone agreed that 0.1 was not stringent enough, and all but the lawyer agreed that 0.01 was adequate. Because the lawyer disagreed, they chose a safety factor of 0.001. Now there may be other reasons for a more stringent safety factor, such as patients taking drugs may not be so healthy, but that story does indicate the "arbitrariness" of selecting an acceptable level. I should add here that different factors may be appropriate, for example, based on the dosing extent of a drug, such as drugs that are dosed *daily for a lifetime* (statins for cholesterol control) versus drugs that may be dosed *for only a week* (antibiotics).

Those of you familiar with my webinars know that I have argued against changing setting of limits from a dose-based calculation to a toxicity based calculation. It should be noted that in both calculations, a factor (or factors) are used to arrive at a safe level. What that factor is may be guided to an extent by science, but there is a sense in both cases of what can be considered as a "generally recognized as safe" criterion; that is, the scientific community accepts it. Part of the reason I argued against the change from a dose-based calculation to a toxicity-based calculation is that for the last 16 years, the scientific community has viewed the dose-based calculation as acceptable, and as adequately protecting patients. If a change is to be made to replace it with a toxicity-based calculation, a careful review of the consequences of such a change should be made (and I am not aware of any publications addressing those consequences). In any case, discussion of dose-based versus toxicity-based calculations for actives is a side issue, except to illustrate that in both cases the conversion factors involve some judgment other than a strict *scientific* formula to decide what is acceptable.

We should also remember that the FDA cleaning validation guidance and the PIC/S cleaning validation recommendations don't mention that limits should be determined *scientifically*. The FDA guidance states that "The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable." (The PIC/S gives a paraphrase of this same statement.) Therefore, we need to be careful in what we communicate when we say we are setting limits on a scientific basis.