

Cleaning Memo for February 2018

Does a High “Margin of Safety” Protect Patients?

A key concept in ISPE’s Risk-MaPP is the “Margin of Safety”. This Cleaning Memo will focus on that concept *as defined in Risk-MaPP*. For clarification, when I use the term “Margin of Safety” (with caps) I am referring to the concept as defined in Risk-MaPP. As used in Risk-MaPP, the phrase is sometimes capitalized (“Margin of Safety”), sometimes not in caps (“margin of safety”) and once called a “True Margin of Safety”. When I refer to a “safety margin” I am using it in a generic sense as that is generally understood.

But before I get into discussing the “Margin of Safety”, I will provide some background in Risk-MaPP’s setting of limits based on ADE’s.

According to Risk-MaPP, the only limit needed for cleaning validation (other than the equipment being visually clean) is one based on an ADE. Section 6.3.2.3 of the 2017 revision (all references to Risk-MaPP will be using the 2017 revision) states that the “only criteria necessary for a robust cleaning process are the health-based, ADE derived limit, a validated analytical method with a sensitivity below the acceptance limit, that is visually clean.” Risk-MaPP also states that a limit based on an ADE adequately protects patients, and setting limits on a *more stringent basis* does not provide additional patient protection. This is explicit in Section 6.3.2.3, which goes on to say that that “The healthbased limit represents a level that is safe for all patient populations and reducing this further does not increase patient safety....”

Now you will notice there is an ellipsis at the end of that last quote from Risk-MaPP, because the sentence goes on to say “... and, as discussed above, actually lowers the apparent margin of safety” (that is to say, limits more stringent than the ADE-based limit lower the Margin of Safety). I will leave the discussion of “Margin of Safety” for just a minute, and will cover a related concept in Risk-MaPP. Risk-MaPP also recommends that while acceptance limits are based on an ADE, the actual data achieved in a cleaning validation protocol should be “as low as possible below” the limit based on an ADE. It states this in two different sections. The actual statement in 6.3.2.1 is that data should be evaluated “to ensure that any residuals after cleaning are as low as possible below the health-based criteria...” The actual statement in 6.3.2.6 is “It is important that the residue data is as far below the health-based residue level as possible.”

Now, if it is true that reducing limits below a limit based on an ADE does not provide additional patient protection, why is there a call for actual data to be as “low as possible” below the ADE-based limit? Well, that brings us to the concept of “Margin of Safety” as defined in Risk-MaPP. One would think that in a document that emphasizes patient safety, any discussion of a safety margin would be related to additional *patient* protections. But, that is apparently not the case, since as I have already pointed out, there is the clear statement about reducing the limit (that is, making it more stringent) *not* increasing patient safety. However, in Risk-MaPP the “Margin of Safety” is *defined* as the difference between the actual residue data and the calculated limit. So, there appear to

be at least two ways to increase the “Margin of Safety”. One way is to achieve lower actual residue data, and a second way is to increase the limit. But, if the residue data is to be as low as possible, is there really a *patient protection advantage* by having a greater “Margin of Safety”? My answer is “no”. What Risk-MaPP does achieve is an increased safety margin *for the manufacturer* in that the manufacturer is less likely to have failing results if it can set higher acceptance limits. In other words, the increased “Margin of Safety” offers an advantage to the manufacturer in terms of less likelihood of a validation failure, and not necessarily a safety advantage to the patient.

One way to look at this is to suppose I am making a product and there are two ways to set limits. One way gives me an acceptance limit of 10X ppm in a rinse sample, and another way gives me an acceptance limit of 2X ppm in a rinse sample. Let’s say my actual residue data was only 0.1X ppm. Is the risk to the patient different depending on which limit I utilize. I think not. But, I am less likely to have a failing result if my limit is set higher. Furthermore, Risk-MaPP explicitly states that manufacturers should not “relax their cleaning processes” just because a higher limit gives a greater “Margin of Safety”. In one sense this is consistent with statements about actual residue data being as low as possible below ADE-based limits.

Of course, Risk-MaPP is assuming that manufacturers will try to achieve limits as “low as possible”. While it is probably true that most firms are not going to change cleaning processes that have previously been validated (as long any limit based on the traditional approach is more stringent than an ADE-based limit), I am not so sure that for new processes this will be the case.

The upshot of this is that Risk-MaPP’s “Margin of Safety” does not provide increased patient protection, but merely reduces the *business risk* of a manufacturer in achieving its residue limits in validation protocols. This “Margin of Safety” concept is a relatively strange concept in any discussion focused on patient risk. The only reason it appears to be in the document is to make ADE-based limits more attractive. While the “ADE only” approach may be more attractive to a manufacturer, except for highly hazardous actives (where ADE-based limits are required for non-dedicated manufacturing), it provides no added patient advantage (unless one believes that by lessening the stringency of the cleaning process pharmaceutical companies would lower the selling price of those drugs).

As a final note, Risk-MaPP advocates may accuse me of quoting the document out of context. I invite all to read the document sections that I have quoted to see that my assertions accurately reflect the inconsistencies in the document. I have now been critiquing the Risk-MaPP approach to limits for at least eight years, and I still have not seen valid responses to my concerns other than statements to the effect that ADE-based limits are the *science-based* ones. In my view, Risk-MaPP advocates play the “science-based” card as a way to silence critics. And they have been relatively successful because, apart from the recent draft EMA Q&A, I appear to be the only one who publically points out the problem with the Risk-MaPP approach. For clarification, the EMA does not directly point out the problems with Risk-MaPP; the recent draft EMA Q&A merely accepts the *traditional* approach as acceptable for actives that are not highly hazardous.