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A Stroll Down Memory Lane

You're probably thinking I have "lost my marbles" with this title, saying "What is this Cleaning Memo about?" Well, over Christmas break I had the opportunity to write three chapters for an upcoming book on cleaning validation. One of the chapters was an introductory chapter, and as part of that I reviewed what was said about cleaning validation in the 1980's. And, the amazing thing is that the critical issues have not changed. We still ask questions about the issues identified in these early papers, including "How do I set limits?", "How do I sample for residues?", and "What analytical techniques do I use?"

One paper is by S. W. Harder, entitled "The Validation of Cleaning Procedures", published in Pharmaceutical Technology in May of 1984. Harder listed five elements essential to cleaning validation.

a.   A "relevant" cleaning SOP
In this section he discussed a "batch record" type documentation for a cleaning procedure, as well as specifying times, temperatures, and volumes of water to be used. He also discussed the difference between procedures used between lots of the same product and procedures to be used at the end of a campaign.

b.   A procedure to determine "level of cleanliness achieved"
What he means here is the sampling procedure. In this section he discussed both rinse sampling and swab sampling. His conclusion was that swab sampling is not as "quantitatively accurate"; however, it should be noted that he was only comparing swab sampling to a separate sampling rinse, not to taking a grab sample of a CIP process rinse.

c.   An assay method for residues
In this section, Harder mentioned that two key items for existing analytical procedures for actives are verifying that it works at the lower levels possible when measuring residues, and also accounting for "interferences from materials not present in the product for which the method was developed" (which could include things like the cleaning agent and degradants).

d.   A "realistic" residue limit
Here Harder listed three considerations. First is that the limit be "practical and achievable". Second is that the limit must be "verifiable by analytical methodology". (This sounds like the origin a phrase in the 1993 FDA guidance document that limits must be "practical, achievable, and verifiable".) The third element is that limits must be "in line with residual limits set for various substances in food". He provided a list of limits of various pesticides in foods, with limits ranging from 0.5 ppm to 200 ppm. He points out that drugs "ingested or applied" would be considerably less than the amount of food eaten, so limits in line the limits given for food are probably reasonable. Obviously, this analogy of Harder's seems to apply to oral doses, but perhaps not to injectables. For limits for bioburden, he referred to another publication suggesting limits of 2 CFU/cm2 for non-sterile manufacturing.

e.   A detailed protocol
Harder said the protocol should tie all the other elements together. In this section, he also referred obliquely to sampling recovery studies when he stated "If the evaluating procedures are not effective in recovering the total

amount of residual drug remaining in the equipment…, the validation studies will be invalid."

Three other topics are "Serial and Non-serial Cleaning Procedures", "Microbiological Considerations", and "Revalidation". For cleaning within a campaign, a water rinse or dry vacuuming is appropriate. Surprisingly he said that the water rinse will leave the equipment visually clean, which is possible but certainly not always the case. In discussing bioburden issues, he emphasized the need for a Purified Water rinse and for adequately drying of the equipment after cleaning to control bioburden. For revalidation, Harder suggested that revalidation should be done on significant changes. In addition, the frequency of revalidation depends on the propensity for microbial growth, with liquid and semi-solid products requiring it more frequently than dry products, until there is a reliable history. This emphasis on microbiological aspects is somewhat unusual, and may reflect the fact that cleaning in 1984 was more manual than automated.

The second early technical article is by Douglas W. Mendenhall (of Abbott at that time), and is entitled "Cleaning Validation". It appeared in Drug Development and Industrial Pharmacy in 1989. In his introduction, Mendenhall emphasized that there is no one "right way" for everyone to perform cleaning validation. He emphasized the need for flexibility to "fit the unique circumstances of their products, processes, facilities and historical practices".

Items covered in Mendenhall's paper include the following.

a.   Establishment of limits
Mendenhall emphasized the relationship between limits and detection capability. Just because something is detectable does not mean it is objectionable. He appealed to the well known concept that below a certain level, a residue may have no biological effect. He gave two criteria for cleanliness. One was a determination of the toxicological and/or medical threshold level, with a safety factor of 10X or 100X. Then based on shared surface area combined with the minimum batch size and maximum dose of any subsequent product, a limit could be calculated. (Note that this may be the basis for the calculation established by scientists at Lilly in 1993, and subsequently referenced in the 1993 FDA guidance.) Mendenhall's alternative criterion was the "very pragmatic approach" that the equipment be visually clean. He pointed out that in his experience (at that time), quantitative calculations "almost universally" established residual levels that were readily visible.

b.   Non-uniform contamination
Mendenhall focused also on whether residues left after cleaning are uniformly dispersed throughout the next manufactured product, or whether in certain "continuous" equipment, such as a tablet press, residues are transferred to relatively small portion of the next product.

c.   Residues to test for
In this section, Mendenhall discussed the need to assess all potential residues (actives, excipients, degradants, cleaning agents) and decide which are appropriate to set limits for and test in the protocol. He did not provide a list of those that should be established, which is consistent with his introductory statement that there was no one "right way" to do cleaning validation.

d.   Use of "models"
By using the term "models", Mendenhall was referring to grouping (matrixing) strategies whereby one

performs validation on a representative product (the "model" product), which is the "most difficult to clean". He also covered "models" for equipment.

e.   Sampling methods

Like Harder, Mendenhall referred to both swab sampling and rinse sampling. In discussing swab sampling, he did refer to "independent studies which demonstrate the swabbing procedure's ability to recover sorbed residues from the contact material", which is a reference to recovery studies. For rinse sampling, he stated that this sampling method is particularly useful when the next product contains the same solvent (such as water) as used for rinsing. He also discussed calculating the limit in the rinse based on the rinse volume. Mendenhall added a third category of sampling, which he called "Pseudo-Product Samples", but which we would call "placebo sampling".

f.   Automated vs. manual cleaning methods

Mendenhall stated (quite correctly) that "from a validation standpoint, there is no fundamental difference between" automated and manual cleaning processes. He did emphasize that the manual cleaning processes requires more "thorough operator training and appropriate supervision".

Like Harder (who wrote five years before), Mendenhall picked up on many of the key issues in cleaning validation for process equipment. I'm not sure where Dr. Harder is now, but following his work at Abbott, Dr. Mendenhall also worked at Glaxo and at Merck (as recently as 2001). While a study of their papers is not a requirement for doing cleaning validation in 2008, I'm sure we all owe them a debt of gratitude for helping to define key issues in performing effective and efficient cleaning validation.