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Regulatory Guidances I'd Like to See Changed – Part 1

A common question I get at my training classes is "When is [fill in the blank with a regulatory agency] going to update their guidance on cleaning validation?" The reason for the question is that most guidance documents were written in the 1990's, and we have learned a lot about cleaning validation over the past 15-20 years. (Note: Apologies to you Canadians. Health Canada updated their guidance once in 2008 and is currently undergoing another update.)

Guidance documents generally point out some basic issues, but some are problematic in terms of how they should be interpreted. This Cleaning Memo focuses on some key statements in guidance documents that I think should be changed at once. However, I doubt that cleaning validation is a key driver for programs at most regulatory agencies, so don't expect any action on these recommendations soon.

1. The following statement is in the PIC/S Recommendation PI 006-03:

> "The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed…." (Section 7.10.2)

Does this mean that a specific analytical method (such as HPLC) should be used, and that non-specific methods (such as TOC) are unacceptable? It certainly is not interpreted that way, since in countries covered by the PIC/S non-specific methods are widely used. I suspect (but have no inside information) that the origin of this phrase is the FDA 1993 guidance that states: "Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process." (Section IV.4.b.). Whatever the origin, the use of the term "specific" leads some people to think that a specific analytical method is required. A suggested change is as follows:

> "The analytical methods used to detect residuals or contaminants should be a direct measure of the substance to be assayed. Both specific and non-specific analytical methods may be used".

2. The following statement is in the FDA 1993 cleaning validation guidance:

> "When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of "visibly clean" for the equipment. Such between batch cleaning processes do not require validation." (Section IV.)

The context of this is in a discussion of cleaning between batches in a campaign and cleaning between different products. So, if I am making tablets in a campaign mode, and I process four different lots of the same product on my equipment, and only do "minor' cleaning (such as vacuuming) between each lot, do I need to demonstrate that the equipment is visually clean after that minor cleaning? It is probably an unreasonable expectation that the equipment will be visibly clean after just vacuuming of surfaces. Certainly the FDA is correct in that such minor cleaning as vacuuming does not require cleaning validation. Does this mean that I have to have a process for minor cleaning which results in visibly clean equipment? If so, I might have to use a detergent, in which case it is probably unreasonable to say such cleaning does not require validation. The issue here is that I might not be concerned about cross-contamination of the active, but I might have other concerns, such as adulteration with the detergent. A suggested change for this section is as follows:

> "When the cleaning process is used only between batches of the same product in a campaign of one product or of the same product for dedicated equipment (or different lots of the same intermediate in a bulk process) and that cleaning process (such as vacuuming or a water/solvent flush) is known not to leave unacceptable residues, such between batch cleaning processes do not require validation. However, the effect of the "between batch" cleaning, as well as the number of batches processed before a validated cleaning process is utilized, should form part of the considerations in determining how to validate such validated cleaning processes."

3. The following statement is in the FDA guidance:

> "However, unlike product residues, it is expected that no (or for ultra sensitive analytical test methods - very low) detergent levels remain after cleaning." (Section VI.b.)

The issue with this statement is that from an analytical perspective, one cannot measure "no" detergent.

In the PIC/S guidance, is the following statement regarding detergents:

> "Ideally, there should be no residues detected." (Section 7.9.1)

This is better than the FDA statement, because it mentions "non-detectability" as compared to "no residues". However, it is also an overstep. Certainly we should use detergents that are freely rinsed from the equipment. However, based on a risk-assessment, limits can be established for a detergent based on toxicological properties or on other effects (such as on product stability or bioavailability of the active) if the detergent is present in the next product. The question is not whether there should be no residues, non-detected residues, or even very low residues of a detergent. The appropriate criteria for limits of detergent are similar to what the FDA listed in a Human Drug CGMP Note (2nd Quarter 2001): the cleaning process should result in residue levels (a) that can be reasonably achieved, (b) that are medical safe and (c) that cause no product quality concerns. A suggested rewrite for either document is:

Residue levels for a detergent should be established based on possible effects on the safety and quality of the next manufactured product.

These statements might require some wordsmithing to have them more easily fit into the applicable document (s). However, they would be steps in the right direction in clarifying issues that can result in industry confusion.

Also, note that these are not the only changes I'd like to see. However, these are three of the more significant ones. Next month I will address some additional changes I'd like to see.