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Test Until Clean?

An advertising promotion for a recent report called "Preparing for the EU GMP Inspection" (<http://www.fdanews.com/products/44215-preparing-for-the-eu-gmp-inspection>) made an unusual statement about a difference between the EU and the FDA for cleaning validation. The statement was "The EU allows a test-until-clean approach to cleaning validation; the FDA does not." That statement was made in the context of the "subtle" differences between the EU GMP's and the FDA GMP's. While the immediate context was the written GMP's, the broader context was inspections, and (of course) CGMP's should also be considered.

For clarification, the idea of "test until clean" ordinarily means that I clean my equipment, and I then test it for residues. If the residues are acceptable, I may release the equipment. If the residues are above my acceptance limits, I can then clean the equipment again, and retest it. This process can continue until I obtain acceptable residues in my testing. Generally "test until clean" does not mean that if the initial test results are unacceptable, I can immediately test again without cleaning again (although that approach may be possible using OOS principles). Also, "test until clean" is not a PAT (Process Analytical Technology) approach to cleaning. In a PAT approach, I will have some measurement (other than time) which indicates the cleaning process is completed, but I will still measure residues once the cleaning process is complete.

So, is there a difference between the two authorities either in terms of written GMP's or in terms of other regulatory documents? Let's look at what the GMP's state. First, there is nothing in the written FDA GMP's (21 CFR Parts 210-211) about cleaning validation, so if we just look at the written GMP's, the FDA is silent. What about the EU? Here is what is given in Annex 15 to EU GMP's about "test until clean" (in paragraph 41):

"Test until clean" is not considered an appropriate alternative to cleaning validation."

In other words, while it might be that "test until clean" can be used, it is not an alternative to cleaning validation. This reading of Annex 15 is just the opposite of what is claimed in the cited report.

I should note that there are statements in other documents, including the FDA's cleaning validation guidance and the PIC/S PI 006-03 recommendations on cleaning validation. Here is what is in the PIC/s PI 006-03 recommendations in section 7.3.10:

It is usually not considered acceptable to "test until clean". This concept involves cleaning, sampling and testing, with repetition of this sequence until an acceptable residue limit is attained. For the system or equipment with a validated cleaning process, this practice of "test until clean" should not be required. The practice of "test until clean" is not considered to replace the need to validate cleaning procedures.

This statement in the PIC/S document reflects what is in Annex 15 about "test until clean", indicating it should not "replace" cleaning validation.

Here is what the FDA says about this subject in its guidance in Section VI.C.:

Test Until Clean

Examine and evaluate the level of testing and the retest results since testing until clean is a concept utilized by some manufacturers. They test, resample, and retest equipment or systems until an "acceptable" residue level is attained. For the system or equipment with a

validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated since these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

Let me clarify here that as written the FDA guidance seems to refer to only resampling and retesting if initial results are unacceptable. However, that practice is one that should be covered by an OOS program. I suspect this is just loose wording by the FDA, and that they actually mean cleaning, sampling and retesting after initial inadequate results (but I might be wrong). Note that the Health Canada cleaning validation guide defines “test until clean” in a manner similar to PIC/S, while others (such as the WHO cleaning validation guide), have a statement similar to the FDA (although the wording “test until clean” does not appear in the WHO guide).

In other words, it is probably not correct to state that there is a significant difference between the FDA and the EU in terms of “test until clean”. As reflected in written documents, both seem to find it “unacceptable” for a validated cleaning process.

Before I close, I should state that while testing until clean (meaning repeated recleaning and retesting) is not appropriate for a validated cleaning process, there are clearly situations where recleaning and retesting can be used. The most common is any situation where I am using “cleaning verification” instead of “cleaning validation”. For example, in a clinical manufacturing where I might only make one batch of product on a given equipment train, cleaning verification makes sense. In that situation, I don’t want to spend a lot of effort on design work (that is more critical for a validated cleaning process). Therefore, I clean the equipment, and if the residues are unacceptable, I clean again and retest until I obtain acceptable results. Remember that in this situation, the data I develop only applies to that one cleaning event.

I am also aware of companies who for routine manufacture, choose to perform cleaning verification on every batch of product. They could have chosen to perform cleaning validation, but decided that cleaning verification on every batch was more appropriate for their situations. To those who might object to this practice, let’s remember the objective of both cleaning validation and cleaning verification – to produce equipment that can be safely used for manufacture of the next product.

The purpose of this Cleaning Memo is to point out that the best sources for what might be required in a regulatory inspection in cleaning validation are the various published regulatory documents. Certainly anecdotal information, as well as documents that might result from a regulatory inspection, can be helpful if they are taken in the proper context (and that context may not always be available).