Cleaning Memo for June 2015
What's in Annex 15

The finalized version of Annex 15 of the EU Guidelines on GMP was released on March 30, 2015. It is a significant change from previous versions of Annex 15, at least from the prospective of cleaning validation. The previous version (2005) was merely a condensed version of key concepts in PIC/S PI 006-3. This new version is a breath of fresh air.

For simplicity I will focus mainly on comments made in Section 10 dealing with cleaning validation (although other sections may impact cleaning validation and I will perhaps add a few items from other sections).

Section 10.1 opens with the statement "Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment." This does not necessarily limit cleaning validation to product contact surfaces, but at least it places the emphasis where it belongs, on *product contact surfaces*.

Section 10.1 adds that "Simulating agents may be used with appropriate scientific justification." Simulating agents probably refers to "mock soils" or "artificial soils" used in place of the actual product to be cleaned (see the February 2014 Cleaning Memo).

Section 10.1 has an *explicit* statement about grouping of *equipment*, and explicitly allows "similar types" to be grouped with an appropriate justification.

Section 10.2 has warnings against two practices: "A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation" but "It is not generally acceptable for this criterion alone to be used." This, of course, is similar to a statement in the FDA's Human Drug CGMP Note of June 1998. My interpretation of this restriction is that visually clean *alone* is not acceptable in a validation protocol unless something else is done, and that is to perform spiking studies to demonstrate that visually clean represents a more stringent criterion as compared to a carryover calculation based on dose- or a health-based limit.

In addition, there is a statement in 10.2 that "Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach." Again, my interpretation is that this statement applies to *validated* cleaning processes. Where cleaning *verification* is done, as in clinical materials, repeated cleaning until acceptable test results are obtained should be acceptable from a compliance perspective (although they would not be preferred from the manufacturer's perspective of production efficiency).

Section 10.3 addresses issues related to the logistics of accomplishing cleaning validation. It recognizes the possible need for products like investigational medicinal products to be verified after each batch to establish that the equipment is clean and safe for manufacture of other products.

Section 10.4 appears to be a statement similar to the FDA in its Process Validation guidance related to getting away from “worst case” conditions in a protocol and validating the *normal* operating range, particularly for automated cleaning processes. The specific statement in 10.4 is “Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.” This interpretation, however, should be taken in light of what is stated in 10.5 about “worst case situations”.

Section 10.5 calls for a determination of the “variable factors” in a cleaning process, and if “variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.” The cleaning “studies” here could refer to design and development studies done as part of a life cycle approach, but they might also apply to the validation protocols themselves.

Section 10.6 deals with limits. It states that limits should be based on a “toxicological evaluation”, with a footnote referencing the EMA guidance on heath-based exposure limits for shared facilities. That section further states that limits should be appropriately documented in a risk assessment. Further, the EMA states that limits should be established for cleaning agents. Finally, this section clearly states that limits should be based on the *cumulative transfer* of residues to a product from multiple equipment items used in a manufacturing train.

Section 10.6.1 provides more detail for “macromolecules and peptides” which degrade in the cleaning process and where residues are not pharmacologically active. The statement is made that a “toxicological evaluation may therefore not be applicable in these circumstances”. That is in slight variance with the EMA guidance on limits in shared facilities, which states something like "limits based on a PDE of the native active may not be appropriate”. I believe it still might be an option to set limits based on the toxicological properties of the degraded actives, or to set limit based on the toxicological properties of the native active as a worst case (assuming the safety issues of the degraded fragments are of a lesser concern).

Section 10.6.2 is in a section on limits, but it appears to be more about specific and non-specific *analytical methods*. It states that if “it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.” This seems to address the situation where the active (for example) is degraded in the cleaning process, and a specific method for the active itself is not applicable. It should be noted, however, that it does seem not exclude the possibility that a non-specific method could be used even if there might be specific analytical methods for that undegraded active (at least that’s my take on this section).

Section 10.7 merely calls for the “consideration” of risks due to “microbial and endotoxin contamination” in cleaning validation protocols.

Section10.8 deals with defining dirty and clean hold times for a cleaning process.

Section 10.9 is one of the clearest statements in a regulatory document related to dealing with campaigns. It states that for campaigns, “the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.”

Section 10.10 deals with *product* grouping, and states that establishment of the worst case product may include consideration of “solubility, cleanability, toxicity and potency”. It further clarifies that there should be a scientific rationale for assessing new products at the site (presumably with the new products being manufactured on the same equipment as a previously validated group).

Section 10.11 deals with sampling. It states the protocols should “specify or reference” the sampling locations, with a rationale given for location selection. There is also a reference to defining acceptance criteria, which could just mean that the acceptance should be defined, or (in context) that the acceptance criteria be given for those sampling locations.

Section 10.12 also deals with sampling. It states that sampling “should be carried out by swabbing and/or rinsing or by other means depending on the production equipment”. This is a good statement because it gets away from a general perception (in my opinion, the general bias) that swab sampling is somehow preferred. There is also a statement that “sampling materials and method should not influence the result”. Finally Annex 15 states that sampling recovery “should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.” This is nice, because it gets away from the belief that recovery is required for *all* materials in the equipment, specifying "all materials sampled”.

Section 10.13 calls for the number of successful runs in a cleaning validation protocol to be determined based on a risk assessment. In this way, it is like the FDA approach for process validation in getting away from specifying a minimum of three runs.

Section 10.14 deals with situations where dedication of equipment or "other appropriate measures” should be considered for manufacturing.

The last paragraph in this section is 10.15, dealing with manual cleaning. It calls for "the effectiveness of the manual process should be confirmed at a justified frequency”. What constitutes “confirmation” and what constitutes a “justified frequency” is not stated. However, this is another clear statement regarding additional concerns for manual cleaning processes.

Other sections have some references to cleaning. For example, the context of everything in Annex 15 suggests that a lifecycle approach is appropriate for cleaning validation. It should be noted that the concept of what I call "validation maintenance" and what the FDA calls “continued process verification” is called “ongoing process verification” in Annex 15. A rationale for that terminology is not given; my

speculation is that the EMA wanted an alternative to the FDA's "*continued* process verification" to avoid confusion with "*continuous* process verification".

While I have summarized the key elements in the cleaning validation section, and have provided my "spin" on certain items, it is highly recommended that this new Annex 15 be carefully reviewed in order to understand its possible impact on a given cleaning validation program.