Comments on Draft Annex 15 (Qualification and Validation) to EU GMPs

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Note that these comments are limited to Section 9 on cleaning validation and the associated glossary terms that may apply to cleaning validation.

1. In the glossary, the definition of "cleaning validation" (page 14) is given as "Cleaning validation is documented evidence that an approved cleaning procedure will remove all traces of the previous product used in the equipment." It is generally not the case that "*all* traces" of the previous product be removed for successful cleaning validation. There is no way to measure removal of all traces if "removal of all traces" means "no residue at all". If "no traces" were to mean "not detected" that would depend on the analytical method, and that criterion alone has generally not been an acceptable practice (it is only acceptable if the detection limit is below a predefined acceptable value). Particularly with newer analytical techniques, residues of the previous product may be detected or quantified, albeit at very low levels. The issue for cleaning validation is that those residues are at a medically safe level and at a level that does not affect product quality. A suggested changed definition is "Cleaning validation is documented evidence that an approved cleaning procedure will remove residues of the previous product used in the equipment to a predefined acceptable level." Other sections of the draft Annex 15 address what that acceptable level should be, so there is no need to specify it here.

2. In Section 9.2 is the statement "A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation however, it is not acceptable for this criterion alone to be used." It has been the practice within the pharmaceutical industry (based on PIC/S PI 006-3) to utilize visually clean alone if it can be documented that visually clean is more stringent than limits determined by carryover calculations. This determination is typically done by laboratory spiking studies and subsequent viewing under conditions which are representative of viewing conditions of actual equipment. Unless the intent is to completely forbid such practices, a suggested revision is "A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation; however, it is not acceptable for this criterion alone to be used unless spiking studies are done to establish that the visually clean criterion is more stringent than the criteria determined by the carryover limit based on patient safety and product quality concerns."

3. In Section 9.2 is the statement "Repeated cleaning "until clean" is also not considered an acceptable approach." This concept is typically referred to as "test until clean". For clarification of what I think is intended, a suggested revision is "Repeated cleaning and retesting until acceptable residue results are obtained is also not considered an acceptable approach for a validated process."

4. In Section 9.3 are the statement "It is recognised that a cleaning validation programme may take some time to complete and validation with ongoing verification after each batch may be required. The level of data from the verification to support a conclusion that the equipment is clean should be evaluated. I believe the intent of this statement is related to the *release* of equipment for subsequent manufacture during cleaning validation protocols. The key issue (I think) is adequate verification data for release of equipment for subsequent manufacture. To clarify this issue, a suggested revision of the second sentence is "The level of data from the verification should be evaluated to support a conclusion that the equipment is clean and can be released for manufacture of a subsequent product."

5. Section 9.4 makes a distinction between manual cleaning processes and automated cleaning processes. There are also many processes which involve both significant manual and automated steps (such as a portable CIP or manual disassembly with washing in an automated parts washer). I believe that it would be more appropriate to require an assessment of variable factors for all cleaning processes (although certainly there is generally more concern in manual cleaning processes). A suggested rewrite is "Validation should include an assessment to determine the variable factors which influence cleaning effectiveness, such as operators, the level of detail in procedures, times, temperatures, and cleaning agent concentration, for both manual and automated cleaning procedures. If significant variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies."

6. Section 9.5 appears to limit the determination of acceptance limits to a toxicological evaluation. There are concerns other than safety that should be considered, such as effects of residues on product quality (stability of the next product, dissolution of tablets, etc.). A suggested rewrite for the first sentence is "Limits for the carryover of product residues should be based on effects on patient safety and product quality, and should include a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value." I assume you will receive many comments about limiting that toxicological evaluation to a PDE, so I will not make any further comments about that.

7. In section 9.5 is the statement "The removal of any cleaning agents used should also be confirmed." While that statement is true, the context of that statement is in a section on limits (or acceptance criteria). A suggested rewrite to address the issue of limits is "Limits should be established for the removal of any cleaning agents used."

8. In Section 9.6 is a reference to the "storage time before cleaning". The time between the end of manufacture and beginning of the cleaning process is not typically referred to as a *storage* time. In addition, the words "should be" probably need to be inserted before the word "taken". A suggested rewrite is "The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process." The last word was changed because the dirty hold and clean hold times should be specified as part of the cleaning *procedure*; they are then challenged in the cleaning validation *protocol*. Finally, the issue

of the dirty and clean hold times is in a paragraph that starts off dealing with microbial contamination. While microbial contamination is a concern (it is generally the major consideration for clean hold time), it is not the only concern (and in most cases is not the major concern for dirty hold time). It might be useful to separate the issue of microbial contamination and the issue of dirty/clean hold times into two distinct sections.

9. In section 9.7 there is a statement that includes a reference to the "ease of cleaning between batches". It is unclear what this means. What should be considered is the nature of cleaning between batches, such as vacuuming between batches for solid processing or water flush between batches for liquid processes. In addition, for certain campaigns, such as in biotechnology manufacturing, a fully validated cleaning process is typically performed after each batch in a campaign for bulk active manufacture. A suggested rewrite is "Where campaign manufacture is carried out, the impact of the nature of cleaning between batches should be considered; the maximum length of a campaign (in both time and number of batches) should be the assessed in cleaning validation exercises."

10. In section 9.8, it is unclear what is the intent of the sentence "When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility." Factors such as solubility, cleanability, and toxicity are generally considered in terms of selection of a worst case product in a grouping (matrixing) approach. Generally if there is no worst case product (or multiple worst case products) based on the criteria for establishing a worst case, then companies will use other criteria such as frequency of manufacture, availability of analytical methods, and/or a worst case based on a certain staging of evaluated parameters. However, there is no need to specify approaches to be used if there are no distinctions between the products in a group (or matrix). A suggested rewrite is "Where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity, and potency."

11. The wording in Section 9.9 is awkward. A suggested rewrite is "Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations, and the acceptance criteria."

12. Section 9.10 discusses sampling done "at the last stage of cleaning". It is unclear whether this is to refer only to rinse sampling or to both swab and rinse sampling. In either case, it should *not* be stated as such. Swab sampling is done after *completion* of the cleaning process, and not "at the last stage" (whatever "the last stage" means). Rinse sampling may be accomplished in one of two ways. One option is to sample the last part of the final rinse; a second option is to perform a *separate* sampling rinse after completion of the cleaning process (that is, after completion of the final process rinse). There is no need to include the phase "at the last stage of cleaning".

Also, the reference to “other means” is not dependent on the “sampling location”, but on the “production equipment”. In addition, recovery should be demonstrated for all materials *sampled*, not necessarily for all materials of construction. If there is a material in production equipment that is *not* sampled, there should be no need to perform a sampling recovery study.

Finally, the reference to interferences in sampling should not be limited to just the swab material; other factors such as the solvent used to wet the swab and the vial the sample is collected in should also be considered.

A suggested rewrite is “Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials should not influence the result. Recovery should be shown to be possible from all materials sampled in the equipment with all the sampling methods used.”

13. Section 9.13 refers to the “cleaning validation” being shown to be ineffective. I think the intent is to cover when the “cleaning *process*” is ineffective, not when the “cleaning *validation*" is ineffective. A suggested rewrite is “Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment should be used for each product.”

    End of comments