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The New FDA Compliance Program Guidance Manual and Cleaning Validation

The new FDA Compliance Guidance Manual has useful information on the expectations of the FDA in investigations involving cleaning and cleaning validation. This new program, being rolled out as a pilot program, is designed to more effectively utilize the limited FDA resources to conduct CGMP audits. It generalizes inspection coverage such that inspection of a system applies to all profile classes utilizing that system.

This program defines six "systems" in the requirement for biennial inspections. The six systems to be evaluated, which tie in to the CGMP Subparts in 21 CFR 211, are:

- Quality Systems
- Facilities and Equipment
- Materials
- Production
- Packaging and Labeling
- Laboratory Controls

At each inspection, a minimum of two systems is to be audited, with one of the two systems always being Quality. Routine audits (basically for companies with good track records) are called the "abbreviated inspection option" and will generally cover only two systems (as well as parts of other systems that relate to the systems being targeted).

The "full inspection option", including an audit of at least four systems (one of which is Quality), is for new facilities and/or facilities with problematic track records.

"Cleaning and validation of cleaning processes as appropriate" is listed under the "Facilities and Equipment" system, whereas "process validation" is listed under "Production" systems. "Change control" is covered under "Quality Systems", so presumably change control of a validated cleaning process could be covered in any biennial inspection. "Status of required validation/revalidation" is also covered under "Quality Systems", so it may be that the validation schedule for cleaning validation (although not necessarily the details of specific validation protocols) could be covered in the biennial inspection.

For each of the other five systems, the initial statement of the FDA in this document is the same: "For each of the following, the firm should have written and approved procedures and documentation resulting there from." In addition, "the firm's adherence to written procedures should be verified through observation whenever possible." What follows is a listing of specific items that should be covered in each system. Specific items related to cleaning and cleaning validation in each of these five systems include the following.

<u>Facilities and Equipment</u>

- cleaning of facilities
- cleaning procedures and cleaning validation for equipment

Materials

- there was nothing specifically and directly dealing with cleaning in this section.

Production

- identification of equipment with contents, and where appropriate phase of manufacturing and/or status (presumably including equipment status during the cleaning process)
- validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- established time limits for completion of phases of production (presumably this applies to the times for the cleaning process)
- prevention of objectionable microorganisms in non-sterile drug production (presumably the basis for addressing microbial control in cleaning validation)
- equipment cleaning and use logs

Packaging and Labeling

- there was nothing specifically and directly dealing with cleaning in this section

Laboratory Controls

- validation/verification of analytical methods (while it can be expected that validation of analytical methods used for cleaning validation would be examined under Facilities and Equipment, this at leaves it open that it might be audited here)

Part V of the manual deals with the "regulatory/administrative strategy" to be considered for firms not operating in a state of control. Examples of items that could lead to a Warning Letter or other district regulatory actions include the following items related to cleaning and cleaning validation:

- a pattern of failure to validate cleaning procedures for non-dedicated equipment
- lack of demonstration of effectiveness of cleaning for dedicated equipment
- lack of validated analytical methodologies

It should be recognized that a cleaning and cleaning validation program, while presumably primarily covered under the "Facilities and Equipment" section, also may overlap other sections (such as analytical method validation in "Laboratory Controls" and equipment and cleaning logs in "Production").

This Cleaning Memo is designed to be an introduction to the new program as it applies to cleaning and cleaning validation. Each facility should carefully review the document itself to see all the possible implications for FDA CGMP audits. As this new program is piloted, industry will surely learn more about exactly how it will be implemented.