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cGMP Maintenance Program Considerations

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ABSTRACT

Facilities governed by current good manufacturing practices (cGMPs) must remain in a validated state. The site preventive maintenance program is a critical part of this effort. Requirements for equipment are stated in 21 Code of Federal Regulations (CFR) 211.67. All facility, process, utility, and laboratory equipment used in the manufacturing, processing, packing, holding, or testing of drug products, biological products, or medical devices must be characterized as GMP or non-GMP. This article provides general elements of a site preventive maintenance program including record-keeping and personnel qualifications.

INTRODUCTION

After all the excitement of qualifying and validating a new facility or new equipment is added to a facility, it falls on the maintenance department to keep that facility and equipment in the validated state. If left to itself, the second law of thermodynamics tells us that the facility and equipment will naturally gravitate to a state of greater disorder. Equipment will wear out, develop corrosion, and so on. As soon as the validation effort is complete, final reports are signed, and the equipment put to use, it starts wearing out and moving toward a different state than when the equipment and facility was originally qualified/validated. All facilities and equipment must be maintained to stave off the effects of disarray. Beyond the financial burden experienced by all industries, the industries governed by cGMPs have the burden to maintain a facility in a validated state required by the cGMP.

REGULATORY REQUIREMENTS

Requirements for equipment are stated in 21 CFR 211.67 as follows:

> *§211.67 Equipment cleaning and maintenance.*
>
> *(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment
(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance
(4) Removal or obliteration of previous batch identification
(5) Protection of clean equipment from contamination prior to use
(6) Inspection of equipment for cleanliness immediately before use

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§211.180 and 211.182. (1)

This is one of the more clear directions provided in the CFR, yet one of the more overlooked. Much too often the maintenance operation is viewed by management as a cost center. Maintenance is considered a necessary evil, but one available for cost cutting and overhead reduction. Maintenance is a quality requirement, clearly laid out in the CFR and an obvious necessity to maintain the validated state. Funds allocated for maintenance must be protected and preserved to maintain the validated state.

What follows are considerations for a compliant maintenance program.

CHARACTERIZATION AND CLASSIFICATION

All facility, process, utility, and laboratory equipment used in the manufacturing, processing, packing, holding, or testing of drug products, biological products, or medical devices must be characterized as GMP or non-GMP according to their use in the GMP environment. This characterization must recognize that in a pharmaceutical, biological, diagnostic or related industry, the majority of equipment exists to monitor or control some aspect of the manufacturing operation and are therefore part of GMP. Filling and packaging equipment and systems should be maintained by a system incorporating the same characteristics as the maintenance system for GMP process, facility and utilities. There should be procedures defining the rationale and approach for classifying equipment as GMP or non-GMP.

Some sites go farther and apply the terms critical and non-critical to equipment in the preventive maintenance program. This adds little benefit, and may present a compliance risk. How would preventive maintenance be done differently for a critical versus a non-critical piece of equipment? This further delineation beyond GMP and non-GMP could be used to establish limits and trigger out-of-tolerance events in a calibration program, but not so in a preventive maintenance program. Likewise a few sites go even further and classify equipment parts as critical and non-critical. This can be an unnecessary complication. The same part, such as a belt, could be used for both GMP and non-GMP equipment. Complexity without a compliance benefit adds compliance risk!

GENERAL PROGRAM ELEMENTS

Maintenance in a GMP environment is part of the overall compliance effort of the site. The maintenance program is not only instituted to maintain equipment correctly, ensuring availability and proper operation, but also to maintain the validated state of equipment used in the manufacturing, processing, packing, holding, or testing of a regulated product. The maintenance program must consider the following components:

- There should be maintenance program administrative procedures outlining details to prepare and approve preventive maintenance regimens, execute preventive and corrective maintenance, review and approve work orders, report late preventive maintenance, open corrective maintenance procedures, and all associated activities.
- There should be individual procedures prepared for the preventive maintenance of specific GMP equipment. These procedures should be reviewed and approved by quality, operations, and technical personnel. The activity procedures required should be associated with risk to patient and organization.
- The preventive maintenance procedures must specify tasks and frequency for each task. Risk analysis should be

considered these determinations.

- There should be a procedure for tracking scheduled maintenance activities.
- The quality unit should review all systems and procedures, including procedures entered into a computerized maintenance management system (CMMS). A computerized list of tasks and frequencies stands in the place of a standard operating procedure (SOP) and should be treated as such.
- Where CMMS is employed, it must be validated/qualified for its intended use. Any associated computerized systems must also be appropriately validated/qualified.
- Equipment should be clearly identified by a unique number.
- Any corrective or non-routine maintenance that can possibly be understood as a change to a piece of validated equipment, especially parts changes, must be processed through change control before being performed.
- Maintenance records should be reviewed regularly to identify any trends.
- Records of non-completed and/or late preventive maintenance must be generated and reviewed by appropriate management personnel. Corrective action plans should be developed.
- Spare parts and consumables should be maintained and controlled to ensure correct replacement parts and consumables are used.
- Functionally equivalent parts should be subject to review and approval prior to use in validated equipment. Note: “Like-for-like” terminology may have different meanings in different organizations. Some identify “like-for-like” as an exact replacement part (i.e., same manufacturer, model number, etc.) as originally provided. Other organizations define “like-for-like” as a replacement part that has the same characteristics. In one organization, the central corporate organization used the term as exact replacement, but the sites used the term to mean an equivalent part. Organizations must clearly define “like-for-like” to be sure that all areas follow the same interpretation. Alternatively, a more descriptive term such as “functionally equivalent” may be used in place of “like-for like.”
- There must be certainty that “like-for-like” /functionally equivalent equipment is correctly installed.
- The maintenance department may be responsible for generation and maintenance of logbooks for facility and utility equipment.
- Any maintenance personnel working on equipment should be complete equipment logbooks in clear, understandable terms.

RECORD KEEPING

- The person fulfilling the work order shall complete preventive, corrective, and changed maintenance records/work orders.
- Records of all maintenance shall be maintained for a specified period beyond the longest expiration date of any product the equipment produces.
- A chronological equipment history file for each instrument shall be established. To maintain and repair equipment (manufacturer’s manuals, drawings, etc.) information must be kept in an equipment information file accessible to technicians who need such information.
- Notations in equipment logbooks by any maintenance personnel shall be completed in clear, understandable terms.

PERSONNEL QUALIFICATIONS

- There must be a system for ensuring the qualification and technical training of technicians and mechanics employed in the maintenance and repair of GMP equipment. This must include technical training on the specific requirements of preventive maintenance procedures. Training must include in-house personnel as well as outside contracted staff.
- There must be a written procedure for the qualification and training of contracted mechanics and technicians used to supplement facility resources.
- There must be regular training sessions for all maintenance personnel covering both cGMP’s and job-specific issues.

FINAL THOUGHTS

The above considerations are offered as a basis for a compliant maintenance program. They do not cover all the aspects of a preventative maintenance program. For example, considerations of how to qualify a maintenance contractor, reporting out-of-frequency events for preventive maintenance, review of open corrective or non-routine work orders, a system for reviewing/approving functionally equivalent parts, and other details must also be considered in a comprehensive program. Developing a maintenance program is a significant undertaking. The fundamentals of a site maintenance program are best done as completely as possible in the early stages of a facility lifecycle.

REFERENCES

1. FDA, “21CFR211.67,” Code of Federal Regulations Title 21, Volume 4, FDA, 2011. **JVT**
