The Requirement of Facilities and Equipment in Pharmaceutical Industry as Per Schedule M And USFDA

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Abstract

The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produce disagreeable or obnoxious odour or fumes, excessive soot, dust, smoke, chemical or biological emissions. Current study is aimed at requirements of Facilities and Equipment as per the different regulatory guidelines viz., Schedule M of D and C Act and USFDA.

Introduction:

Each of the selected guidelines describes the requirement of Facilities and Equipment under the different chapters as below.

Schedule M: Schedule M describes about the Building and facilities requirement in **PART 1Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products.**

USFDA describes about the Building and facilities in**Title 21: Food and Drugs**

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS - Subpart C—Buildings and Facilities

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Current Step 4 version dated 10 November 2000

5. PROCESS EQUIPMENT

Detailed comparison of the selected guidelines with respect to Equipment is made as follows

Schedule M

11. Equipment:

11.1 Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Each equipment shall be provided with a logbook, wherever necessary.

11.2 Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in-process control operations and these shall be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.

11.3 The parts of the production equipment that come into contact with the product shall not be reactive, additive or adsorptive to an extent that would affect the quality of the product.

11.4 To avoid accidental contamination, wherever possible, non-toxic/edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricants do not contaminate the products being produced.

11.5 Defective equipment shall be removed from production and Quality Control areas or appropriately labelled.

USFDA

Title 21: Food and Drugs

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Subpart D—Equipment

§211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

§211.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
§211.67 Equipment cleaning and maintenance.
(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized 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.
§211.68 Automatic, mechanical, and electronic equipment.
(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.
(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.
(c) Such automated equipment used for performance of operations addressed by §§211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections relating to the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section, and one person checks that the equipment properly performed the operation.
§211.72 Filters.
Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing

filters may be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber-releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. The use of an asbestos-containing filter is prohibited.

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PROCESS EQUIPMENT

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

− Assignment of responsibility for cleaning of equipment;
− Cleaning schedules, including, where appropriate, sanitizing schedules;
− A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment; − When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
− Instructions for the removal or obliteration of previous batch identification;
− Instructions for the protection of clean equipment from contamination prior to use;
− Inspection of equipment for cleanliness immediately before use, if practical; and
− Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.
5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.
5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.
5.32 Records of these calibrations should be maintained.
5.33 The current calibration status of critical equipment should be known and verifiable.
5.34 Instruments that do not meet calibration criteria should not be used.
5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.
5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.
5.44 Written procedures should be available for the operation and maintenance of computerized systems.
5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.
5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.
5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.
5.49 Data can be recorded by a second means in addition to the computer system.

Results:

Equipment

All the selected guidelines describe the requirement of equipment for production of drug products. The equipments should be installed, qualified and maintained in such a way to fulfil the requirement of product, all the equipment should be cleaned properly to avoid any cross contamination before start of manufacturing activity, same shall be verified and confirmed. The equipment shall be identified properly for its usage, calibration status, content along with

date and sign of the personnel identified. If any defective equipment is identified same shall be isolated from the area with proper means or shall be labelled appropriately to avoid usage of such equipments.

Starting and packing materials

The detailed requirement of raw materials or starting materials are given under different chapters of the selected guidelines, however all the selected guidelines are not described this requirement under production and process control accordingly schedule M of D and C act describe this in chapter 10 Raw materials, WHO guidelines describe this under chapter 14 Materials.

USFDA describe the requirement of starting materials under 211.101 Charge-in of components.

MHRA and TGA/PICs guidelines describe the requirement of starting materials under section Starting materials 5.25 to 5.34 and from 5.40 to 5.43 for packing materials

Weighing and measurement

As per the guidelines selected for study all the materials used in the production of drug products should be weighed accurately before charging in for production, the measuring, weighing, recording and control equipment and instruments should be serviced and calibrated at prespecified intervals and records of the same shall be maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Prevention of cross contamination

The GMP guidelines selected for study describe the prevention of cross contamination by suitable means. All the guidelines emphasis on the subject under different sections as described below

WHO describe this under **Prevention of cross-contamination and bacterial contamination during production**from clause 6.10 to 6.14

Schedule M of D and C act describe this requirement under 3.2

USFDA guidelines details about the prevention of microbial contamination under 211.113 Control of microbiological contamination.

MHRA and TGA/PICs describe this requirement under Prevention of Cross-contamination in Production 5.18 to 5.20

In-process testing

All the guidelines selected for study describe the requirement of in-process testing to confirm that the product is conforming to predetermined specification.

USFDA describes this requirement under 211.110 Sampling and testing of in-process materials and drug products.

Sampling and testing requirements are not detailed under production in MHRA and TGA guidelines whereas the same is detailed under chapter 6 Quality Control

WHO describe the same requirement under chapter 17 good practices in quality control.

Schedule M of D and C act describe this under 22.4 testing.

Calculation of yield

Yield calculation is essential to understand the loss during production and to take measures to minimize the loss. Calculation of yield is given under 16.4 of WHO guide, 211.103 of USFDA, 5.8 of MHRA and TGA/ PICs. Schedule M of D and C act describe this requirement under section 12.1 documentation, however schedule M does not specify this requirement under production.

Packing operations

WHO describes the packing operations under 16.25 to 16.36

D and C act describe the packing labelling and storage under different category of dosage forms in the act

MHRA and TGA/PICs describe about packing under section **Packaging Operations**5.44 to 5.57

USFDA details the packing operations under subpart G packing and labelling control

Equipment

The Equipment used in the production of pharmaceutical products should be of required quality and size. Equipment should not affect the product adversely and it should be designed in such a way that the equipment should be user friendly, safe and cleaning should be easy. Material of construction should not affect the quality of the product.

Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

References:

1. Schedule M- PART 1 -GOOD MANUFACTURING PRACTICES FOR PREMISES AND MATERIALS-In General requirements covered building and premises. .
2. WHO -Annex 3 -good manufacturing practices for pharmaceutical products – Building and facilities section 12 to 16.
3. USFDA- CFR- PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS-Subpart C—Buildings and Facilities.
   §211.42 Design and construction features.
   §211.52 Washing and toilet facilities.
   §211.44 Lighting.
   §211.46 Ventilation, air filtration, air heating and cooling.
   §211.48 Plumbing.
   §211.50 Sewage and refuse.
   §211.56 Sanitation.
   §211.58 Maintenance.
4. GUIDANCE ON GOOD MANUFACTURING PRACTICE (GMP) -EU Guidance on Good Manufacturing Practice PART I: Basic Requirements for Medicinal Products – chapter -3 PREMISES AND EQUIPMENT.
5. TGA/PICS - guide to good manufacturing practice for medicinal products part I CHAPTER 3 PREMISES AND EQUIPMENT.