Review Article

An Innovative Study on Pharmaceutical Equipments

***Sharma Pawan Kumar, Priyadarshani R. Kamble, Ravindra Kamble, Chetan Singh Chauhan, Sissodiya S. S., Mahendra Singh Ranawat**

Bhupal Nobel's College of Pharmacy, Udaipur-313001, Rajasthan, India.

ABSTRACT

Equipment's are very important factor which can affect the quality of the formulation to a great extent, therefore design, construction, installation, location, cleaning and the maintenance of equipment should be followed the guidelines of cGMP, FDA, WHO and considered very carefully equipments used in manufacturing processing or holding of drug product should be of adequate size and suitable location to facilitate operation for its internal use. Pharmaceutical equipment are nothing but the any piece of plant, machinery which is used to carry out specific activity or operation such as mixer, granulator, dryer, U.V, H.P.L.C, etc. and should work on the principle to minimize the risk of errors, to permit effective cleaning and maintenance, and to avoid cross contamination, dust and dirt build up. Validation of cleaning system of equipment is done by SWAB technique (involve the use of swabbing material saturated with the solvent to physically sample the surface), solvent rinse method (passing a known volume of solvent over a large area and analysing the recovery solution), placebo rinse method (to detect residue on equipment through the processing of a placebo batch subsequent to the cleaning process). This method involves passing a known volume of solution over a large area and analysing the solution. These factors should be considered, while selecting the equipment and operating condition.

Keywords: Cleaning validation, design, installation protocols, maintenance, principle, purchasing, selection

Received 28 March 2014 Received in revised form 15 April 2014 Accepted 17 April 2014

***Address for correspondence:**
Sharma Pawan Kumar,
Bhupal Nobel's College of Pharmacy, Udaipur-313001, Rajasthan, India.
E-mail: ps04330@gmail.com

INTRODUCTION

In the bulk drug industry, solid is the desired product. Its size, physical properties and purity are important. These factors should be considered, while selecting the equipment and operating condition. Some of them are:

Materials related

I. Properties of the fluid-Viscosity.
II. Nature of the solids-particle size, shape, size distribution and packing characteristic.
III. Concentration of solid in suspensions.
IV. Quantity of material to be handled.
V. Whether it is necessary to wash the filtered solids.
VI. Whether any form of pre-treatment will be helpful.

Equipment and process related

Flow rate:

It should be absolute in the sense, the limit to size of particles passing through the filter should be known.

It should be sterilisable by heat, radiation or gas (examples are ethylene oxide, formaldehyde etc.).

Independently checking the efficiency of filter. It should be economical [1].

Objectives:

To review the requirements for equipment selection, design, use and maintenance.

To discuss problems related to issues around selected items of equipment.

Principle:

Equipment layout and design must aim:

- To minimize risks of error.
- To permit effective cleaning.
- To permit effective maintenance.

And to avoid:

- Cross-contamination.

- Dust and dirt build-up.
- Any adverse effect on the quality of products.

Equipment must be installed to:

- Minimize risks of error.
- Minimize risks of contamination [2].

EQUIPMENT DESIGN

A variety of equipmentis used in a testing laboratory. The design may be simple or complex but it should serve intended purpose, someguidelines which may be useful in relation to equipment are given below.

[1] Except for disposable plastic ware .These should be resistant to effect of corrosion, high temperature and vigorous cleaning operation.

[2] Plastic item should of clear, inert, non-toxic material and should retain accurate graduation or calibration mark.

[3] All glassware should be free of chips, cracks.

[4] Glassware that is used for purpose which may subjected to heat or chemical should be of borosilicate glass.

[5] Metal utencils made of stainless steel should be preferred.

[6] For certain important glassware, I.P has made certain recommendation and these are mentioned below.

6.1 Nessler cylinder- Nessler cylinders are match tube of clear colourless glass with a uniform internal diameter and a flat transparent base. These comply with Indian standard I.S:4161-1967.

6.2 Volumetric glass-I.P recommends that design, construction and capacity of volumetric glass ware should be in conformance with standards laid down by "Bureau of Indian standards"(B.I.S).

6.3 In this standards there are two grade of apparatus these have been designated as Class A and Class B

6.4 Class A are intended for use in work of highest accuracy whereas Class B are used in routine work.

6.5 Relevant Indian standards are

6.6 I.S:1997-1982-Specifications for burette.

6.7 I.S:1117-1975-Specification for one mark pipette.

6.8 I.S:915-1975-Specification for one mark volumetric flask

[7] Culture tube should be of borosilicate glass or other corrosion resistant glass and should be of sufficient size to contain culture medium as well as sample portion employed without being more than three fourths full.

[8] Dilution bottles should be of borosilicate glass and should be free from chips and cracks at the top.

Major equipment's

The requirements of instruments will depend upon the type samples that are to be tested in a testing laboratories carry out testing of a variety of sample. Major equipment that a testing laboratory may require is given in list printed below.

-Analytical balance including monopan balance.
-I.R spectrophotometer
-UV visible spectrophotometer.
-Gas chromatograph.
-Polari meter.
-Disintegration test apparatus.
-Potentiometer.
-IR hydraulic pellet press with dies.
-Karl –Fischer titrator.
-Oxygen flask combustion apparatus.
-HPLC.
-Flame photometer or atomic absorption spectrophotometer.
-HPTLC.

Equipment for microbiological laboratory are also given below

-Autoclaves.
-Microscopes (Bacteriological).
-Incubators.
-Centrifuge with refrigeration.
-Membrane filters assembly for sterility test.
-Colony counters with magnifying glass.
-Laminar flow bench.
-Hot air sterilizer.
-Spectrophotometer (visible range).
-Nephelometer.
-Refrigerators.
-Deep freezer.
-Large plate microbiological assay.[3,22,23]

GENERAL SPECIFICATION

1.1 What operation we want to perform in this equipment?

1.2 What materials we are going to use in this equipment?

1.3 They should cause any interaction with materials.

1.4 How this equipment will be cleaned?
1.5 Avoid the problem cleaning validation.
1.6 Do we have trained operators to operate this equipment?
1.7 How many people are required to operate this equipment?
1.8 What is the starting and stopping time of equipment?

SELECTION

1.9 Equipment processing inflammable materials should be equipped with explosion proof electrical part.
1.10 Parts of equipment which came into contact with the raw material, bulk or finished product should be made of material which would not be reactive.
4.3Equipment used for critical steps should have, or far as possible regarding device. If not, other measuring device like pressure gauge, temperature gauge etc should be fixed.
1.4 To confirm equipment design has GMP principle, design qualification should be carried out.

PURCHASING

It is the procurement of materials, supplies, machinery, tools, implements, equipment and services, which are necessary for the production of certain goods includes the planning and policy and activities, research and development and selection of source of supply etc.

Stores and purchase committee

Constitution of the stores and purchase committee

The Policies and functions of the Purchase and Stores Department shall be controlled and guided by Stores and Purchase Committee in each company. The Committee may generally be composed of the following:

I. A Curator at 'E' or 'c' level : Chairman
II. Two Officers from Exhibit Development Centre : Members
III. Finance & Accounts Officer : Member
IV. Stores & Purchase Officer: Member/Convener The Committee shall be constituted by Director in museums and D.G. in Headquarter.

Objective and function of stores and purchase committee

- **Objective**

- To maintain uninterrupted flow of materials to support the development schedules.
- To procure materials economically at a cost consistent with the quality and service required. However, generally all purchases may be attempted at the lowest cost.
- To provide the necessary expertise, advice, information to the Curators and Education Officers with regard to the best quality of material available in the market, supplier's capability and performance etc.
- To develop and maintain good buyer-seller relationship.
- To promote source development.

- **Function**

The main functions of the Purchase Department are defined as follows:

- Follow-up of purchase orders for delivery in due time
- Verification and passing of suppliers bills to see that payments are made promptly.
- Correspondence and dealing with suppliers, carriers etc., regarding shortages, rejections etc., reported by the Stores Department.
- Maintenance of purchase records.
- Maintenance of vendor performance records/data.
- Arrangement for Insurance Surveys, as and when necessary.
- Serving as an information centre on the materials knowledge i.e. their prices, source of supply, specification and other allied matters [4].

CLEANING

- The purpose of cleaning of cleaning is to remove product residues of previous product or batch and to clear and sanitise the equipment for next batches.
- Equipment should be cleaned regardless of their size.
- Large equipment which is fixed or too heavy to move should be clean on location.
- Written cleaning procedure or Standard operating procedure (SOP) should be prepared for all equipment.
- SOP should be in the language that is understood by the workers.

VALIDATION OF CLEANING SYSTEM

(I) Swab technique.
(II) Solvent rinse method.
(III) Placebo rinse method.
(IV) Analytical techniques in cleaning validation like HPLC, TLC etc.

Swab technique

1. Select the equipment surface to be sampled.
2. Open the sterile swab container.
3. Grasp the end of the sterile swab stick, being careful not to touch any portion
That might be inserted into the vial.
4. Remove the swab aseptically without touching the cotton end.
5. Open a vial of Letheen Broth, moisten the swab head, and press out the Excess solution against the interior wall of the vial with a rotating motion.
6. Hold the swab handle to make a 30° angle contact with the surface.
7. Rub the swab head slowly and thoroughly over approximately 50 cm2 of
Surface three times, reversing direction between strokes.
8. Return the swab head to the solution vial, rinse briefly in the solution, then
Press out the excess.
9. Swab four more 50 cm2 areas of the same surface being sampled, as above, Rinsing the swab solution after each swabbing, and removing of excess.
10. After the areas have been swabbed, position the swab head in the vial, and Break or cut it with sterile scissors leaving the swab head in the vial.
11. Replace the screw cap.
12. Mark the outside of the sterile vial with sample identification Number.
13. Repeat numbers 1through 12 for each sample.
14. Place the samples into a cooler with sufficient blue ice to maintain the sample
Condition during transport to the laboratory facility.
15. Samples need to be analyzed within 24 hours.
16. Cellulose, cottonwool, synthetic fibre is used as swabbing material.

Note: If using water based ice, ensure that it is double-bagged to prevent Contamination of the sample.

Remarks-[1] do not open sterile swabs until you start sampling.

Solvent rinse method

This method involves passing a known volume of solution over a large area and analyzing the solution. OR involve sampling the clean surface with an additional volume of rinising fluid following the final rinse sequence of the cleaning process. Example closed container, tank, blender, fill the equipment with the specified volume of solvent, set the equipment into operation for the specified period of time and allow the solvent to circulate.

Placebo sampling method

This method can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process [5,24-26].

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

High performance liquid chromatography (HPLC) with U.V-Visible is the traditional method for cleaning detection. Its weakness is that if impurities are present, the response at a particular wavelength for those impurities must be known. In addition any residual material on the equipment that does not have a chromophore will not give a response HPLC with charged aerosol detection provide a more accurate detection tools since operate independently of U.V wave length and does not require the presence of chromophore for detection.

INSTALLATION PROTOCOLS

Installation qualification (IQ)

It is documented procedure perform at site and time of installation indicate that installation of equipment comply with manufacturers specification, codes, design parameter. OR Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommend-dations and/or user requirements.

The IQ section handles the obvious installation criteria:

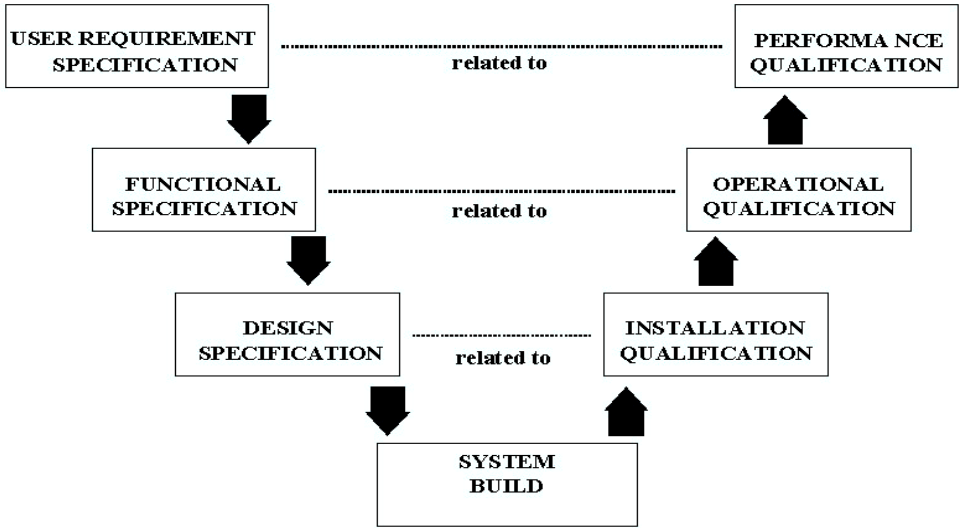
- Is the machine installed correctly? (plumb and level, in a room suited to the purpose)
- Are the utilities satisfactory for the equipment?

Information should be available:

- The validation team should be identified in a validation team document
- Are the manuals in place and correct?
- Are the drawings up to date, and do they represent the actual installation?
- Are all the major pieces of equipment identified in the manual for ease of Replacement.
- Configuration of configurable devices should be recorded (switch settings, Programming of recorders, etc.)
- Identification of manufacturer, model number and serial number of critical Equipment for any service that may be required.
- Are all the product contact materials identified, and if necessary, verifiable?[6]

Design qualification [7]

Design Qualification is used at the stage where a design that has been developed from the, VRS/URS/cGMP and other Health and Safety Guidelines, is reviewed and documented by competent persons to ensure that the designed equipment, if built, will satisfy all the detailed specified requirements.The Design Qualification is the only document that is going to confirm that the design will work (**Table 1**).



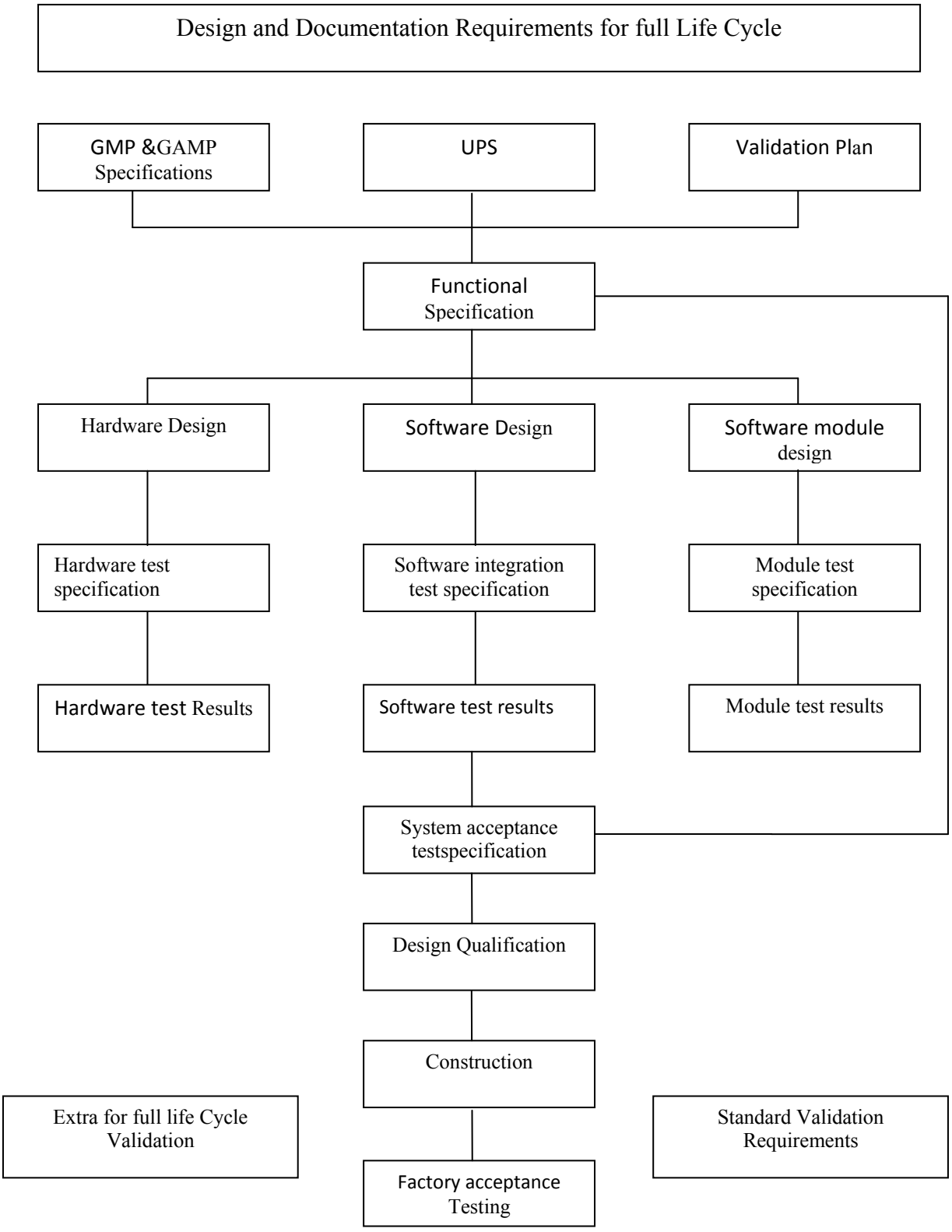
GMP supplier Guide[8]

Operational qualification

This Operational Qualification (OQ) protocol comes with an interactive SOP as a prefixed document. As you complete the SOP you are auto populating the OQ. A really easy and straight forward document to use. In the preparation of the Operational Qualification validation protocols, it is important to allow a degree of flexibility. This must and should be specified in the Validation Plan (VP). Should the OQ remain untouchable until the Installation-Qualification is completed and signed off? There are many instances where this is not just undesirable but senseless and deleterious to project progress and costs. Should every function in a system or Piece of equipment be qualified? It makes little sense to fail something for not reaching a parameter that you are not going to use. The Operational Qualification includes a review of the Standard Operating Procedure (SOP's) for start-up, operation, maintenance, safety, and cleaning / sanitization as applicable, must they be in fully approved format? These flexibilities must be built into the qualification process. However there is an abundance of rules and guidelines that are not flexible, and must be rigorously adhered to. The modular process has been followed in constructing this Operational Qualification, in as much that where tests / inspections are standard for systems and or equipment, they are built into the basic protocol. Where they are not they are available as test protocols. Functional and software tests are authored in this stand-alone test scrip protocol format. When the OQ is being raised they are pasted in. The document format will paginate them, and automatically add them to the 'Table of Contents'. They are then

part of the OQ. These Test Scripts can be held as Method Statements or SOP's. This allows the generation of a standard OQ that covers all the many items the regulators are looking for, with the facility to have integrated into it, the equipment specific testing tasks. It also means that these stand-alone test scripts are available for tasks other than validation, i.e. when system re-testing is required [9,10,21,24,27,29].

Table 2: Design and Documentation Requirements for full Life Cycle



DESIGN AND DOCUMENTATION REQUIRE-MENTS FOR FULL LIFE CYCLE & STANDARDVALIDATION [10]

Performance qualification

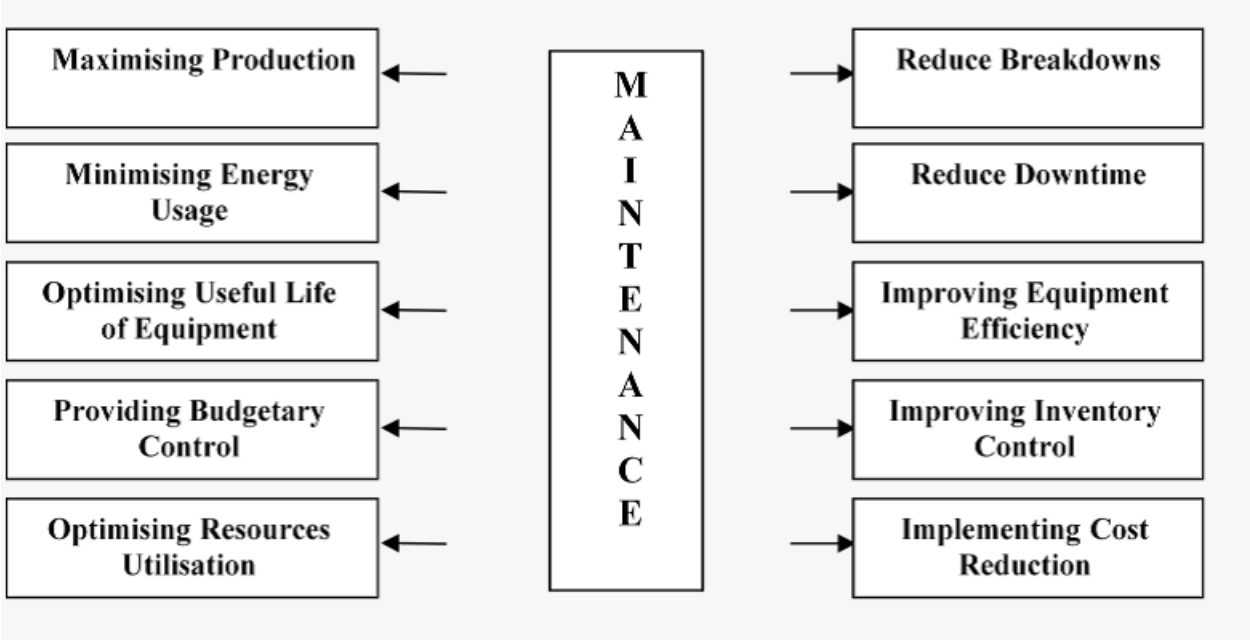
It is often used to qualify equipment throughout the full range of the equipment capabilities that is only concerned about capabilities that the process under validation uses.

MAINTENANCE

The combination of all technical and administrative actions, including supervision actions, intended to retain an item in, or restore it to, a state in which it can perform a required function. & Maintenance is a set of organised activities that are carried out in order to keep an item in its best operational condition with minimum cost acquired.

Table 3: Maintenance objectives [11]

Plant



Types of maintenance

Run to failure maintenance (RTF)
Preventive maintenance (PF)
Corrective maintenance (CM)
Improvement maintenance (IM)
Predictive maintenance (PDM)

Run to Failure Maintenance

The required repair, replacement, or restore action performed on a machine or a facility after the occurrence of a failure in order to bring this machine or facility to at least its minimum acceptable condition

Preventivemaintenance

It is a set of activities that are performed on plant equipment, machinery and system before the occurrences of a failure in order to protect them and to prevent or eliminate any degradation in their operating condition.

British Standard 3811:1993 Glossary of terms defined preventive maintenance as: The maintenance carried out at predetermined intervals or according to prescribed criteria and intended to reduce the probability of failure or the degradation of the functioning and the effects limited.

Some researchers classified predictive maintenance as a type of preventive maintenance. The main difference between preventive maintenance and predictive maintenance is that predictive maintenance uses monitoring the condition of machines or equipment to determine the actual mean time to failure whereas preventive maintenance depends on industrial average life statistics.

Corrective maintenance

In this type, actions such as repair, replacement, or restore will be carried out after the occurrence of a failure in order to eliminate the source of this failure or reduce the frequency of its occurrence.

In the British Standard 3811:1993 Glossary of terms, corrective maintenance is defined

as: the maintenance carried out after recognition and intended to put an item into a state in which it can perform a required function.

Improvement maintenance

It aims at reducing or eliminating entirely the need for maintenance. This type of maintenance is subdivided into three types as follows:

Design-out maintenance which is a set of activities that are used to eliminate the cause of maintenance, simplify maintenance tasks, or raise machine performance from the maintenance point of view.

Predictive maintenance

Predictive maintenance is a set of activities that detect changes in the physical condition of equipment (signs of failure) in order to carry out the appropriate maintenance work for maximising the service life of equipment without increasing the risk of failure [12-14,27].

CONCLUSION

In above study we are understood that all equipment including laboratory glassware, plastic ware, major and minor instrument, equipment for microbiological laboratory should be taken according to their use and specification. Selection of equipment must be considered that equipment used for inflammable material should be equipped with explosion proof electrical part and each equipment when possible containing recording devices like pressure gauge, temperature gauge should be fixed. The cleaning of every equipment depends on the stability of products so the purpose is to remove product residues of previous product or batch and to clear and sanitise the equipment for next batch. The equipment validation protocols provide the knowledge of installation qualification, design qualification, operational qualification, and performance qualification. All of these are a documented procedure provide equipment uses, specification, safety, capability, codes, etc.

REFERENCES

1. Subrahmanyam C.V.S. 'et al' Pharmaceutical engineering Principles and Practices.
2. Cherukuri R 'et al'. KMCH College of Pharmacy Coimbatore 2010-11.
3. Sharma P.P, How to Practice GMP' second edition 'A Plan for total quality control.
4. Carter, P. L., Carter, J. R., Monczka, R. M., Slaight, T. H., & Swan, A. J. (2000). Future of Purchasing and Supply: A Ten-Year Forecast. The Journal of Supply Chain Management, winter2000, 14 – 26.
5. William E. Hall, Validation and verification of cleaning Processes, Hall & Pharmaceutical associates, Inc., Kure Beach, North Carolina, U.S.A., 2003
6. Good Laboratory Practices for Non-Clinical Laboratory Studies.21 CFR, 58:2002.Rookville, MD: USP/NF, USPC.
7. Donald M. Rosendale; 'Validation group manager'. Vector corporation validation of Pharmaceutical Process Equipment.
8. Pharmaceutical Inspection Convention, "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation", 2007.
9. Donald M. 'Vector Corporation'.
10. FDA Presentation 'ICH Q7A GMP Guidance for API and its use During Inspections'; 'http://www.fda.gov/cdr/meeting/ICH_Q7A /index.htm, 2002.
11. Cherukuri R 'et al'; KMCH College of Pharmacy Coimbatore 2010-11.
12. Bedson P, and Sargent M, The development and application of guidance on equipment qualification of analytical instruments, Accreditation and Quality Assurance. 1996; 97 (6): 265-274.
13. Coombes P, Laboratory Systems Validation Testing and Practice, DHI Publishing, LTD, Raleigh, USA 2002.
14. Freeman M, Leng M , Morrison D and. Munden R.P from the UK Pharmaceutical Analytical Sciences Group (PASG), Position Paper on the qualification of analytical equipment, Pharm. Techn. Europe, 40-46, November 1995.
15. United States Food and Drug Administration (FDA), General Principle of Software Validation: Final Guidance for Industry and FDA Staff, Rockville, MD, Jan 2002.
16. GAMP Good Automated Manufacturing Practice, Guide for Validation of Automated Systems, Version 4, 2001
17. GAMP Good Automated Manufacturing Practice, A Risk-based Approach for Compliant Computerized Systems, Version 5: 2008.
18. GAMP Good Practice Guide for Validation of Laboratory Systems, 2005.
19. Huber V, Validation of Computerized Analytical and Networked Systems, Inter pharm, Englewood, CO, USA, April 2002.
20. Parenteral Drug Association (PDA), Validation and qualification of computerized

laboratory data acquisition systems (LDAS), Technical paper 31, 2000.
21. Nassani Mowafak, "Cleaning Validation in the Pharmaceutical Industry", Institute of Validation Technology, 38.
22. Sharma PP, How to practice GMPs, A Guide for CGMP Compliance along with PAT &HACCP, 2004 (5), 28-35.
23. William E. Hall, "Validation and Verification of Cleaning Processes" Hall & Pharmaceutical Associates, Inc., Kure Beach, North Carolina, U.S.A., 2003.
24. Shah DH, QA Manual, 1-7.
25. Pharmaceutical Inspection Convention, "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation", 2007.
26. Destin A. LeBlanc, "Validated cleaning technologies for pharmaceutical manufacturing" Interpharm / CRC, London, 1-10.
27. Alcock, P. and Motise, P .FDA statement: Human Drug cGMP Notes.
28. FDA Websites [http://www.fda.gov].
29. GMP training Organization websites [http://gmptraining.com/news.html].
30. Other websites [http://www.ispe.org/; http://www.dihome.org; http://www.raps.org/; http://www.pda.org/;].