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A Review on validation of Autoclave, Membrane Filtration

B. Venkateswara Reddy*, B. Rasmitha Reddy, K. Navaneetha

St.pauls College of Pharmacy, Turkayamjal, R.R (Dist) -501510, Andhra Pradesh, India

Abstract

Validation is one of the important steps in achieving and maintaining the quality of the final product batch after batch. Without equipment, we cannot manufacture a product. If equipment is validated, we can ensure that our product is of the best quality. Validation of the equipment is called the Qualification. To manufacture different types of dosage forms, different equipments are used. Here, this article concentrates on the equipment qualification for Autoclave and Membrane filtration.

Keywords: Validation, Equipment Qualification, Autoclave and Membrane filtration.

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Corresponding author
B. Venkateswara Reddy
E-mail: basu.pharmacist@gmail.com
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1. Introduction

In manufacturing facilities, validation test procedures are used to validate equipment and processes that may influence product quality. The tests for validation are used in accordance with approved written qualification procedures. All necessary activities and responsibilities for the qualification and validation are controlled and specified in this Validation Master Plan. Every step of the described validation program for facilities, equipment, processes, process controls, and cleaning is in accordance with the current European Community Guidelines for GMP and FDA, and the cGMP guideline for finished pharmaceutical manufacturers.

Definition:

Validation may be defined as "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." It has been made mandatory by the regulatory bodies to prove the safety, efficacy, purity & effectiveness of the drug product, medical devices & biologics in the market place & health system.

Importance of Validation

- Increased throughput
- Reduction in rejections and reworking
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer complaints about process-related failures
- Reduced testing in-process and in finished goods
- More rapid and reliable start-up of new equipment

• Easier scale-up from development work
• Easier maintenance of equipment
• Improved employee awareness of processes
• More rapid automation

Types of Validation

1. Retrospective validation
2. Prospective validation
3. Concurrent validation
4. Revalidation

1. Retrospective validation

Validation of a process for a product already in distribution based on accumulated production, testing, and control dates. Summary of existing historical data. The retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. In each case of retrospective validation it must be decided which elements of the validation lifecycle should be used. In general, the design qualification is left out of the retrospective life cycle.

The life cycle for retrospective validation is divided into the following steps:

1. Actual survey of facilities, processes, and process control
2. Validation Master Plan (VMP)
3. Design Qualification (DQ)
4. Risk Analysis (RA)
5. Installation Qualification (IQ)
6. Operational Qualification (OQ)
7. Performance Qualification (PQ)
8. Process Validation (PV)
9. Cleaning Validation (CLV)
10. Computer Validation (CV)
11. Validation Report (VR)
12. Revalidation (ReV)

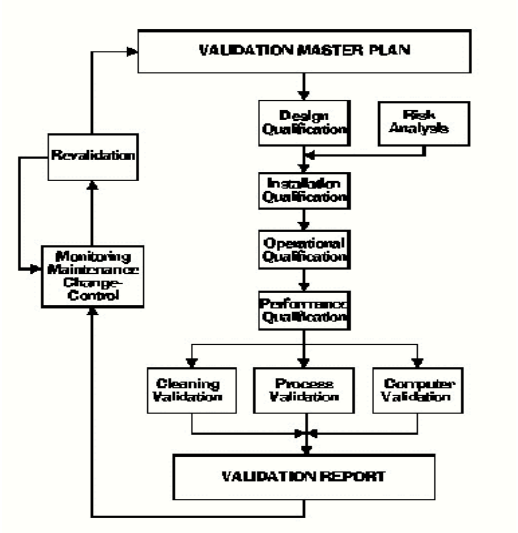

Figure 1. Retrospective validation

2. Prospective validation

Validation conducted prior to distribution either of a new product, or a product made under a revised manufacturing process. Validation is completed and the results are approved prior to any product release.

The life cycle for prospective validation is divided into the following steps:

1. Validation Master Plan (VMP)
2. Design Qualification (DQ)
3. Risk Analysis (RA)
4. Installation Qualification (IQ)

5. Operational Qualification (OQ) 6. Performance Qualification (PQ)
7. Process Validation (PV)
8. Cleaning Validation (CLV)
9. Computer Validation (CV)
10. Validation Report (VR)
11. Revalidation (ReV)

Each prospective validation step will be described in Qualification/Validation documents. In these documents, except for the Validation Master Plan and the Validation Report, the test methods for validation and acceptance criteria for the results are specified. Also described are whether the equipment has to be prepared for the test method and whether the original status of the equipment has to be restored after testing.

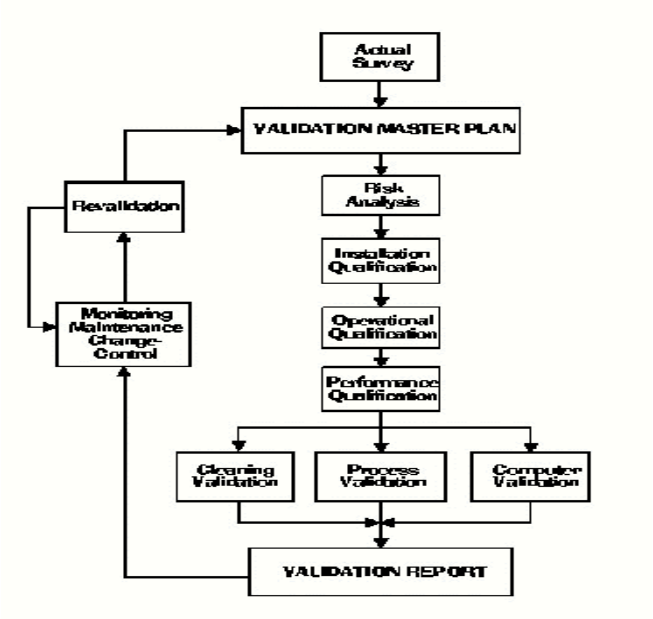

Figure 2. Prospective validation

3. Concurrent validation

It is a combination of retrospective and prospective validation. Performed against an approved protocol but product is released on a lot-by-lot basis. Usually used on an existing product not previously validated or insufficiently validated. Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.

The life cycle for concurrent validation is divided into the following steps:

1. Validation Master Plan (VMP)
2. Design Qualification (DQ)
3. Risk Analysis (RA)
4. Installation Qualification (IQ)
5. Operational Qualification (OQ)
6. Performance Qualification (PQ)
7. Process Validation (PV)
8. Cleaning Validation (CLV)
9. Computer Validation (CV)
10. Validation Report (VR)
11. Revalidation (ReV)

Each concurrent validation step will be described in Qualification/Validation documents. In these documents, except for the Validation Master Plan and the Validation Report, the test methods for validation and acceptance criteria for the results are specified. Also described are whether the equipment has to be prepared for the test method and whether the original status of the equipment has to be restored after testing.

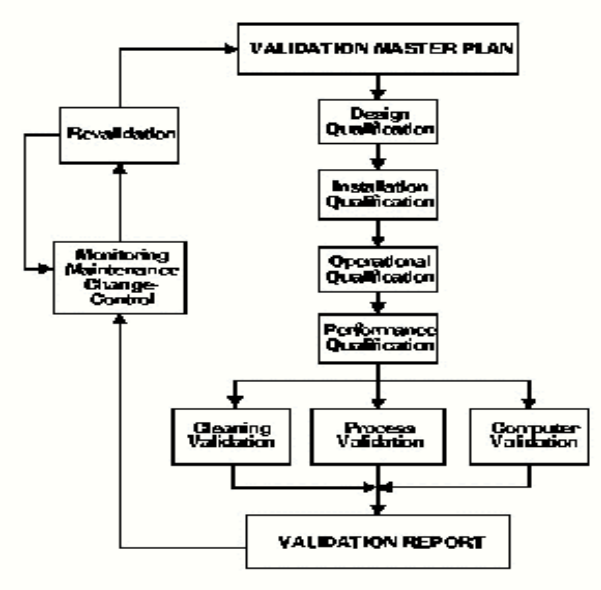

Figure 3. Concurrent validation

4. Revalidation

To validate change in equipment, packaging, formulation operating procedure, or process that could impact product safety, efficacy or potency. It is important to establish a revalidation program for critical equipment to maintain validity.

Equipment Qualification

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

1 Design Qualification (DQ)
2 Installation Qualifications (IQ)
3 Operational Qualifications (OQ)
4 Performance Qualifications (PQ)
5 Maintenance Qualifications (MQ)

Who should do Equipment Validation?

The vendor or the user has the ultimate responsibility for the accuracy of the analysis results and also for equipment qualification. DQ should always be done by the user. While IQ for a small and low cost instrument is usually done by the user, IQ for large, complex and high cost instruments should be done by the vendor. OQ can be done by either the user or the vendor. PQ should always be done by the user because it is very application specific, and the vendor may not be familiar with these. As PQ should be done on a daily basis, this practically limits this task to the user.

Design Qualification (DQ):

"Design qualification (DQ) defines the functional and operational specifications of the instrument and details for the conscious decisions in the selection of the supplier". The steps that should be considered for inclusion in a design qualification. Description of the analysis problem, Description of the intended use of the equipment, Description of the intended environment, Preliminary selection of the functional and performance specifications, Preliminary selection of the supplier, Final selection of the equipment, Final selection of the supplier, Development and documentation of final functional and operational specifications,

Installation Qualification (IQ):

"Installation qualification establishes that the instrument is received as designed and specified, that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument." The qualification involves the Coordinate efforts of the vendor, the operating department and the project team. (which provide input into the purchase, installation, operation and maintenance of the equipment).

Operational Qualification (OQ):

"Operational qualification (OQ) is the process of demonstrating that an instrument will function according to its operational specification in the selected environment". The proper operation of equipment is verified by performing the test functions specified in the protocol. A conclusion is drawn regarding the operation of equipment after the test functions are checked and all data has been analyzed. Following are the contents of equipment operation qualification: 1. Application S.O.P's, 2. Utilization List, 3. Process Description, 4. Test Instrument Utilized To

Conduct Test, 5. Test Instrument Calibration, 6. Critical Parameters, 7. Test Function (List), 8. Test Function Summaries.

Performance Qualification (PQ):

"Performance Qualification (PQ) is the process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use ". PQ should always be performed under conditions that are similar to routine sample analysis. PQ should be performed on a daily basis or whenever the equipment is being used. In practice, PQ can mean system suitability testing, where critical key system performance characteristics are measured and compared with documented.

Validation of Autoclave

Introduction:

Sterile products have several unique dosage form properties, such as Freedom from micro-organisms, Freedom from pyrogens, Freedom from particulates, Extremely high standards of purity and quality; However, the ultimate goal in the manufacture of a sterile product is absolute absence of microbial contamination.

Three principles are involved in the validation process for sterile product.

1. To build sterility into a product
2. To demonstrate to a certain maximum level of probability that the processing and sterilization methods have established sterility to all units of a product batch
3. To provide greater assurance and support of the results of the end product sterility test.

D value:

"It is time required for a 90% reduction in microbial population. Quantitative expression of rate of killing of microorganism." In other words, the D value will be affected by The type of microorganism used as BI, The formulation components and characteristics, The surface on which the micro-organism is exposed, The temperature, gas concentration, or radiation dose of sterilization process.

Z value:

Z value Used exclusively in validation of heat sterilization process. Z value is reciprocal of slope of plot of log D verses T at which D value is found i.e. increase in temperature required to reduce D value of organism by 90 % (1 log reduction). F value Used exclusively in validation of heat sterilization process. It is time in min required to kill all spores in suspension at 121 o C.

Methods of Sterilization of Products:

1. Heat sterilization moist heat (autoclave), Dry heat oven or tunnel.
2. Gas sterilization Ethylene oxide, per aceticacid, Vapor phase hydrogen peroxide, Chlorine dioxide.
3. Radiation sterilization Gamma, Ultraviolet.
4. Membrane filtration

Design Qualification:

Design qualification includes: Facility layout. Utility requirements and specifications. Required capacity of the sterilizer. Type of materials to be sterilized (Liquids, wrapped, hollow or porous materials). Requirement for Prevacuum cycles.

Installation Qualification:

The IQ process is intended to demonstrate that as autoclave installed meet all specification installed properly and supporting program (SOP, Maintenance sheet) are in place. The IQ includes following checks: Supplier or manufacturer name & address shall be checked. Any deviation observed should be informed to the supplier or manufacturer through purchase department for corrective action. Equipment name, make & model no. shall be noted down. In-house equipment Code No.Shall be allocated to check the Location of installed Equipment Mechanical equipment specification (chamber, valve, filters, and vacuum pump.)Site specification / utilities, Construction material, Change / spare parts. Operating and maintenance manuals. Preventing maintenance programmed.

Operational Qualification:

The OQ process intended to demonstrate that components of autoclave operate properly and ready for performance or load testing. OQ includes following checks: Operational tests (Operator modes, emergency stop, doors, display checks, switch, interlock checks and programmable parameter). Saturated steam check. Filter sterilization. Leak / air removal test. Power loss recovery test. Several utilities need to be verified like clean steam generator, air filtration system, power source and cooling water. Selection and Calibration of Thermocouples must be durable for repeated use as temperature indicators in steam sterilization validation and monitoring. Copper constantan wires coated with Teflon are a popular choice as thermocouple monitors. Accuracy of thermocouples should be 0.5°C. Temperature accuracy is especially important in steam sterilization validation.

Selection of BI:

Sterilization process Biological Indicator (BI) 1. Autoclave B. stereo thermophiles spores B. subtilis var. niger spores B. subtilis, 5230 spores B. coagulance spores Clostridium supergenes spores 2. Dry heat B. subtilis var. niger spores B. subtilis, 5230 spores 3. Ethylene Oxide B. subtilis var. niger spores 4. Radiation B. pumilus spores Micrococcus radiodurans vegetative cells

Performance Qualification:

Heat-Distribution Studies Heat-distribution studies include two phases: 1) Heat distribution in an empty autoclave chamber, 2) Heat distribution in a loaded autoclave chamber. The trips where the wires are soldered should not make contact with the autoclave interior walls or any metal surface. Heat-distribution studies may employ thermocouples at the cool spot in the chamber. The principle is the location of the cool spot and the effect of the load size and/or configuration on the cool spot location. The difference in temperature between the coolest spot and the mean chamber temperature should be not greater than • 2.5°C. Greater temperature differences may be indicative of equipment malfunction.

Heat-Penetration Studies:

This is the most critical component of the entire validation process. The main purpose is to determine the cold spot inside the commodity. The container cold spot for containers ≥100 ml is determined using container-mapping studies. Thermocouple probes are inserted within a container and repeat cycles are run to establish the point inside the container.Thermocouples will be placed both inside and outside the container at the cool spot location(s), in the steam exhaust line, and in constant-temperature baths outside the chamber. The difference in temperature will be calculated based on the temperature recorded by the thermocouple inside the container at the coolest area of the load.

Microbiological Challenge Studies:

Microbiological challenges studies are employed to provide additional necessary assurance that adequate lethality has been delivered to all parts of the load. Calibrated BIs used as bio burden models providing data that can be employed to calculate for the microorganisms used to challenge moist heat sterilization cycles are stereothermophillus and Clostridium sporogenes. After the sterilization cycle is complete, the inoculated items or spore strips are recovered and subjected to microbiological test procedures. Strips are immersed in a suitable growth medium (soybean casein digest medium is typical) and incubated for up to seven days. F 0 value for B. steriothermophillus is 12 min at 121 °C.

Filter Evaluation:

Microbial filters are employed on most parts of sterilizers to ensure that loads are not contaminated by air used to vent the chamber as it cools or dries. Product loads are protected from such contamination by their primary containers (vials, bags) and many non-product loads are protected by wraps to provide a microbial barrier. For filters, two issues are of concern: Sterility and Integrity. If the load will undergo a bio burden cycle, it may be necessary to sterilize the filter in a separate phase of the cycle. To ensure that filters will remain functional under all expected conditions, the integrity tests should be done following the maximum cycle time and temperature. Triplicate studies are recommended.

Design Qualification (DQ)

DQ defines the functional and operational specifications of an instrument.

DQ defines the functional and operational specifications of the instrument and details the conscious decisions made in the selection of the supplier. DQ should ensure that instruments have all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet user requirements.

The list below shows the recommended steps that should be Considered for inclusion in a Design Qualification:

• Description of the analysis problem
• Description of the intended use for the equipment
• Description of the intended environment
• Preliminary selection of the functional and performance specifications (technical, environmental, safety)
• Preliminary selection of the supplier
• Final selection of the supplier and equipment
• Development and documentation of final functional and operational specifications

Vendor Qualification:

As part of the DQ process, the vendor should be qualified; the question is how should this be done? Is an established and documented quality system enough (e.g. ISO 9001), or should there be a direct audit? The answer is that there may be situations where a vendor audit is recommended: for example, when complex computer systems are being developed for a specific user. However, this is rarely the case for analytical instruments. If equipment does not include a computer system, a good reputation, one's own experience or good references from other users – together with ISO 9001 certification - can be sufficient. Installation Qualification (IQ)IQ ensures that an instrument is received as designed and specified. It documents the installation in the selected user environment.IQ establishes that the instrument is received as designed and specified, that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument.

Before installation:

- Obtain manufacturer's recommendations for installation site requirements

- Check the site for the fulfillment of the manufacturer's recommendations (utilities such as electricity, water and gases plus environmental conditions such as humidity, temperature, vibration level and dust).
- Allow sufficient shelf space for the equipment itself, related SOPs, operating manuals, logbooks and software

Operational Qualification (OQ)

OQ demonstrates that an instrument will function according to its operational specification in the selected environment. Operational Qualification (OQ) is the process of demonstrating that instrument will function according to its operational specification in the selected environment. Before OQ testing is done, one should always consider what the instrument will be used for? Testing may be quite extensive if the instrument is to be used for all types of applications and where some of these place great demands on the performance of the system. According to a specification appropriate to its routine use. The test frequency is much higher than for OQ. Another difference is that PQ should always be performed under conditions that are similar to routine sample analysis.

Performance Qualification (PQ)

PQ demonstrates that a balance or instrument consistently performs according to a specification appropriate to its routine use. Performance Qualification (PQ) is the process of demonstrating that an instrument consistently performs according to a specification appropriate to its routine use. PQ should be performed on a daily (or at least a weekly) basis, or whenever the instrument is used. The test frequency depends not only on the stability of the equipment but also on everything in the system that may contribute to the analysis results.

1. Define the performance criteria and test procedures.
2. Select critical parameters.
3. Define the test intervals

Maintenance Qualification (MQ)

MQ describes and documents any maintenance required on the equipment and includes the professional training of the user. The MQ describes and documents any maintenance required on the equipment. This includes routine servicing and any repairs necessary. Details of any maintenance contracts are also documented in this section, together with a list of authorized service engineers. In addition, the MQ includes the routine cleaning of the equipment and also its ultimate disposal.

Validation of Membrane Filteration

Introduction:

Unit operation of filtration is the separation of solids from a liquid by passage through a filter medium. Membrane filtration is used for sterilization of drug product and used in sterilization process. There are two types of filter used in filtration process: Depth filters: Consist of fibrous or granular materials so packed as to form twisted channels of minute dimensions and they are made of diatomaceous earth, unglazed porcelain filter, sintered glass or asbestos. Membrane filters: These are porous membrane about 0.1 mm thick, made of cellulose acetate, cellulose nitrate, polycarbonate, and polyvinylidene fluoride, or some other synthetic material.

Pre-requisites:

In order to efficiently conduct validation of the membrane filtration method, ensure that the following requirements are fulfilled: Validated aseptic facility to carry out the validation all equipments to be used for validation are qualified and operational SOP's established and followed. All the equipments and culture media required for the validation should be sterile. Clean glass wares with sterile 70% IPA solution. Membrane filter: - Sterile individually packed cellulose nitrate or cellulose acetate having average pore size of 0.45µm. Validation tasks are to be carried out by trained personnel using techniques and equipment, which minimize the risk of accidental microbial contamination of the test and of the testing environment. Personnel conducting sterility testing or associated aseptic manipulations should wear sterilized garments. Identification of critical control / m onitoring parameter each lot of media used must be tested for its growth promoting qualities as per SOP. During validation carry out environmental monitoring by settle plate and personnel monitoring by swab method as per SOP. If any CFU observed during monitoring on swab method, all CFU must be identified up to species level.

Validation study element:

Physical parameter: Sterilization, Integrity test, Operating condition, Shedding, Microbial challenge test. Chemical parameter: Inertness, Activity/stability, Test for antimicrobial activities, Consistency and reliability. Biological parameter: Endotoxin, Toxicity.

1. **Sterilization:** Validation of sterilization method of filter is necessary because filter itself cause contamination of the product. To validate use of sterilizing grade filter not only prove that the filter is adequately sterilized but also method does not damage the filter. Most preferred method is moist heat sterilizing. Variable like heat up, cool down, pressure, temperature, time, if it is uncontrolled it lead to filter failure.
2. **Integrity test:** It should be non-destructive and provide an indication of "fitness for use" This include bubble point pressure test, Retention of bacteria. This test of filter should be performed prior to processing and should be performed routinely and conducted after filtration to detect any filter leaks or perforation that might have occurred during the filtration. In bubble point test, filter medium wetted with a liquid and test

gas pressure is increased until steady stream of bubble appears from tube which is immersed in water. The pressure at which the bubble first appears is recorded as the bubble point pressure.

3. **Operating condition Time:** Long processing time could allow bacteria filtered which have been trapped by the filter. Filter manufacturer can provide the data on the retention tests that have been conducted for specific membrane and generally suggest that filter should retain bacteria excess of 48hr. Filter manufacturer decide the time by performing test. Temperature: Manufacture of filter recommended the limit of 20-25c. Pressure: Inlet pressure to the filter must be monitored to ensure that there is no potential for structure damage the differential pressure across the membrane must comply with the filter manufactures recommended limits.
4. **Shedding:** It includes particulates and fiber. Particulates: USP limits when tested by light obscuration method. For LVPs not more than 25 particulates per ml ≥ 10 µm and not more than 3 particulates per ml ≥ 25 µm. For SVPs not more than 6000 particulate per container ≥ 10 µm and 600 particulate per container ≥ 25 µm. Optical microscopy, light obscuration, light microscopic image analysis, scanning electron microscope are used in particulates count. To measure removal of particulates by filter known amount and size distribution of particulates filtered and amount of retention is measured. Fiber: Fiber releasing filter may not be used in filtration process unless it is not possible to manufacture such drug product without the use of such filters than use subsequently 0.22 µm mean porosity / 0.45 µm membrane filter.
5. **Microbial challenge test:**
6. To ensure filter is not undergoing degradation, deformation or some change under condition of use. Drug product not causes the organism to shrink resulting in non-sterilizing condition. Sterilizing filter one that when challenged with 10 7 B. Diminution per cm 2 of filter area will produce sterile effluent. Care should be taken that drug product should not be toxic to organism.
7. **Filter inertness:** There may be extraction and adsorption phenomena occur. Various techniques for determining inertness like compatibility, pH., conductivity, gravimetric extractable, weight change, adsorption, USP oxidizable substance test etc. Stability of the product should not be affected by the filter. In gravimetric extractable test, weight of the extractable are measured when filtered are shocked in ASTM grade water for 24 hr.
8. **A test for antimicrobial activity:** The test is performed to ensure that, any residual of Antimicrobial Activity is satisfactory eliminated by using the steps mentioned in this protocol. An inoculums of viable cells of the specific bacteria and fungi has been passed through the filter, inoculate filter paper in FTM & incubate at 30 to 35ºC or in SCDM and incubate at 20 to 25ºC.. If conspicuous growth does not occur within 3 days for bacteria and 5 days for fungi, the test procedure indicate that filter have antimicrobial activity.
9. **Endotoxin:**
10. Validation must address filter does not add endotoxin to drug product. It depend on quality control process of the filter manufacturer, water used in manufacturing, choice of filter vendor, verification are not done properly. Millipak filter unit contain less than 0.5 units of endotoxin per ml as per USP bacterial endotoxin test.
11. **Toxicity:**
12. A validation study should determine that passage of the drug product through a filter does not cause any toxicological effects. Construction material of filtration system should be non-toxic. Manufacture provide relevant test data such a compendia plastic test similar to USP class 6 test for plastics / USP mouse safety test for all construction materials.

In USP class 6 test was performed to conform that filter are suitable and non-toxic with contact with parenteral. Testing includes systematic and intracutaneous injection as well as intramuscular implantation of filered into mouse. If no toxicity found then filter passes the test.

3. Conclusion

Allot extra time for validation. It always takes longer than we think, particularly with a new installation. All phases of validation successfully completed and final report signed off. Review overall validation process and deviations to determine how process could be handled better in the future. The important points are: Carefully write protocols and acceptance criteria, try to anticipate problems or issues in advance. Coordination with other ongoing activities to ensure required resources will be available when needed. Coordination with vendors. Unless equipment qualification has not already been legally mandated today, in the near future it will have overriding importance, primarily in the pharmaceutical industry and in the food and cosmetics sectors. The main goal in qualifying laboratory equipment is to ensure the validity of data. The current equipment qualification programs and procedures used within the pharmaceutical industry are based on regulatory requirements, voluntary standards, vendor practices, and industry practices. The result is considerable variation in the way pharmaceutical companies approach the qualification of laboratory equipment and the way they interpret the often vague requirements.

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