International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

Process Validation of Sterile Manufacturing

Aniket Khatekar*, Anamika Kakad, Ashwini Nehe
department of pharmacy, vidya nikektan institute of pharmacy and research centre, Bota, Maharashtra, India

Submitted: 09-01-2023 Accepted: 19-01-2023

ABSTRACT

The pharmaceutical industry places a high priority on quality, so several aspects must be taken into account in order to maintain that quality, including process parameters, vendor selection, production protocol, control parameters, and in-process and end-process testing. In a quality assurance programme, process validation is crucial. Through this validation, each step of the production process confirms that it complies with all parameters within acceptable bounds. The benefits of process validation and the regulatory element with regard to product quality are discussed in this study.

Keywords :- Procedure testing, cleanliness, and reliability

I. INTRODUCTION

Pharmaceutical products that are sterile are extremely sensitive and important. These goods must be free of pyrogens, live microorganisms, and undesirable particulates. This product should be handled with extreme caution in a specific setting. Any failure directly affects the caliber of the final output.(1)

Sr. No.	USFDA	MHRA/TGA	ISO
1	Class 100	A & B	5
2	Class 10,000	C	7
3	Class 1,00,000	D	8

Table 1: Area classification

Grade	Types of operation
A	Aseptic preparation and filling
B	Background room condition for activities requiring Grade-A
C	Preparation of solution to be filtered
D	Handling of components after washing

Table 2: Types of operation

Process validation is the process of creating written proof that offers a high level of assurance that a certain process will consistently produce a product fulfilling its set specifications and quality attributes. Process validation, in accordance with EMEA, is described as "recorded evidence that the process, operating within predefined parameters, can perform effectively and reproducibly to generate a medical product matching its predetermined requirements and quality attributes."

1. WHY PROCESS VALIDATION IS DONE

1. Reason

1) Changes to the process, composition, equipment, batch size, crucial parameters, API vendor, or excipients are some examples of reasons for process validation.
2) To ensure that the product's specifications are met.
3) Number of change controls, Annual Product Review (APR), Out of Trend (OOS), and Out of Specification (OOS) (OOT).
4) To specify a manufacturing process that satisfies all requirements for acceptance.(2)

2. TYPES

1. Potential confirmation
2. Parallel validation
3. Revalidation;
4. Retrospective validation

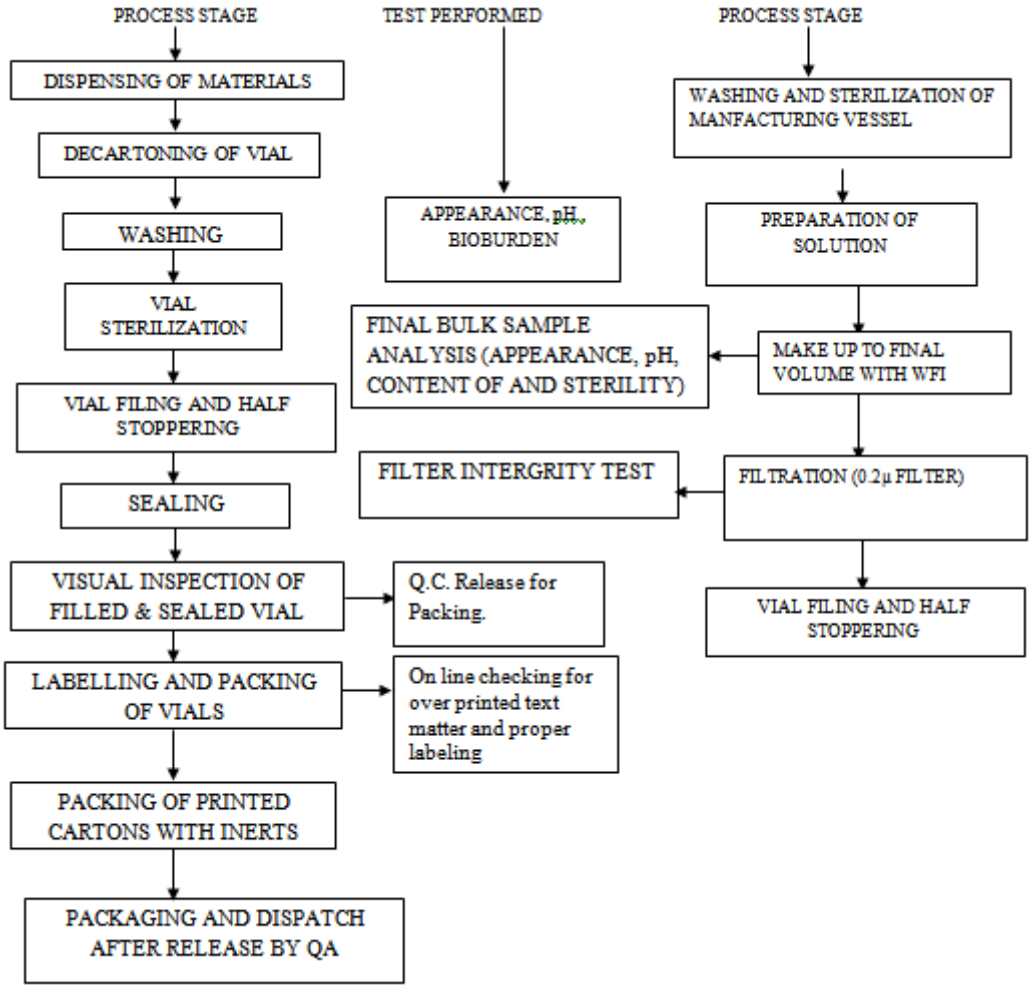
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

3. TEAM RESPONSIBILITY

Responsibility	Designation / Department
To facilitate validation and to create a report and Validation Protocol.	Chemist of Q.A.
Retrieve in-progress samples, complete samples, and carry out IPQA tasks.	Chemist of Q.A.
to conduct an analysis of the finished product sample in accordance with the approved specifications.	Chemist of Q.A.
to produce a product using the regular manufacturing procedure.	Manufacturing chemist
to examine and report on the validation protocol. gathering and analysis of QC raw data.	Manager Q.A.
Examining and approving the protocol	Manager Q.A.

Table 3: Team responsibility

4. MANUFACTURING OVERVIEW[4]



5. MANUFACTURING PROCESS:

A. Raw Materials (API and Additives)

From receipt and storage to consumption, raw materials should be managed cautiously by avoiding or reducing exposure to uncontrolled

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

environments that could result in microbial contamination or quality degradation. According to the process used to set up the conditions for terminal sterilisation, it is advised that the sterility of raw materials be guaranteed by routinely checking the level of bioburden. To ensure that raw materials fulfil endotoxin standards, controls should be in place. Suitable depyrogenation techniques should be implemented if raw materials are depyrogenated throughout the manufacturing process, taking into account the materials' physicochemical characteristics and any potential endotoxin levels. Prior to depyrogenation, the materials' endotoxin content must also be measured and recorded.[5]

B. **Containers and Closures**

Through prevent contamination with bacteria and foreign particles, containers and closures should be treated properly throughout the entire process, from receipt and storage to consumption. By taking the proper precautions, sterilised containers and closures should be shielded from contamination with germs, pyrogenic bacteria, or particulate matters/foreign particles.

C. Filtration Process

By taking into account pertinent control parameters for terminal sterilisation procedures, the filtering process should be constructed to provide sufficient sterilisation of materials and products. Pharmaceutical solutions should have their bioburden levels evaluated before filtration, if necessary, and on a regular basis. Based on their chemical and physical characteristics, biological safety profile, and extractable profile, filters for filtration should be chosen.[6]

D. Filling and Sealing Processes

The steps from preparing the pharmaceutical solution and sterilising it through cleaning and washing after filling and sealing should all be outlined in procedures for sterile filling and sealing of liquid drug preparations. The protocols should also involve responsibility assignment. According to approved (or confirmed to be effective) sterilisation methods, equipment surfaces that come into direct or indirect contact with sterile pharmaceutical items should be managed to appropriate bioburden levels. To maintain the tightness of the seal on containers (achieved by terminal sterilisation) under the predetermined parameters for a specific amount of time, operating conditions for sealing equipment should be sufficient and ideal.

E. Design of Sterilization Process

Designing the sterilization process in a way that pharmaceutical products are produced and controlled to predetermined quality characteristics and consistently supplied to the market in high quality is crucial. This design must be based on information and data gathered through research, development, industrialization efforts, and experience. In theory, moist-heat sterilization should be carried out at 121.1°C for 15 minutes, or, if that is not possible, at an F0 value of at least 8 minutes. Alternative sterilization conditions should be devised by defining process parameters to provide a SAL of less than 10-6 if F0 8 minute sterilization of pharmaceutical products is not practical due to low heat tolerance of the formulation or containers. Thus, sterilization conditions were created.[7]

2. The Basic quality control tests which are performed on sterile parenteral products include:-

A. Sterility Test
B. Pyrogen Tests
C. Leaker Tests
D. Particulate matter testing

A) Sterility tests:-

The most critical and fundamental quality of parenteral products is sterility. Sterility means that there are no living microorganisms present at all. This phrase is absolute. Sterility tests are conducted using the following techniques:

I. Simple payment method.
II. Film filtering Method

I. Simple Payment Method

It is a conventional sterility test technique that entails directly inoculating the necessary volume of a sample into two test tubes containing FTM, SCDM as the culture medium. This procedure is straightforward in theory, but it can be challenging in practise because of the possibility for operator fatigue and deterioration in skill when repeated operations like opening containers, moving samples, and mixing are required. Therefore, there is a potential of accidental contamination.

II. Flim Filtering Method

Compared to direct transfer, it is a more well-liked and frequently utilised method. More skill and information are needed for successful employment than can be transferred directly. The

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

main step in this procedure is to filter the sample via hydrophobic membrane filters with a porosity of 0.22 micron and a diameter of 47 mm. After the filtration is complete, the membrane is divided into two halves and one of the halves is inserted in two test tubes with FTM, SCDM medium. The filtration is helped under vacuum.

B). Pyrogen Test: -

Pyrogens are byproducts of microorganism metabolism, and the most potent pyrogens are produced by Gram-ve bacteria. These lipopolysaccharides are capable of passing through bacteria-retentive filters and are chemically and thermally stable. These pyrogens cause a distinct response in the body, including fever, body aches, and vasoconstriction, within an hour after introduction. Basically, two tests are used to check for the presence of pyrogens in sterile parenteral products:

I. The LAL Test
II. The Rabbit Test.

I. The LAL test:-

This test generally entails injecting a sample of the solution to be tested into rabbit test subjects through an ear vein. Before injecting the test solution, the temperature-sensing probe (clinical thermometer, thermosistor, or a similar probe) must be warmed to 37 degrees in a rabbit's rectum cavity at a depth of 7.5 cm. Then, 1, 2, and 3 hours after the injection, the rectal temperature is measured. This test is carried out in a special location created just for it in a setting similar to an animal house, away from any disruptions that would arouse them. The test is initially conducted on three rabbits, but if the necessary results are not obtained, the test is repeated on five additional rabbits using the same sample solution that was given to the first three rabbits. The control temperatures of the rabbits are established before the sample solutions are injected after an hour. Use only rabbits whose control temperature doesn't fluctuate by more than 10^0C.

II. The Rabbit test :-

It is a recently created in vitro test method for pyrogen that makes use of the gelling ability of lysates of amebocytes from the rare species of limulus polyphemus, which is only found in certain regions along the east coast of North America and along southeast Asia. The basic method involves mixing 0.1 ml of the test sample with LAL Reagent and incubating the mixture for an hour at 37 degrees Celsius to check for the presence of a gel clot. It is derived from the horse shoe crab. The presence of endotoxin is indicated by a positive LAL Test result. Its principal uses are in pharmaceutics, biology, medical equipment, disease states, food, and heat cycle validation. This approach provides a number of benefits over the rabbit test, including more specificity, reliability, reduced fluctuation, and a larger.

3. SAMPLING PLAN AND ACCEPTANCE CRITERIA[8]:

Sr. No.	Stage	Tests	Sampling Quantity	Sampling Container	Responsibility	Acceptance Criteria
1.	Manufacturing - Bulk	Appearance			IPQA	
		pH				
		Bioburden			Microbiologist	
2.	Manufacturing – after filtration	Appearance			IPQA	
		PH				
		Assay				
		Sterility			Microbiologist	
3	Vial filling finished product (Start / middle / end)	Appearance			IPQA	
		Assay				
		pH				

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

		Sterility (Shelf wise)				
4.	Finished product	Appearance			IPQA Microbiologist	
		pH (After Reconstitution)				
		Assay				
		Sterility				
5.	Primary packaging material Vial (start / middle /end)	Sterility			Microbiologist	

Table 4: Sampling plan and acceptance criteria

4. TEMPLATE FOR PROCESS VALIDATION PROTOCOL[9]

Sr. No.	Section Title	Page No.
NA	Content	
NA	Protocol approval sheet	
1	Objective	
2	Scope	
3	Responsibility	
4	Validation team member	
5	Abbreviations	
6	Pre-requisite for validation	
7	Manufacturing procedure under validation	
8	Critical process step and process parameters for validation and justification	
9	Process step – Sampling and analysis plan with acceptance criteria	
10	Revalidation	
11	Validation report	
12	Reference documents	
13	List of annexures/format attached	

5. PROTOCOL APPROVAL SHEET

A. Prepared by:-

Functional area	Name	Designation	Signature	Date
Quality assurance				

B. Checked by

Functional area	Name	Designation	Signature	Date
Production				
Quality assurance				

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 792-798 www.ijprajournal.com ISSN: 2249-7781

C. Approved by

Functional area	Name	Designation	Signature	Date
R&D				
Production				
Quality control				
Quality assurance				

1. OBJECTIVE

The ability of the manufacturing process to consistently produce completed goods of the needed quality, adhering to their specified specifications, and possessing the desired quality attributes, and to give recorded confirmation of this with a high degree of assurance.

2. SCOPE

In accordance with the demands of (market name) at the formulation plant, this process validation protocol is applicable to the process validation of (Product name) for the first three consecutive commercial batches.

3. RESPONSIBILITY

Quality assurance	Prepare, review and approval of process validation protocol
Production	Production to approve of process validation protocol
Quality control	QC to approve of process validation protocol
IPQA	Sampling as per sampling plan
Engineering	To provide support for utilities

4. VALIDATION TEAM MEMBERS

a. Quality assurance
b. Production
c. Quality control
d. In-process Quality Assurance
e. Engineering

5. PRE-REQUISITE FOR VALIDATION

a) Process equipment

Sr. No.	Equipment name	Equipment ID no.	Processing area

b) MANUFACTURING PROCEDURE UNDER VALIDATION

Process step	Process parameters	Justification

6. PROCESS STEP – SAMPLING AND ANALYSIS PLAN WITH ACCEPTANCE CRITERIA

7. CRITICAL PROCESS STEP AND PROCESS PARAMETERS FOR VALIDATION AND JUSTIFICATION

8. REVALIDATION

9. VALIDATION REPORT

10. REFERENCE DOCUMENTS

11. LIST OF ANNEXURES/FORMAT ATTACHED[10]

II. CONCLUSION:

According to the review validation data on pharmaceutical process validation and process control, process validation is a key criterion of cGMPs regulation for the process effectiveness and robustness. Additionally, it lowers the cost of process testing, sampling, and monitoring. The review's conclusion is that pharmaceutical validation and process controls are crucial to ensuring that the drug product can meet requirements for identification, strength, quality, purity, and stability.

REFERENCES:

[1]. United States Pharmacopoeia. 29 National formulary 24(USP 29- NF 24) Supplement1 is current from April 1, 2006 through July 31, (2006) 37.

[2]. M. Jayasree, C. Sowmya, L. Divya, M.Niranjan Babu, V. Rajasekhar Reddy, V. Lavakumar: Injectable Preparations-An Emerging Dosage Forms: International Journal of Advanced Pharmaceutics: 4, 1 (2014) 36-41.
[3]. Good Manufacturing Practices for Pharmaceutical Products. WHO Expert Committee on Specifications for Pharmaceutical Preparations.32nd Report, WHO Technical Report Series no. 823. Geneva: WHO, 1992: pp 14-96.
[4]. Akers, J. Simplifying and improving process validation. J. Parent. Sci. Technol. 1993, 47, 281–284.
[5]. Guidance for Industry: Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), November 2011.
[6]. Guide to good manufacturing practice for medicinal products PE 009-10 (Part I). Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, January 2013.
[7]. Lambert J. Validation Guidelines For Pharmaceutical Dosage Forms. Health Canada / Health Products and Food Branch Inspectorate, 2004;7-15.
[8]. Chitlange S.S, Pawar A.S, Pawar H.I, Bhujbal S.S. and Kulkarni A. A Validation.. 2006;4: 318-320.Cited from http://www.pharmainfo.net/reviews/validation.
[9]. Aleem H, Zhao Y, Lord S, McCarthy T and Sharratt P. Pharmaceutical process validation: an overview. J. Proc. Mech. Eng. 2003;217: 141-151.
[10]. Guidelines for Process Validation of Pharmaceutical Dosage Form – Saudi Food & Drug Authority; Version 2; February, 1992.