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RESEARCH ARTICLE

PROCESS VALIDATION OF PARENTERAL: A BRIEF DESCRIPTION ON PROCESS

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ABSTRACT

To survive in competitive market and to be successful, it is necessary to achieve high level of product quality 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. By validating each step of production process we can assure that the final product is of best quality. This review provides information on objectives and benefits of process validation, types of process validation, critical process parameters of parenteral product with special reference to the requirements stipulated by the United State Food and Drug Administration (USFDA).

Key words: Process Validation, Process parameters, Equipment, Parenteral

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INTRODUCTION

This article traces the importance of Process validation of Parenteral Product as the main role in quality assurance. "Quality assurance" is a universal concept shields all circumstances that individually or collectively guide the quality of a product. It is the entire organization made with the object of assuring that pharmaceutical products are of the quality desired for their intended use. Quality assurance therefore embraces GMP and other factors, including those outside the scope of this guide such as product design and development (World health Organization, 2007). Pharmaceutical Process Validation is the major key role and acknowledges parameters of cGMPs. It confirms that a process uniformly produces a product that meets its requirements. There are two major purposes for validating a process: firstly is to decrease the price of production of sorting and rework due to the manufacture of invalidated products mean products that do not meet their requirements. The second is to fulfill regulatory requirements designated by regulatory bodies, to know that the equipment employed on the product yields result we wanted or not (Chakarvarty Gourish *et al.,* 2013). The aim of any pharmaceutical plant is to manufacture products at a lowest rate, and Government regulation such as FDA that should be compliance with cGMP.

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Although validation of drug product have been conducted in the pharmaceutical industry for a very long time ago, there's an ever increasing interest in validation owing's to their industry in recent years on assurance of quality and productivity improvement (US Department of human and health services, 2008). Considering in the case of parenteral products, parenteral are those preparations intended for injection through the skin or other external boundary tissue. These products must be pure and free from physical, chemical and biological contaminants and should be sterile and should be prepared under aseptic condition, isotonicity, specific and high quality packaging (Sujata *et al.,* 2015).

Process validation

In January 2011, FDA declared the availability of a final guidance for industry entitled Process Validation: General Principles and Practices (the 2011 Guidance). The 2011 Guidance revises and replaces FDA's Guidance for industry entitled Guideline on General Principles of Process Validation, issued in May 1987 (the 1987 Guideline) which states that "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics". The 2011 Guidance defines process validation as "the collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product."

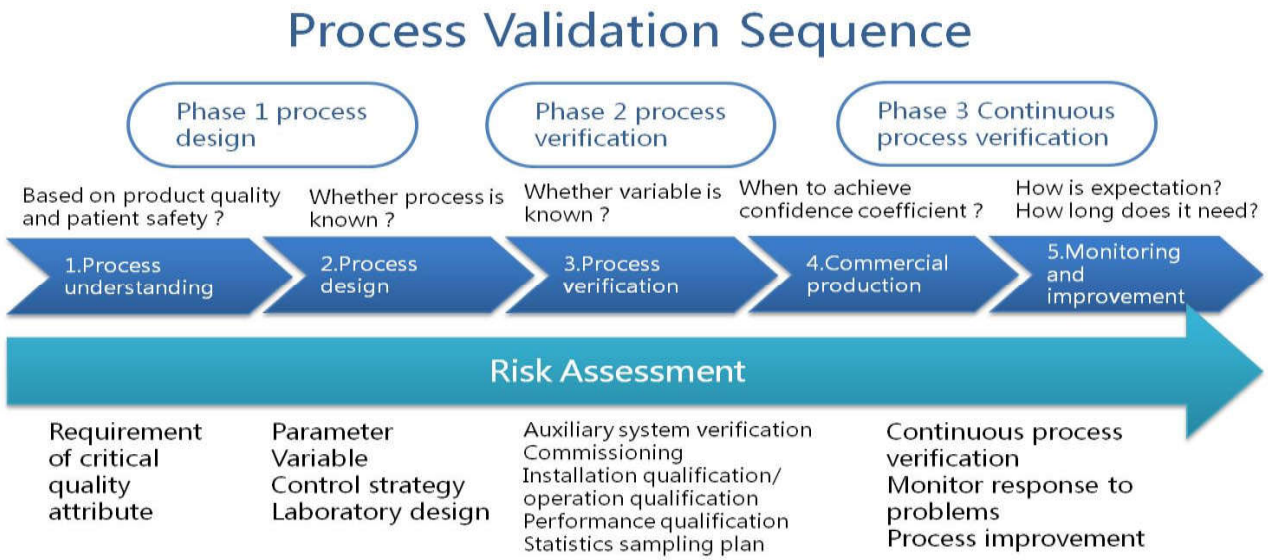

Figure 1. Process validation sequence

The 2011 Guidance promotes a "lifecycle" approach to process validation that includes scientifically sound design practices, robust qualification, and process verification.

Types of process validation

The guidelines on general principles of process validation mention Options: Prospective process validation (also called premarket validation), Retrospective process validation, Concurrent validation and Revalidation.

- **Prospective process validation:** In this type of validation, protocol is executed before the process is put to commercial use. Itis carried out in the introduction of new drug products and their manufacturing processes (Chao *et al.,* 1993).
- **Concurrent Process validation:** This type of validation involves in –process monitoring of critical processing steps and product testing. It is carried out during normal production (Nash, 2003).
- **Retrospective Process validation:** Retrospective Process Validation involves the examination of past experienced on the assumption that composition, procedure and equipment remain unchanged. It iscarried out during Validation of a process for a product which has been marketed (Avallone, 1983).

Approaches to process validation

Two basic approaches to the validation of the process itself exist namely the experimental approach and the approach based on the analysis of historical data (FDA, 2004). Process validation involves a series of activities taking place over the life cycle of the product and process.

Responsibilities

Head Quality Assurance

Quality Assurance is responsible for preparation and evaluation of the validation data as well as deviations during execution of process validation protocol.

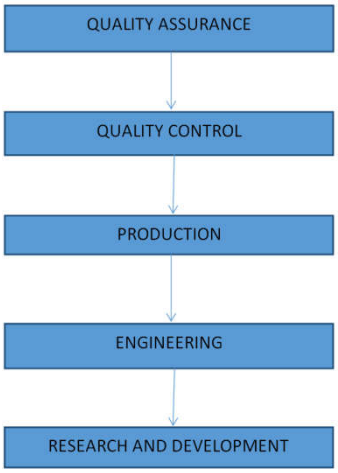

Figure 2. Validation Team Structure

Head Quality Control: QC department is responsible for analysis and evaluation of the analytical results for in-process and finished product samples as per validation sampling plan.

Head Production: Production department is responsible to hand over data generated during manufacturing of validation batches to QA for execution and filing.

Engineering: Engineering department is responsible for qualification and calibration of all the processing equipment/instrument/utilities and maintain its efficacy during the manufacturing.

Research & Development: R & D is responsible to provide necessary support in the validation activity (Gupta *et al.,* 2008).

Contents of validation protocol

- General information
- Objective
- Background/Pre-validation Activities
- List of equipment and their qualification status
- Facilities qualification
- Process flow charts

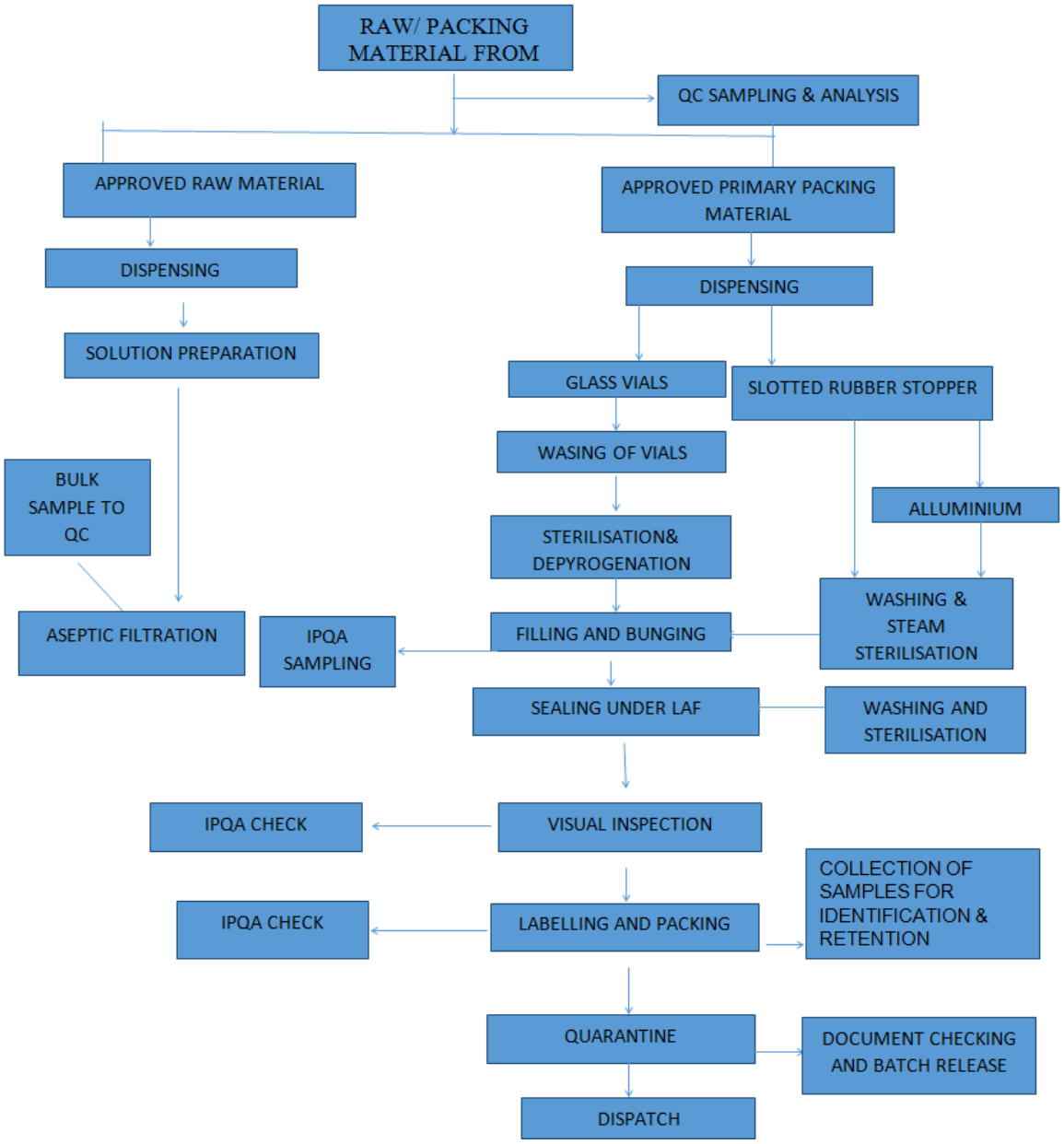

Figure 3. Manufacturing process flow chart

- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, tests and specifications
- Acceptance criteria (Thaduvai *et al.,* 2012).

Contents of Process Validation program

The following points should be included in the Process Validation Program:

- History of development and a description of the product(if available, the development report would be useful)
- A manufacturing procedure and flowchart of the manufacturing process.
- A list of all equipment required for production.
- A list of production stages that may be critical for product quality.
- A schedule for PV test procedures.

Table 1. Process control parameters

Sl. No.	Parameters	Source
1	Description	
2	Water Content	
3	Average Weight of Cake	
4	Uniformity of Dosage form	
5	Constituted solution	End product testing
5.1	Description	
5.2	Reconstitution Time	
6	Particulate matter	
7	pH	
8	Bacterial Endotoxins	
9	Sterility	
10	% Assay	
11	Final Mixing	
11.1	Description	
11.2	pH	In process testing
11.3	% Assay	
12	Filtration	
		In process testing
12.1	Sterility Test	
13	Filling	
13.1	Filled Volume	
13.2	% Assay	
14	Sealed Vials(Full Stoppered)	
14.1	Leak Test	

Table 2. Process validation parameters

Sr. No	Process	Objective	Variable (monitor)	Test (response)
1	Solution Preparation	To ensure a colorless/specified color solution with specified pH and % assay(specified % of labeled amount	Load, Mixing time, Mixing Speed	Assay, clarity, pH
2	Filtration	To comply the sterility test	Filtration Rate, Pressure	Sterility
3	Sealing	To ensure integrity of seal		Leak test, Seal Integrated

Identification of critical process variable parameters:

Probable causes that may affect final product:

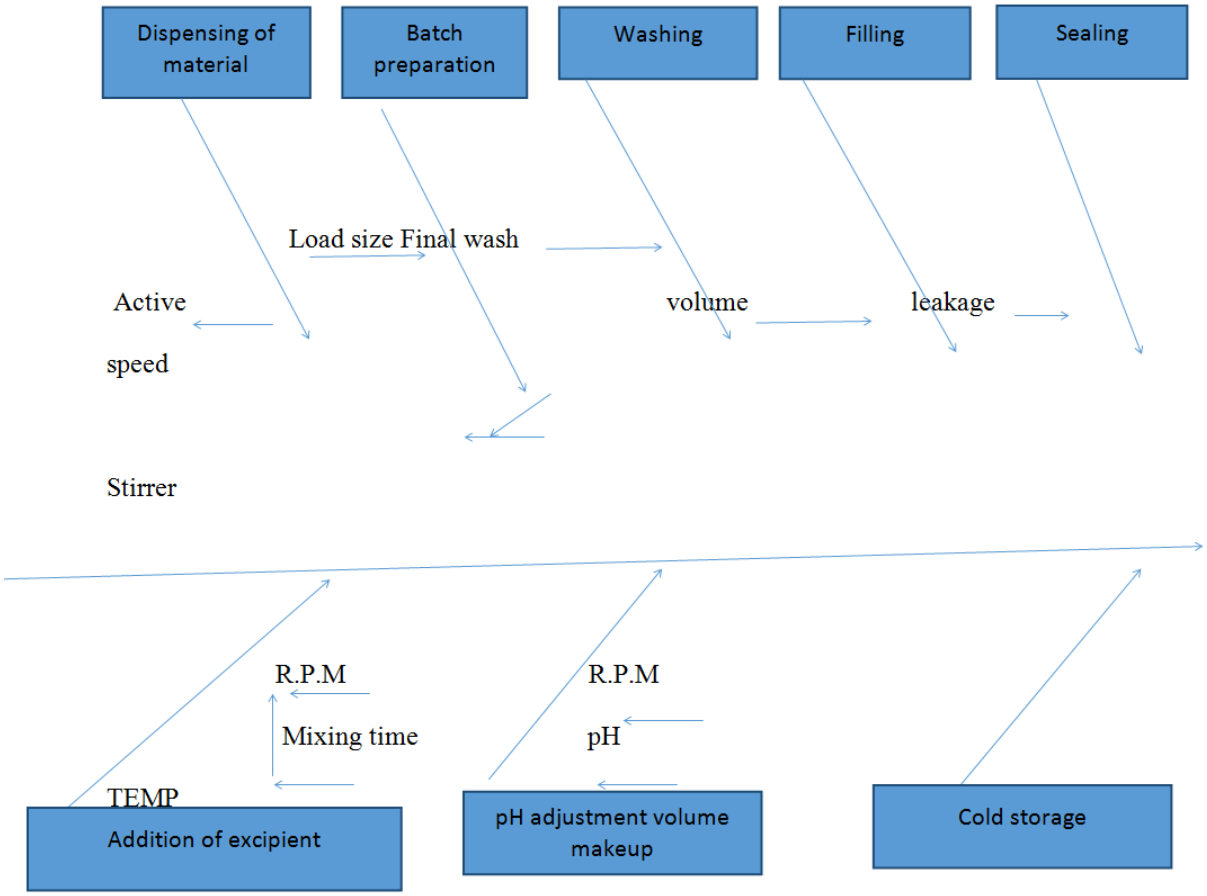

Table 3. Critical process parameters

Sr. No.	Critical process variables	Response parameters	Remarks
1.	Batch mixing time	Uniformity	Fixed speed Fixed batch size
1.	Final mixing and volume make up mixing time	Uniformity of active drug	Fixed speed Fixed batch size
3.	Rubber stopper washing Detergents with heating Purified water WFI washing siliconization	Cleaning of rubber stopper	Clarity checking Avoid the clumping
4.	Vial washing Purified water pressure WFI water pressure Compressed air pressure Washing cycle Alignments and blockage of needles	Cleaning of vials Washing effficiency	Fixed pressure for washing Fixed temperature for washing Fixed pressure of air Fixed cycle Fixed direction
5	Filling Speed of filling machine	Volume uniformity	Fixed speed Volume variation Leakage
6	Sealing Speed of sealing machine Leak test	Volume uniformity	Fixed speed Volume variation Leakage
7	Optical inspection	clarity	
8	Labeling and packing	Clean, position and proper sealing	Clean label Position sealing

Table 4. Equipment to be used

Sr. No	Equipment	Stage	Variables	Response (Test)
1	Manufacturing tank	Before manufacturing	Size Location Time	BET
2	Rubber stopper washing machine	After washing	capacity Identification number Visual inspection	Sterility
3	Vial washing machine	Beginning of washing Middle of washing End of washing	Method:visual inspection, Capacity(vials per minute), Identification number	
4	Filling machine	Beginning of filling Middle of filling End of filling	Identification, machine speed, standard volume	
5	Membrane filter			
6	Autoclave			
7	Sealing machine	Beginning of sealing Middle of sealing End of sealing	Identification number, machine speed	Leak test
8	Labeling machine	After machine setting, beginning, middle and at the end of setting	Identification number, machine speed, position of label, number of vials tested	
9	Cold storage			

A detailed description for all test procedures, including:

- Sampling procedure
- Labeling of the samples
- Test procedure
- Evaluation procedure
- Specification for the intermediate and finished products
- Acceptance criteria (World health Organization, 2007).

Conclusion

This study of Process Validation of Parenteral product involves validating the process variables of this product to show that the process was under control. The study was conducted on a three batches, which includes the validation of critical steps of Manufacturing such as Final Mixing, Filtration, Filling, Partial Stoppering, Full stoppering, Sealing and packing. Overall manufacturing process and packing process was Concluded as validated. The process validation data reveals that there was no significant variation between batch to batch and all the process variables were studied. Therefore, it can be concluded that the process of Parenteral Formulation for the three batches stands Validated.

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