WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 5, 241-253. Review Article ISSN 2277 – 7105

PROCESS VALIDATION OF PARENTERAL FORMULATION

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Article Received on
18 May 2014,

Revised on 12 June 2014,
Accepted on 06 July 2014

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ABSTRACT

To validate the reproducibility and consistency of a process, the full defined process is carried out using validated equipment, under the established procedure usually at least 3 times. The process must successfully and consistently meet all acceptance criteria each time, to be considered a validated process. The objective of study is to systemically conduct the validation study pertaining to manufacturing activities of parenteral preparation & confirm that the product manufacture with the present method consistently meets the predetermined specifications and quality attributes. The validation of the reproducibility & consistency of the process is carried out using validated equipment under established procedure usually at least three times. The process must successfully & consistently meet all acceptance criteria each time, to be considered a validated process. “Worst case” conditions are used for the validation to ensure that the process is acceptable in the extreme case. Sometimes worst case conditions for systems can only really be tested over time & hence must be evaluated using a long term monitoring.

KEY WORDS: Validation, Parenteral, process, reproducibility and consistency.

INTRODUCTION

Process is a series of inter related functions and activities using a variety of specified actions and equipment which is designed to produce a defined result. To validate the reproducibility and consistency of a process, the full defined process is carried out using validated equipment, under the established procedure usually at least 3 times. The process must successfully and consistently meet all acceptance criteria each time, to be considered a validated process. In many cases, "worst case" conditions are used for the validation to ensure

that the process is acceptable in the extreme case. Sometimes worst case conditions for systems can only really be tested over time and hence must be evaluated using a rigorous long term monitoring programme. Process validation studies examine a process under normal operating conditions to prove that the process is in control. Once the process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications to the process are made, or problems occur, or equipment or systems involved in the process are changed, a re-validation of the process would be required.

Objectives

The objective of study is to systemically conduct the validation study pertaining to manufacturing activities of parenteral preparation & confirm that the product manufacture with the present method consistently meets the predetermined specifications and quality attributes. The validation of the reproducibility & consistency of the process is carried out using validated equipment under established procedure usually at least three times. The process must successfully & consistently meet all acceptance criteria each time, to be considered a validated process. "Worst case" conditions are used for the validation to ensure that the process is acceptable in the extreme case. Sometimes worst case conditions for systems can only really be tested over time & hence must be evaluated using a long term monitoring.

Definition of Validation[1]

The following are the current definitions of pharmaceutical process validation as described by the EMEA, FDA and PIC/S. EMEA defines "Process validation is the means of ensuring and providing evidence that processes are capable of consistently producing a finished product of the required quality".FDA defines "Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics".PIC/S defines "Process validation is the means of ensuring and providing evidence that processes are capable of repeatedly and reliably producing a finished product of the required quality.

Scope of validation[2]

The scope of validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system at time of production. In general, an entire process is validated; a particular object

within that process is verified. The regulations also set out an expectation that the different parts of the production process are well defined and controlled, such that the results of that production will not substantially change over time. Validation should be performed for

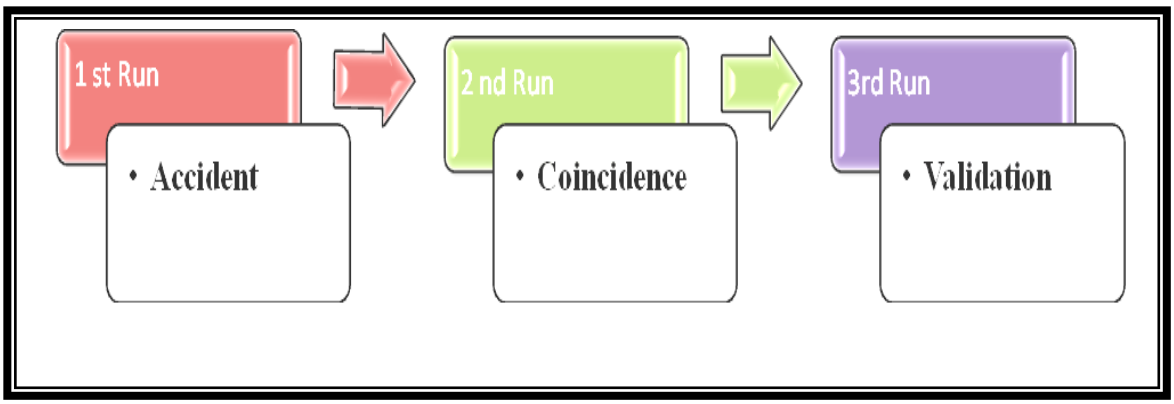
1. New premises, equipment, utilities and systems, and processes and procedures,
2. At periodic intervals, and
3. When major changes have been made.

There should be a clear distinction between in-process controls and validation. In process tests are performed during the manufacture of each batch using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

Process Validation[3]

Process knowledge depends on accurate and precise measuring techniques used to test and examine the quality of drug components, in-process materials, and finished products. Validated analytical methods are not necessarily required during product- and process-development activities or when used in characterization studies. Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. New analytical technology and modifications to existing technology are continually being developed and can be used to characterize the process or the product. Use of these methods is particularly appropriate when they reduce risk by providing greater understanding or control of product quality. However, analytical methods supporting commercial batch release must follow cGMP in parts 210 and 211. Clinical supply production should follow the cGMP appropriate for the particular phase of clinical studies.

The number of process for the validation should depend on the complexity of the process or the magnitude of the process change being considered. Three batches are taken for the purpose of process validation, to demonstrate the Consistency.



Types of process validation

Depending on the time when validation is performed relative to the production, process validations can be classified as:

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

A. Prospective validation

Prospective validation is establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. It is conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics. In prospective validation process validation, validation protocol is executed before process is put into commercial use (i.e. qualification trails). This type of process validation is usually carried out in connection with introduction of new drugs.

B. Concurrent validation

Is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price This validation involves in process monitoring of critical processing steps and product testing.

C. Retrospective validation

Retrospective validation establishes documented evidence that a system does what it is supposed to do based on a review and analysis of historic information. It is establishing document conducted for a product already marketed based on extensive data accumulated

over several batches and over time. It is normally conducted on a product already being commercially distributed and it is based on accumulated production, testing and control data.

D. Revalidation

It is the repetition of a validation process or a specific part of it. This is carried out when there is any change or replacement in formulation, equipment, plant or site location, batch size and in the case of sequential batches that do not meet product and process specification.

Process flow of parenteral dosage form[4]

In the preparation of parenteral dosage form mixing, filteration, filling & sealing are the most critical step. Flow diagram shows the process flow of parenteral dosage form.

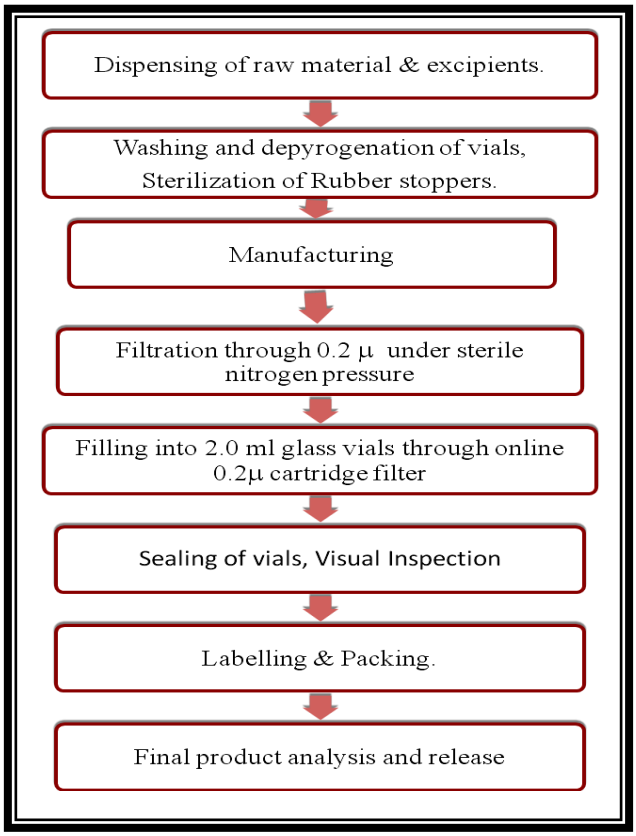


Fig.: Process flow diagram of parenteral dosage form

Processing variables in parenteral[5]

Following are the common variations that may occur during the process of parenteral formulations. These variations can be minimized by proper calibration of instruments and qualification of equipments, materials, utilities, facility, personnel, supporting systems and validating the process as a whole.

1. Dispensing

Dispensing is one of the critical factor which may lead to product contamination while transferring or dispensing. There are also chances of dispensing more or less quantity of API.

1.1. Assay

The calculation for the amount to be dispensed is done with respect to the COA of the material, the calculations are done as on dried basis only thus Assay value have great impact in the quantity of material dispensed, which may affect the final product.

1.2. Approved vendors

All the materials used for the production should be procured from approved vendors only. The vendors are approved by prior vendor audit. If the materials are procured from approved vendors the standard of the materials should be validated. If materials are procured from unapproved vendors the purity and standard of the materials cannot be assured.

1.3. LAFΔP and room temperature and RH

Pressure differentials in a controlled environment is important to ascertain that the correct degree of over pressure is maintained relative to the adjacent areas of lower classifications in order to minimize the contamination drawn into the controlled environment from its surroundings. The LAF ΔP should be maintained within limits to maintain a controlled environment.

1.4. Temperature and RH

Temperature and RH of the dispensing area should be within the specified limit since the products can be detoriated at extreme environmental conditions. The temperature and RH are monitored regularly to verify whether the area is in controlled state. The failure of AHU leads to changes in temperature & RH.

1.5. Balance calibration

All the balances used for dispensing should be calibrated before starting the days work. Apart from this calibration by external party should be conducted for periodically. If balances are not calibrated there are chances of dispensing wrong quantity of materials which may affect the final product assay.

2. Sterilization

Sterilization is the process by which a product made free of viable organisms with a specified probability. Sterilization is carried out in a sequence of defined operating parameters such as time, temperature and pressure and conditions required to render an item sterile.

2.1. Validated load pattern

When a multiple products are processed using the same cycle, a minimum lethality to be delivered for product specific loads. By a validated load pattern a safety margin is built into the minimum F_0 requirements. It assures that the lethality requirements are constantly delivered to each load. During the load pattern study the exact physical nature of each product and materials are studied and an appropriate sterilization process are selected.

2.2. Clean-in-place / Sterilize-in-place

Validation of these systems may be difficult because of the potential incompatibilities in requirements for the design of CIP and SIP facilities. All systems have dead legs to a greater or lesser extent and the required orientation of the dead legs differ for CIP and SIP. The orientation for CIP dead legs is slightly sloping so that the cleaning solution can enter and also drain away. The dead leg for SIP is vertically up so that steam can downwardly displace the air. The CIP and SIP procedures should be validated as the containers are not supposed to be cleaned manually and the parameters used during process should consistently provide the acceptance limits.

2.3. Hold time for sterilized goods

The hold time for the sterilized goods should be validated to determine the effectiveness of the sterility process. The time period until which the products remain sterile if not opened from the pack is determined. The products that lapses the hold period must be sterilized and used (provided the packs are not opened).

3. Manufacturing process[6]

3.1. LAF∆P, Temperature and RH in manufacturing area

These parameters should be maintained within the limits throughout the process in all the stages of manufacturing, filling, sealing and packing. To avoid the product failure, the possible defects are mentioned in the earlier section.

3.2. Subdued light

The intensity of the light in different areas is qualified during area qualification. In some cases the products which are light sensitive should not be dispensed at normal light. The activity should be carried out in subdued light which are of less intensity than normal light. If the product is not manufactured under subdued light it may leads to product detoriation.

3.3. Environmental monitoring[7]

Measurement and determination of the number and size of airborne particulate contamination is essential to ensure that a suitable environment is maintained for preparation of asepticaly prepared products. If any changes from the normal acceptance limit may lead to product failure due to product contamination. Acceptable methods for monitoring the microbiological quality of the environment include

A] Surface monitoring

Environmental monitoring involves sampling various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, and equipment should be tested on a regular basis. Touch plates, swabs, and contact plates can be used for such tests.

B] Active air monitoring

Assessing microbial quality of air should involve the use of active devices including but not limited to impaction, centrifugal, and membrane (or gelatin) samplers. Each device has certain advantages and disadvantages, although all allow testing of the number of organisms per volume of air sampled.

C] Passive air monitoring (Settling plates)

Passive air samplers are such as settling plates (petri dishes containing nutrient growth medium exposed to the environment). Because only microorganisms that settle onto the agar surface are detected, settling plates can be used as qualitative, or semi-quantitative, air monitors. Their value in critical areas will be enhanced by ensuring that plates are positioned in locations posing the greatest risk of product contamination.

3.4 Mixing time and RPM[8]

The product processing is done by mixing of the active and excipients together in the solution preparation tank with water for injection. Mixing time is the critical parameter as the dissolution of the materials mainly depends on mixing time. The mixing time is determined

during the validation process. If mixing time is not followed it may lead to improper dissolution of API thus leads to wrong assay results. Mixing is facilitated by using the stirrer. The stirrer speed should be validated so that we can assure that proper mixing has occurred each time. The validation is conducted at different speeds and the optimized.

3.5. pH

One of the main parameter used to chek the product quality is by checking the pH of the solution prepared, since the parenterals solutions are being injected directly it should be adjusted to the pH that is more or less equal to that of blood. In some cases due to drug solubility characterestics the pH may be acidic or basic. The pH is checked by using a calibrated pH meter in the manufacturing area. Before starting every day's activity pH meter should be calibrated.

3.6.Volume make up

Volume make up for the solution can be done by two ways such as by weighing or by dip stick. Dipstick method is done by using the calibrated dipstick present along with the manufacturing vessel. The dip stick has a measuring scale. If volume make up is done wrongly it may leads to increase or decrease in the assay values. It should be carried out at ambient temperature (25°±2°C).

3.7. Hold time study

The product manufactured aseptically should be subjected to hold time study to confirm that the product produced remain sterile, without any chemical change. During hold time study the product is frequently sampled to determine any change has ocurred in stability and sterility aspects. This is carried out since there are chances of any of equipment failure during process.

3.8. Filtration activity

In aseptic processing the product is sterilized only by filtration, thus the filtration activity should be adequately validated. The integrity of the sterilization filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, or diffusive flow or pressure hold test etc. The integrity of critical gas and air vent filters should be confirmed at appropriate intervals.

4. Vial washing and depyrogenation

4.1. LAFΔP (across the HEPA filter), Temperature and RH

These parameters should be maintained within the limits throughout the process in all the stages of manufacturing, filling, sealing and packing.

4.2. Water and compressed air pressure

The vials are washed first by series of water at a high pressure. The pressure of the water should be maintained throughout the process as the pressure is directly proportional to the effectiveness of the washing process. If the pressure is less than the acceptable value it may lead to improper washing. Compressed air is used for drying the washed vials before it reaches the tunnel. Thus any deviations in the pressure maintained will leads to improper drying which will affect the depyrogenation of the vials.

4.3. Clarity check

The washed vials are checked manually for the effectiveness of the washing process. The vials which are broken or containing any dirt can be identified during these check's which prevent the rejections after filling.

4.4. Depyrogenation temperature and conveyor belt speed[9]

Vial depyrogenation is another critical factor to be checked. Depyrogenation of vials can be achieved at a temperature between 280˚C to 350˚C. If the temperature is not maintained throughout the process it may affect the depyrogenation of the vials. The tunnel should be qualified before starting the process. During the qualification stage the depyrogenation temperature and the conveyor belt speed for the different vial size are done and established. The validated limits should be followed during the process.

4.5. ΔP (across the HEPA filter and across the zones & rooms)

Pressure differentials in the tunnel is important to ascertain that the correct degree of over pressure is maintained relative to the adjacent areas of lower classifications in order to minimize the contamination drawn into the controlled environment from its surroundings. The ΔP should be maintained within limits to maintain a controlled environment. The difference in ΔP may be due to blocked or partially blocked HEPA filters. The ΔP across various zones of tunnel and the ΔP between the tunnel cooling area and vial receiving area should be maintained.

5. Vial filling and sealing[10]

5.1. Gowning procedure

The persons entering the sterile area should not contaminate the area by shedding contaminants from own body. The person should follow the gowning procedure strictly. The gowning qualification is done by taking swabs from the gowned persons at the commonly used parts of the body on consecutive three days and incubated for checking the presence of any viable organism in it. The results showing less than the alert level is the criteria for acceptance. Person without proper training may lead to product contamination, thus proper training is given to all personnel entering sterile area.

5.2. LAFΔP (across the HEPA filter), temperature and RH[11]

These parameters should be maintained within the limits throughout the process in all the stages of manufacturing, filling, sealing and packing, to avoid the product failure. The possible defects are mentioned in the earlier section.

5.3. Filling speed and fill volume

The filling speed of the machine should be validated during the machine qualification stage. The filling speed depends upon the size of the vial and volume of the liquid filled. The fill volume may be altered due to increasing or decreasing the speed of the machine and also depends on the product physical nature. The changes from the established limits may leads to reduced extractable volume. Thus it should be frequently monitored by doing fill volume checks by using calibrated syringes or measuring cylinders.

5.4. Filter integrity testing[12]

Fiteration is the only process of sterilization in aseptically filled products, thus to confirm the sterilization has achieved filter integrity should be done. The integrity of the sterilization filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, or diffusive flow or pressure hold test.

5.5. Sealing of vials

The vials filled asepticaly should be closed and sealed immediately after filling of the solution. The sealing gives the proper closing of the vials. The sealing activity can be confirmed by doing leak testing for the sealed vials frequently. Sealing prevents the leakage of the containers during the transporting or shipping.

CONCLUSION

If the Process validation of the product Injection, was carried out and the results of aseptic media fill confirm that the area for manufacturing and aseptic filling is in controlled state. The environmental monitoring of the area and personnel reveals that, all the personnel involved during aseptic activity does not contaminate the area during production process. Environmental monitoring results confirm HVAC system for aseptic manufacturing area is functioning as per the predetermined specifications. If the conditions are maintained as such during the routine production process, the product will have consistent quality. The aseptic process validation conducted for the product Injection, was found to be complying with the acceptance criteria. Thus documented evidence for the manufacturing process for the product Injection, was shown that the process has consistently produced the product within the predetermined specifications. From the review of data recorded during manufacturing process, in process testing and finished product analysis of all the three validation batches, it is concluded that the manufacturing process is consistent and meets the pre-determined specifications and quality attributes. Hence the manufacturing process of Injection, stands validated.

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