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STUDIES IN PROSPECTIVE PROCESS VALIDATION OF RANITIDINE AND ONDANSETRON COMBINATION INJECTION DOSAGE FORM

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ABSTRACT

The purpose of the research investigation was to study prospective process validation of Ondansetron 2 mg/mL, Ranitidine 25 mg/mL, Injection USP, 2ml, Single Dose Vial. Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. Therefore building of quality requires careful attention to a number of factors, such as the selection of materials, product and process design, control variables, in process control and finished product testing. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower and upper release specifications. Three initial process validation batches of same size, method, equipment & validation criteria were taken. The critical parameter involved in addition of water for injection, mixing, filtration, filling, sealing, leak testing, visual inspection & packing stages were identified and evaluated as per validation plan. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. 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 Ondansetron 2 mg/mL, Ranitidine 25 mg/mL, Injection USP, 2ml, Single Dose Vial, stands validated.

KEYWORDS: Prospective Process validation, Control variables, Ondansetron- Ranitidine Injection USP.

INTRODUCTION

Validation Principles

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. In order to meet this principle, a good understanding of the processes and their performance is important. Quality cannot be adequately assured by in-process and finished product inspection and testing but it should be built into the manufacturing processes. These processes should be controlled in order that the finished product meets all quality specifications. Therefore, building of the quality requires careful attention to a number of factors, such as the selection of quality materials/components, product and process design, control of processes, in-process control, and finished product testing. Careful design and validation of system and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications.

Purpose

Process validation is intended to establish that the proposed manufacturing process is a suitable one and yields consistently a product of the desired quality. i.e. that the process is suitable and under control.

Importance of Process validation

The main advantages to be obtained from validation are assurance of quality and process optimization, both resulting in a reduction of total costs.

1) Assurance of Quality
2) Process Optimization
3) Reduction of quality costs
4) Safety

Processing Variables in Parenteral

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.

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.

A. 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.

B. Approved Vendors

All the materials used for the production should be procured from approved vendors only.

C. 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.

D. 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.

E. Balance Calibration

All the balances used for dispensing should be calibrated before starting the days work.

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.

A. 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 F0 requirements.

B. Clean-in-place / Sterilize-in-place

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.

C. 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.

Manufacturing Process

A. LAFΔP, 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.

B. 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.

C. Environmental Monitoring

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. 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, 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.

D. Mixing Time and RPM

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.

E. pH

One of the main parameter used to check 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. 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.

F. 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).

G. 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 occurred in stability and sterility aspects.

H. Filtration

In aseptic processing the product is sterilized only by filtration, thus the filtration activity should be adequately validated.

Vial Washing and Depyrogenation

A. 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.

B. 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.

C. 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.

D. Depyrogenation Temperature and Conveyor Belt Speed

Vial depyrogenation is another critical factor to be checked. Depyrogenation of vials can be achieved at a temperature between 280˚C to 350˚C. The tunnel should be qualified before starting the process. The validated limits should be followed during the process.

E. 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 difference in ΔP may be due to blocked or partially blocked HEPA filters.

Vial Filling and Sealing

A. 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.

B. 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, to avoid the product failure. The possible defects are mentioned in the earlier section.

C. Filling Speed and Fill Volume

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. Thus it should be frequently monitored by doing fill volume checks by using calibrated syringes or measuring cylinders.

D. Filter Integrity Testing

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.

E. Sealing of Vials

The vials filled aseptically should be closed and sealed immediately after filling of the solution. 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.

MATERIAL AND METHOD

Product Name

Table 1: Drug product used in process validation

Packaging Material	Name of Manufacturer
Ondansetron 2 mg/mL, Ranitidine 25 mg/mL, Combination Injection USP, 2ml, Single Dose Vial.	Ranbaxy Labs. Ltd, Devas.

Equipments Used

Table 2: Equipments used in process validation

Sr.No.	Name of the equipment / Instrument	Manufacturer
1	Balance	Motter Toledo
2	Vial washer	Pyroklenz
3	Tunnel sterilizer	Fedegari
4	Steam sterilizer	Metalchem industries
5	Vial filling and plugging machine	Macofar(Romaco)
6	Vial sealing machine	Macofar(Romaco)
7	Filtration assembly	Adam
8	Integrity tester	Fartorious
9	20 L capacity jacketed manufacturing vessel	Adam
10	30 L capacity jacketed manufacturing vessel	Adam
11	Visual inspection hood / machine	Umasons
12	Online Filter	Adam
13	Nonviable Particle Counter machine	Met-1
14	pH meter	Mettler Toledo
15	CIP Unit	Adam
16	Leak test Apparatus	Millipore
17	Domino Inkjet Printer	Domino
18	CVC labeling machine	CVC

Method

Processing Controls of Parenteral Dosage Form

Following are the processing control steps which carried out during process validation.

1) Dispensing

Check and ensure dispensing booth is clean & expiry date of raw material is later than that of batch expiry date. Retest date is older than day of dispensing & check that temperature and humidity of the dispensing room is within limit.

2) Washing and Depyrogenation of Vials

Wash all the vials & sterilize all the equipment's coming in contact with the product during processing, filtration and filling. Inspect each and every vial.Check the depyrogenation time, conveyor belt speed and ΔP between the different zones and rooms.

3) Processing

Check and ensure that processing area is in aseptic condition or not. Check and ensure that the processing operations are carried out as per BMR instructions. Check and ensure the temperature of the solution processed in the tank is maintained. Check the final pH and record it. Collect the samples at regular predetermined intervals during stirring form the top and bottom of the vessel using sterile sampling tool.

4) Filtration

Filter the solution by 0.22 µ sterilization filter. Collect the clear filtrate in a clean, sterilized holding tank. Store the solution as per specifications.

5) Filling and In Process Checking

Inspect filling and packing lines. Check and ensure that the vial washing, drying and depyrogenation, filling, sealing are carried out. Filter the solution by 0.22 µ online filter before filling. Check and record the fill volume. Collect two filled vials at every one hour interval and subject it for fill volume check and sealing (leak test) as per in-house specification. Check the pH and Assay of the Solution form vials filled immediately after setting the filling machine, and during initial, middle and end filling and every break. Samples shall be collected every hour from all filling heads.

6) Visual Inspection

Inspect manually or on the inspection machine each and every vial Inspect all the vials. Store the inspected vials with appropriate status label.

7) Labeling and Packing

Check and record the temperature at the heating roller and sealing roller. Check and record that the over printing instructions on labels and cartons as per instructions of BPR. After ensuring the proper labeling of vials, check, for correctness of cartons packing for the same.

8) Finished Product Analysis and Release

Finished product needs to be analyzed as per in-house specification. Product needs to be released only after pre-determined specifications and quality attributes are met.

Determination of Critical / Non critical Process Parameters

Table 3: Critical / Non critical process parameters

Process Steps	Process Parameter Setting	Rationale	Critical/ Non-Critical	Assessed by Testing
Raw Materials	Approved vendors used for the process	All the materials received will be tested against approved specification and released before use.	Non-critical	All the materials are tested as per approved specification before use.
Dispensing	Validated and calibrated balance & LAF used for dispensing.	Balance calibrated regularly as per procedure. Process does not have variable effect on quality as dispensing .	Non-critical	Weighing is done by Warehouse / stores and in presence of Production (Checker).On receipt
Water for Injection	Approved water for injection is used at all stages.	Water for injection system is qualified	Critical	Daily testing of WFI is done as per sampling plan and specification.
Mixing	1. Mixing speed (65±5) rpm Mixing Time Nitrogen bubbling	Mixing is required for complete dissolution of the ingredients, to get homogeneous solution and clarity of the solution. Nitrogen bubbling is required for reduction of oxygen.	Critical	Mixing time and speed of stirrer shall be monitored and recorded based on complete dissolution of ingredients.
	2. Mixing speed (65±5) rpm Mixing time	After addition of drug mixture is required to get homogeneous solution and uniform distribution of drug content and clarity of the solution.	Critical	Mixing time with the nitrogen bubbling and speed of the stirrer shall be monitored and based on complete dissolution of drug and clarity of the solution.
Final Mixing	Mixing speed (65±5) rpm Mixing time 15min.	Volume make up is necessary to get desired drug content per 0.5ml. Mixing is required to get homogeneous solution and uniform distribution of drug content and ingredient.	Critical	Tested for 1.Appearance and Clarity 2. pH (5.5 -6. 5) 3..Assay (95 % - 105 %) 5..Bioburden
Filtration	Filter type and filter size, filter integrity, filtration time, pressure	0.2µ PVDF cartridge using for filtration of the product filtration is most critical step to ensure sterile solution check the integrity of product filter by using bubble point	Critical	Filter integrity check by Bubble point test before and after filtration Appearance and clarity pH Assay

		2070mbar.		Sterility
Online-Filtration	Filtration through 0.2 µ filters.	Online filter before and after filling step.0.2µ PVDF cartridge filter using for online filtration.	Critical	Bubble point test performed before and after filtration.
Filling	Filling speed, Fill volume	Filling speed is critical to the volume variation Fill volume checked at minimum machine speed 200 vial/min. Max. speed 120 vials and optimum 117 vials/min.	Critical	Fill volume shall be checked from each nozzle at minimum maximum & optimum speed at the start of filling. Fill volume checked after 1 hr ±15min by production and 2 hr ±15 min by QA.
Sealing	Seal integrity	Critical with the reference to integrity of the filled vials , so check the closer integrity	Critical	Leak test at the beginning and every 1hr ± 15min including initial and at the end of filling.
Leak Testing	On-line checking for integrity of vials	leak test at every 1hour interval including initial and at the end of filling	Critical	Checking leaked vials by vacuum method.
Visual Inspection	Suspended particles, cosmetic defects	Removal of defective vials and vials with suspended particles	Critical	200% visual inspection against Black and white background with sufficient light.
Packing	Sticker labelling, cartooning and box / shipper packing.	Part of the packing automatic and controlled. Regular online checks available in force.	Critical	Inspection.

Sampling Plan and Acceptance Criteria

Table 4: Sampling plan and acceptance criteria

Process Stage	Sample ID	Sampling Details	Testing Method	Acceptance Criteria
Solution Preparation				
Time for solution preparation			Time for solution preparation as per BMR	NMT 5 hrs, If exceeds 5 hrs, solutions need to be tested for pH & estimate bio burden.
Time for mixing	T1,B1 -5 min T2,B2 -20 min T3-15 min	25 mL each sample solution from Top and bottom	In-process Specification	1. pH 2. Assay – 95% to 105 %
Unfiltered Bulk	Pooled sample	(200mL) sampled to be collected from the bottom of the tank.	In-process	1. pH-5.5 to 6.5 2. Assay - 95 to 105 % 3.BET (NMT 5.8

solution			Specification	EU/mg) 4. Bioburden (NMT 20CFUml)
Filtration				
Filtration		Approximately 250ml of solution be collected 50 ml for chemical analysis and 200 ml sterility testing after filtration process	In-process Specification	
Online filtration		Approximately 25ml of filtered bulk solution is to be collected from filling nozzles after priming and submitted for analysis.	In-process specification	1.pH 2.Assay
Filling and stoppering		20 Vials from each nozzle to be collected at minimum, maximum and optimum speed of filling machine.	In-process specification	0.65 to 0.75mL per vial
During filling and stoppering		middle, End of filling 2.pooled sample collected from initial middle and at the end of filling	In-process specification	1.pH 2.Assay 3.BET 4.Sterility 5.Complete Analysis of chemical and microbial
Leak Testing				
Sealing		5 vials after 1hr 15min by production and every 2hr 15min by QA	In-process specification	Not a single vial should found leaked.

RESULTS AND DISCUSSION

Dispensing

All the raw materials used for production were procured from approved vendor only. All the materials were in approved status and the materials were dispensed in right quantity by the warehouse person which were checked by production person and approved by QA.

Equipment Qualification

All the equipment and instruments used during production activity were qualified and calibrated within the due period. All the instruments had their calibration status label.

Environmental Monitoring

Environmental monitoring was carried out for the process validation batches as per the standard procedures. Environmental monitoring included continuous non-viable particle count in all the predetermined locations and viable particle monitoring of all the critical areas and also done by surface swabs and active air sampling. Personnel monitoring to the persons entering the sterile area was carried out. Personnel monitoring included collection of swab samples from the parts of the body which had the chances of reaching the product filling or sealing area. Swabs were collected from the fingers and arm from the persons.

Table 5: Environmental monitoring reports

Sr.No	Control Stage	Acceptance Criteria	Results/Remarks		
			Batch 1	**Batch 2**	**Batch 3**
1	Active Air Sampling (Volumetric)	**Class100 :** Action <1CFU/m3	Nil	Nil	Nil
		Class 1000 : Alert – 2 CFU /m3 Action -5 CFU/m3	Nil	Nil	Nil
2	Settle Plate Exposure	All limits as per the SOP	All counts are within the alert level	All counts are within the alert level	All counts are within the alert level
3	Personnel Monitoring	**Gloves :** Action – <1 CFU/5 fingers	Nil	Nil	Nil
		Gown : Alert-1 CFU/ Plate Action-3CFU/Plate	Nil	Nil	Nil
4	Monitoring (Swab method)	Monitoring locations and limits as per the in-house specifications.	Nil	Nil	Nil

All results obtained from environment monitoring complied with in-house specification.

Mixing Samples Analysis Results

The mixing samples were collected as per sampling plan at regular intervals such as 10, 15, 20 mins from top and bottom of the vessel. All the samples collected during mixing were tested as per the specifications and the reports are tabulated as follows:

Mixing Samples pH

Table 6: Mixing samples pH results

Mixing Samples	Location	Batch 1	Batch 2	Batch 3
pH (5.5-6.5)	Top 1 (5 min)	5.8	5.9	5.8
	Top 2 (10 min)	5.8	5.9	5.8
	Top 3 (15 min)	5.8	5.9	5.8
	Middle 1 (5 min)	5.8	5.9	5.8
	Middle 2 (10 min)	5.8	5.9	5.8
	Middle 3 (15 min)	5.8	5.9	5.8
	Bottom 1 (5 min)	5.8	5.9	5.8
	Bottom 2 (10 min)	5.8	5.9	5.8
	Bottom 3 (15 min)	5.8	5.9	5.8

pH of mixing sample was found within acceptable limit.

Mixing Samples Assay Results

Table 7: Mixing samples assay results

Mixing Samples	Location	Batch 1		Batch 2		Batch 3	
		RAN	OND	RAN	OND	RAN	OND
Assay 95.0% - 105.0%	Top 1 (5 min)	99.1	98.2	98.5	101.3	99.5	98.3
	Top 2 (10 min)	99.3	99.6	99.3	100.5	99.1	99.1
	Top 3 (15 min)	99.1	100.5	99.3	99.9	98.5	101.4
	Middle 1 (5 min)	98.5	98.1	100.4	100.4	99.7	100.4
	Middle 2 (10 min)	99.7	99.6	99.5	99.5	100.6	99.1
	Middle 3 (15 min)	100.1	99.9	99.1	100.7	99.3	99.6
	Bottom 1 (5 min)	99.2	98.9	98.5	99.2	99.3	100.5
	Bottom 2 (10 min)	100.4	99.5	99.6	100.5	100.4	99.5
	Bottom 3 (15 min)	101.5	100.1	100.3	100.1	100.4	99.4

Assay of mixing sample was found to be within acceptable limit.

Unfiltered Sample Analysis Results

The unfiltered samples were collected as a part of production process sampling to estimate the bio burden level in the prepared solution.

Table 8: Unfiltered sample analysis results

Tests	Acceptance Criteria	Batch 1	Batch 2	Batch 3
pH	5.5-6.5	5.8	5.9	5.8
Assay	NLT 95.0% - NMT 105.0%	RAN-99.8, OND- 99.3	RAN-99.9, OND- 100.1	RAN- 100.5, OND- 100.1
BET	NMT 5.5 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL
Bio-burden	Complies	Nil	Nil	Nil

All the result of unfiltered sample complied with in house specification.

Filtered Sample Analysis Results

The filtered solutions were collected to estimate the effectiveness of the filtration process. The reports are tabulated as follows,

Table 9: Filtered sample analysis results

Tests	Acceptance Criteria	Batch 1	Batch 2	Batch 3
pH	5.5-6.5	5.8	5.9	5.8
Assay	NLT 95.0% - NMT 105.0%	RAN-99.8, OND- 99.2	RAN-99.9, OND- 100.5	RAN-100.4, OND-100.8
Sterility	To Comply as per USP	Complies	Complies	Complies

All the result of filtered sample complied with in house specification

Fill Volume Determination Results

To determine the quantity of solution dispensed by the filling heads fill volume check was done for every one hour during the filling activity. The results of fill volume are tabulated as follows.

Table 10: Fill volume results

Sr.No.	Batch	Limit 2.10mL to 2.15mL	
		Minimum	Maximum
1	Batch 1	2.10mL	2.15mL
2	Batch 2	2.10mL	2.15mL
3	Batch 3	2.10mL	2.15mL

Fill volume results for all the batches were found to be within specification limit.

Leak Test results

To determine the effective sealing activity, vials were sampled at regular frequency and leak test was carried out. The results of leak tests are tabulated as follows,

Table 11: Leak testing results

Sr.No.	Batches	Leak Testing	
		Passes	Fails
1	Batch 1	√	X
2	Batch 2	√	X
3	Batch 3	√	X

Filling Sample Analysis Results

The filled vials were collected during the filling activity at initial, middle and end filling stage, to evaluate any change that had occurred during filling stage and also the effectiveness of online filter.

Table 12: Filling sample analysis results

Sample	Tests	Acceptance Criteria	Batch 1	Batch 2	Batch 3
Initial of Filling	pH	5.5-6.5	5.8	5.9	5.8
	Assay	NLT 95.0% - NMT 105.0%	RAN-99.1, OND-99.6	RAN-98.9, OND- 99.2	RAN-99.1, OND- 99.7
	BET	NMT 5.5 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL
	Sterility	Should comply as per USP	Complies	Complies	Complies
Middle of Filling	pH	5.5-6.5	5.8	5.9	5.8
	Assay	NLT 95.0% - NMT 105.0%	RAN-99.2, OND- 98.6	RAN-99.2, OND- 99.8	RAN-99.3, OND- 98.5
	BET	NMT 5.5 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL
	Sterility	Should comply as per USP	Complies	Complies	Complies
End of Filling	pH	5.5-6.5	5.8	5.9	5.8
	Assay	NLT 95.0% - NMT 105.0%	RAN-99.2, OND-99.4	RAN-99.2, OND- 98.4	RAN-99.3, OND-98.2
	BET	NMT 5.5 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL	< 2.1 EU/mL
	Sterility	Should comply as per USP	Complies	Complies	Complies

The result of all the batches were found to be within acceptance limit.

Finished Product Analysis Results

The finished product samples were collected after the filling of the batch is completed and the results are tabulated as follows,

Table 13: Finished product analysis results

Sr.No.	Tests	Acceptance Criteria	Batch 1	Batch 2	Batch 3
1	Appearance and Clarity	Clear colorless to slight yellow solution	Clear slight yellow solution	Clear slight yellow solution	Clear slight yellow solution
2	Identification by IR	Complies with specification.	Complies	Complies	Complies
3	Identification by HPLC		Complies	Complies	Complies
4	pH	5.5 to 6.5	5.8	5.9	5.8s
5	Assay (by HPLC)	NLT 95.0% - NMT 105.0% w/v of labelled claim.	RAN-100.3%, OND- 99.9%	RAN-100%, OND- 98.9%	RAN-100.2%, OND- 100.5%
6	BET	NMT 5.8EU/mL	<2.9EU/mL	<2.9EU/mL	2.9EU/mL
7	Sterility	Comply as per USP	Complies	Complies	Complies

Result of all the batches was complying with in house specification limit.

DISCUSSION

From the above results it was found that no growth observed for any single bacteria or fungi in the growth media, except growth promotion test and thus the media fill conducted for aseptic validation of the aseptic process was found to be complying. The result of media fill confirmed that the area for manufacturing and aseptic filling is in controlled state. Hence the capability of aseptic processing by simulating the entire aseptic formulation and filling process by microbial growth medium is evaluated and qualified. 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.

CONCLUSION

The Process validation of the product Injection, was carried out and the results were compiled. The results of aseptic media fill confirmed that the area for manufacturing and aseptic filling is in controlled state. The environmental monitoring of the area and personnel revealed that, all the personnel involved during aseptic activity did not contaminate the area during production process. Environmental monitoring results confirmed that HVAC system for aseptic manufacturing area is functioning as per the predetermined specifications. 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, in process testing and finished product analysis of all the three validation batches for the product Injection, was shown that the process has consistently produced the product within the predetermined specifications and quality attributes. Hence the manufacturing process of Injection, stands validated.

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