Document Name: Performance Qualification Document for Lyophilizer	
Equipment/ System ID:	**Document Number:**
Effective Date:	**Version Number:** 00

Performance Qualification Protocol

Lyophilizer

Equipment ID:

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1.0 Approval:

This document is prepared by the Validation team for the project "Sterile Formulations Facility" under the authority of their Unit head & QA Head. Hence this document before being effective shall be approved by the Unit Head & QA Head.

PREPARED BY		
NAME/ FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE /DATE**
Validation & QA		

CHECKED BY		
NAME/ FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE /DATE**
Validation & QA		
Production		
Engineering		
Quality Assurance		

APPROVED BY		
NAME/ FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE /DATE**
Unit Head		
Quality Assurance – Head		

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2.0 Objective:

The objective of this document is to provide written procedures and/ or guidelines and respective acceptance criteria for the Performance Qualification of Lyophilizer and to demonstrate with documented evidence that the equipment produces the required output by integrating procedures, personnel and systems.

3.0 Scope:

The document includes the Performance Qualification procedure of the following system:

In-house name of the equipment	Lyophilizer
Equipment identification number	…….
Purchase order reference	…….
Supplier Name and address	…….
Installation location	
Facility	Sterile Formulations Facility
Floor	…….
Room name & number (if applicable)	…….

This protocol should be generated to qualify the initial performance of the system. In case of further modification or relocation, some part of the same protocol can be used or separate protocol or addendum can be generated.

4.0 Reference Document:

Following documents are referred during preparation of the protocol:

Document Name	Document Number
Validation Master Plan	
Project Validation Plan	
Design Qualification	
Supplier design document	
Drawings	
Equipment Manual	

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5.0 System description:

5.1 Use

The Lyophilizer shall be used to freeze-dry the sterile solution of product filled in half-stoppered glass vials or the aseptic lyophilizing of Parenterals drugs. Only aqueous solutions filled in vials and partly closed with lyophilizer-stoppers will be processed. Lyophilizer shall stopper the vial before unloading.

5.2 Capacity:

Shelf Dimensions: 1000 mm (W) x 1500 mm (D) x 80 mm (H) _Uniformity ± 0.75 mm or less.
Total surface area 19.5 square meters for product

5.3 Operation and Design Features:

Lyophilization is the removal of solvent while the product is frozen to that level no longer support biological or chemical activity. The purpose of this procedure is to produce a stable product that can be stored for long periods of time, and later reconstituted by the addition of solvent. Lyophilizer consists of the following design features:

Product chamber with door & sub door: The main purpose of the chamber is to hold the product while providing selectable shelf temperature control and pressure, and to provide reliable stoppering of the product container, The Lyophilizer chamber is made up of SS316L, which is welded with rectangular chamber. The Lyophilizer shall be full width opening Main door & sub door (MOC SS316L) type for loading and unloading from the same aseptic room.

Product shelves and hydraulic stoppering: Shelf system consist 14 shelves (13 + 1 radiant) with the temperature control range of -50°C to +65°C. Shelf temperature uniformity across the shelf and between the shelves is ±1.5°C.Top down hydraulic Stoppering with adjustable pressure, Hydraulic cylinder RAM covered with SS316L Bellows seal to avoid the contamination of Hydraulic oil.

Condenser chamber & coil: The condenser serves primarily as a cold trap for the Lyophilizer. It is designed to optimize the removal of solvent from the vapor stream prior to it reaching the vacuum pump. By removing water vapor the condenser module acts as an integral tool in maintaining the low-pressure Conditions within the Lyophilizer. Condenser chamber with dished end bolted, vertical. Condenser is constructed of SS316L with a condensing surface comprised of independent SS coils. It is rated for full Vacuum. Total capacity of condenser is 360 kg.

Fluid circulation system: The circulation system utilizes vacuum pump to achieve a vacuum. The system is connected to the condenser with stainless steel pipe. An electronic valve is located close to the condenser to isolate the vacuum system from the condenser.

Refrigeration system: Refrigeration system consists of three 30 HP, 2 stage Carlyle compressors, R404A CFC free refrigerant. Refrigerant circuits are designed to service either the shelves or condenser during various stages of the process. Sufficient refrigeration standing pressure should be (150-175 PSI) available in the system for smooth operation of the system.

Vacuum system: The vacuum pump provides the initial evacuation of no condensable gases from the system and steadily removes these gases that have entered the system through real and/or virtual leaks. In this way the vacuum pump helps to maintain the lower pressure required for Lyophilization. Alcatel vacuum pumping system roots combined with two stage vacuum pumps.

CIP-SIP System: CIP system consists of multiple nozzles installed throughout the chamber.

System can automatically/ semi automatically controlled by PLC, which can be programmed and protected for different cycles.

Automatic

Lyophilization up to 99 Recipe Manager

- Freezing up to 10 Steps
- Primary Drying up to 24 Steps
- Secondary Drying
- Pressure Rise Test
- Nitrogen Backfill
- Auto Stoppering

System Test
Steam In Place
Clean In Place with shelf dynamic movement
Leak Rate Tests with Bellows Leak Test
Defrost
Media Fill Test

Semi Automatic

Shelf temperature indication and control
Condenser temperature indication
Vacuum indication and control
Product temperature indication

6.0 Performance Qualification Test Plan

6.1 Performance qualification test shall include following test:

1. **General Test as per Test ID #2 which contains following test**

Test Name	RA Ref no.	Test ID
Availability of OQ test report	--	# 2.1
Document Verification	--	# 2.2

2. Performance Test as per Test ID #3 which contains following test

Test Name	RA Ref no	Test ID
Steam quality test	--	# 3.1
Coverage study	--	#3.2
Cleaning in Place performance check and SIP validation.	--	#3.3
System Leak rate Test	--	#3.4
Temperature Mapping During empty Lyophilization Cycle	--	#3.5
Process simulation with Mannitol	--	#3.6
Condenser Defrosting	--	#3.7

6.2 General Steps and Precautions to be followed during Performance Qualification Study;

6.2.1 Validation schedule shall be decided prior to execution the validation activities.

6.2.2 Prepare at least 49 Nos. calibrated temperature sensors with location and channel tag and one pressure transducer.

6.2.3 46 nos. of external sensors are to be inserted through the validation port into the Lyophilizer. Calibrated T-type Thermocouples are to be used.

6.2.4 The drain sensor should be inserted such that it is as close in proximity to the sensor located there.

6.2.5 Criteria for selecting the locations for studies shall be as per step 6.3.

6.2.6 The biological indicators are to be attached to each sensor during SIP cycle. Determine the initial spore population for each lot of Biological indicator used (the methodology for determination of spore population is as per the SOP “Total Viable Spore Count of Biological Indicator” of Microbiology section of Quality control department. Alternatively the Indicators can be sent to an external lab for determination of Total viable spore count.

6.2.7 Attach the thermograph, data and chemical indicator strips along with the data of the relevant cycle.

6.2.8 Record the minimum & maximum pressure inside the Lyophilizer chamber after the sterilizing condition of the temperature has been achieved.

6.2.9 For calculation of F0 value take measured temperature value for each probe separately. Refer step 6.4 for details of calculations.

6.2.10 The process simulation shall be carried out with maximum batch size and largest vial size which will be prepared in future.

6.2.11 The 10 ml pack size is selected considering the maximum pack size for Lyophilization in routine production activity.

6.2.12 In case of testing being done in succession (wherein a cycle is preceded by another cycle) allow the chamber to cool to at-least 65°C before starting the next sterilization cycle.

6.2.13 If during a thermometric test the sensors inserted for temperature profiling purposes are damaged / short / open / faulty; review & evaluate the total data. If the location where the sensor was placed is a drain sensor, near the controlling probe or any other critical locations requiring monitoring, repeat the cycle.

6.2.14 The minimum time for which a cycle should operate in sterilization mode shall be based upon the validation reports / experience (this will be the time for which the temperature at the controlling probe / location will be in the range of sterilization temperature band).

6.2.15 The lyophilizer will be evaluated for the cleaning process followed as the CIP .The CIP will be challenged with Riboflavin solution which will provide a better assurance level for the cleanliness produced by the CIP. This gives assurance that the CIP can be used for cleaning after product change over or batch change over.

6.2.16 The lyophilizer will be evaluated for the sterilization process followed as SIP .The SIP will be challenged with the Biological Indicator which will provide a better assurance level for sterility which will be produced by the SIP.

6.2.17 The performance of lyophilizer will be evaluated as performance test which will give assurance of carrying the Lyophilization process in the lyophilizer.

6.2.18 The temperature distribution study of shelf will be done during the Lyophilization process in empty chamber which will give assurance of maintaining the uniform temperature in the shelf and hence in the product during the Lyophilization process.

6.2.19 The Lyophilization process and ice condensing capacity will be evaluated by simulating the process with the Mannitol solution which will give a better assurance for carrying out the Lyophilization process and provides better assurance level for ice condensing capacity of lyophilizer.

6.2.20 The De-icing process will be evaluated for removing the ice formed in the condenser. The de-icing process will be challenged with Lyophilization of maximum volume of solution which will provide a better assurance level for carrying the de-icing process for maximum ice condensed in the condenser.

6.3 Selection Criteria for Locations of Sensors, Biological and Chemical Indicators for SIP:

6.3.1 The SIP shall be carried out after CIP and shall be carried out as a combined study.

6.3.2 A minimum of 49 sensors are to be positioned/ attached at strategic locations on different shelf in the chamber for heat distribution study, while the one sensor shall be placed inside the condenser drain, one inside the chamber drain and one inside the vaccum break filter during SIP.

6.3.3 The location of 6 sensors which are to be placed in the critical locations during SIP is defined as below:

a. In the chamber discharge (Drain).
b. In the condenser discharge (Drain).
c. Inside the vaccum break filter
d. Inner side of door of the chamber
e. Rear wall of chamber in upper left corner
f. Rear wall of chamber in lower right corner

6.3.4 All the other 43 sensors shall be placed on the different shelf in the chamber.

6.3.5 Ensure that there is a temperature sensor located on different shelf in the chamber free space.

6.4 Calculation of F_0 Values / Sterility Assurance Level:

6.4.1 Calculate the F_0 values (mathematical) at each identified location using the equation:

$$F_0 = \Sigma L \times dt = \Sigma 10^{(TA-121)/10} \times dt$$

Where –
- F_0 = Equivalent sterilization time (in minutes) at 121°C.
- L = Lethal rate
- T_A = Actual temperature measured.
- dt = Time duration (in minutes) between- 2 successive temperature measurements

6.4.2 Calculate the minimum required F_0 value for producing a 12 log reduction of the biological indicator used using the equation

$$F_0 = D_{121} (\log N_0 - \log N_t)$$

Where –
- F_o = Equivalent sterilization time (in minutes) at 121°C.
- D_{121} = D Value of the biological indicator used (as given in the manufacturers certificate).
- N_0 = Initial Spore Count of the biological indicator (as determined experimentally).
- N_t = Spore Count of the biological indicator at time 't' (determined by sterility testing i.e. $N_t = 0 \cong 10^{-6}$ for obtaining a 12 log reduction).

6.4.3 $SAL_{Desired}$ (Desired sterility assurance level):

$$SAL_{Desired} = 10^{-6}$$

6.4.4 $SLR_{Measurable}$ (Spore log reduction that can be measured by the biological indicator used):

$$SLR_{Measurable} = \log N_0 - \log SAL_{Desired}$$

Where –
- $SLR_{Measurable}$ = Spore log reduction that can be measured
- $SAL_{Desired}$ = Desired sterility assurance level
- N_0 = Initial Spore Count of the biological indicator (as determined experimentally)

The desired spore log reduction is ≥ 12

6.4.5 Calculate the actual spore log reduction achieved (SLR_{Actual}) using the equation:

$$SLR_{Actual} = \frac{F_0}{D_{121}}$$

Where – SLR_{Actual} = Actual spore log reduction
F_0 = Minimum F_0 value calculated mathematically
D_{121} = D value of the biological indicator (as in the certificate of analysis).

6.4.6 Calculate the actual sterility assurance level (SAL_{Actual}) using the equation

$$SAL_{Actual} = 10^{[(\log N_0) - SLR_{Actual}]}$$

Where – SAL_{Actual} = Actual sterility assurance level.
SLR_{Actual} = Actual spore log reduction
N_0 = Spore Count of the biological indicator (as determined experimentally)

6.5 Brief Process Plan:

The qualification of the Lyophilizer shall be done by verifying / testing the parameters as listed in the following table –

S.No.	Tests	No. of Runs	Remarks
1.	Calibration of the data logger & temperature sensors used for temperature profile / thermometric tests	–	To be done initially & then after completion of PQ
2.	**Steam Quality test**		To be done for qualifying quality of steam.
	Non-condensable gas test	03	
	Superheat test	01	
	Dryness test	01	
3.	Coverage study	03	To be done for qualifying the efficiency of cleaning process.
4.	Cleaning in Place performance check and SIP validation.	03	To be done with sensors for qualifying the effectiveness of CIP and uniform heat distribution inside chamber and condenser during SIP Cycle. Chemical as well as biological indicator to be used with each sensor.
5.	F_0 /…./ sterility assurance level calculation	–	Applicable for the thermometric tests, refer step 6.4 for details of calculations

S.No.	Tests	No. of Runs	Remarks
6.	System Leak rate Test	01	To be done for checking the system leak rate after completion of CIP and SIP
7.	Temperature Mapping During empty Lyophilization Cycle	03	To be done with sensors for qualifying the effectiveness of lyophilization process for maintaining the uniform temperature in the shelf.
8.	Process simulation with Mannitol	01	To be done for qualifying the efficiency of lyophilization process.
9.	Condenser Defrosting	01	To be done for qualifying the efficiency of De-icing process for maximum ice condensed in the condenser.

The above-mentioned tests provide a documented verification of the intended performance of the equipment throughout the representative / anticipated range & ensure that the Lyophilizer is performing satisfactorily & will produce desired results when operated according to SOP & also provide evidence of appropriate and reliable performance when challenged with worst case scenario.

The purpose of performing the tests & the methodology of performing / executing of each test along with the provision of recording the observations is given in respective test data sheets.

7.0 Responsibility:

Responsibilities of different department/ personnel involved in different activities related to the Performance qualification of the system are defined below:

Functions	Responsible
Preparation of PQ protocol	
Review of the PQ protocol	
Approval of the PQ protocol	
Clearance of the system for execution	
Execution of PQ protocol	
Preparation of PQ report	
Review of executed PQ protocol and report	
Approval of the Executed PQ protocol and report	

8.0 Test Execution Method:

8.1 Pre –Requisites:

Prior to conducting/ executing the Performance qualification protocol following conditions must be fulfilled:

- System should be safe for execution.
- Approval of Operational Qualification report
- Ensure that the Steam Quality Tests performed and complies as per specifications.

8.2 Signature Registration & Training:

All personnel who are executing or reviewing the protocol must enter his/her name and signature in signature registration page. Provide the location of training record or attach the appropriate training record with the report to indicate that the personnel should be trained on the following:

- Execution of PQ protocol
- Writing GMP critical record
- Deviation handling procedure
- Review of executed validation protocol and GMP critical records

A signature registration page should be given as Data sheet # 01

8.3 General Recording Instruction:

- Execution will be carried out as per the SOP for Qualification protocol execution SOP.
- Recording of observation will follow good documentation practice as per SOP.
- In the test data sheet test parameter and criteria will be pre-defined. Other cells e.g. observation and signature will be completed by the person manually.
- Where observation is to be recorded as ‘Y/N/NA’, write ‘Y’ when the observation is in compliance with acceptance criteria, write ‘N’ when observation is a non-compliance. If it is not applicable write NA, if unobvious write suitable justification for being not applicable
- Any mistake in the approved protocol format if identified before or during execution shall be recorded as comment rather canceling it manually. This mistake will be verified during review of executed protocol.
- Comment summary sheet will be available separately as Data sheet # 5. This test sheet should be separate for a specific test sheet. Required number of comment summary sheet shall be issued during execution.
- Comments and deviation will be recorded as per the instruction given in the following section.

8.4 Deviation Handling:

- During execution the comments if any will be noted in the respective datasheet.
- All comments shall be numbered as "X-YY" where "X" is test sheet no. and "YY" is the sequential serial no. for that particular test sheet; For example in test sheet no. 3, second comment shall be numbered as 3-02. Comment number shall be allotted on the test data sheet and comments shall be written on comment summary sheet.
- During review or execution all comments will be verified and if any comment is made to specify non-compliance to that test acceptance criteria, comment will be escalated as "Deviation".
- The deviation will be identified and it will be suitably numbered in the comment section of the comment summary sheet as per SOP for Deviation Management.
- The deviation will be assessed whether it has any GMP criticality. GMP non-critical deviations can be justified whereas GMP critical deviation may require investigation and corrective actions. Appropriate justification, investigation, corrective action and verification of effectiveness of corrective action will be performed and recorded as per SOP – Deviation management.

8.5 General Safety Instruction for Execution

Safety will be one of the key considerations during the execution of this protocol. The following guidelines must be observed during the execution stage.

- All personnel involved with the execution shall identify hazards associated with performance of PQ testing and precautions to be taken.
- All personnel involved with the execution shall inform to company management any hazard, to themselves or others, associated with the materials, system, method of working and the precautions to be taken.
- All personnel involved with the execution shall check that utilities are safely isolated when energizing or de-energizing.

9.0 Acceptance Criteria:

The system successfully passes PQ if all the tests meet the predefined acceptance criteria as defined in individual test data sheets.

Thus it is shown that the system

- Meets the Specifications and Quality requirements identified by the User
- Is correctly performed and documented

10.0 Summary Report and Conclusion:

In order to close the PQ, the tests results shall be evaluated and the PQ report shall be formally approved. During the review of the report it is necessary to assess to what extent all tests were successfully completed. GMP critical deviations must be completely fulfilled before releasing equipment for routine activity.

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11.0 Enclosed Documents

S. No.	Document	Document Name	Document No.
1	Data Sheet # 1	Identification of Signatures / Participants	
2	Data Sheet # 2.1	Availability of OQ test report	
3	Data Sheet # 2.2	Document verification	
4	Data Sheet # 3.1	Steam Quality Tests	
5	Data Sheet # 3.2	Coverage study	
6	Data Sheet # 3.3	Cleaning in Place performance check and SIP validation.	
7	Data Sheet # 3.4	System Leak rate Test	
8	Data Sheet # 3.5	Temperature Mapping During empty Lyophilization Cycle	
9	Data Sheet # 3.6	Biological challenge study	
10	Data Sheet # 3.7	Process simulation with Mannitol	
11	Data Sheet # 3.8	Condenser Defrosting	
12	Data Sheet # 4	Verification of measures identified in Risk Analysis	
13	Data Sheet # 5	Comment Summary Sheet	
14	Report	Performance Qualification report	
15	Attached documents	List of attached document	

12.0 Abbreviations:

Acronym	Definition
cGMP	Current Good Manufacturing Practices
GMP	Good Manufacturing Practice
QA	Quality Assurance
NRV	Non return Valve
OQ	Operation Qualification
PLC	Programmable Logic Controller
SAL	Sterility Assurance Level
SLR	Spore Log Reduction
PQ	Performance Qualification
SOP	Standard Operating Procedure

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13.0 Change history details:

Version no.	Reason for revision	CRF no.	Effective date
00	First Issue	Not Applicable	