Performance Qualification Protocol

For

Incubator

(EQ-QCM-026)

LIPTIS

6th of October City

LIPTIS Pharmaceuticals

Protocol Issue date	:	01/04/2025
Protocol Number	:	PQP-T-06925
Number of Pages	:	16

EGYPT: 26 Al Israa St., Lebanon Sq., Mohandseen, Giza, Egypt
KSA: 3910 Prince Mamdouh Bin Abdulaziz st., Al Sulaimaniya District, Riyadh, KSA
UAE: Sharjah Media City, Sharjah, UAE
www.technoairgate.com
info@technoairgate.com
+20233034440
+966555478676
+971502013049
+201023310801

Index

1. Protocol Review and Pre-Approval

- Prior to the initiation of qualification testing activities, this document will be issued, reviewed and approved by the appropriate personnel.

- The signatures below signify prior approval of the format and content of the final report, ensuring an accurate representation of the qualification activities planned for *LIPTIS*.

***TAG* Author(s)**

Name	Title	Company	Date	Signature
Mohamed Hassan	Technical Office Team Leader	TAG	01/04/2025	

***TAG* Reviewer(s)**

Name	Title	Company	Date	Signature
Noha Essam	Technical Office Senior	TAG	01/04/2025	
Ahmed Adel	SR. QA Specialist	TAG	01/04/2025	

***TAG* Approver(s)**

Name	Title	Company	Date	Signature
Ahmed Tarek	Technical Manager	TAG	01/04/2025	

***LIPTIS* Reviewer**(s)

Name	Title	Company	Date	Signature

***LIPTIS* Approver(s)**

Name	Title	Company	Date	Signature

Change History				
No.	**Version No.**	**Amended Page No.**	**Reason for change**	**Issued Date**
1.	01	NA	NA	01/04/2025

Note: *Any amendment will be indicated with italic and bold font.*

2. Glossary/Abbreviations

- **Performance Qualification (PQ):** is the final step of qualifying equipment. In this phase, the qualification and validation team verify and document that the user requirements are verified as being met. It is the method of validating or qualifying equipment. The purpose is to ensure that every part of the system will maintain a stable temperature during use.
- **Key operating parameters:** parameters that must be maintained in order to process or produce products with consistent quality attributes and those that may have an impact on the proper operation of the equipment.
- **Controller:** A device that interprets a mechanical, digital or analogue signal, generated by a sensor, to control an equipment or component
- **Sensor:** A mechanical device (pressure switch, bimetal temperature switch, etc.), or a digital or analogue transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates a mechanical or electrical signal to an instrument or a controller in order to be interpreted.
- **Electronic data logging monitor (EDLM):** A small portable device that measures and stores temperature readings at predetermined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analyzed via proprietary hardware, software, desktop applications or through hosted databases.
- **TTSPP**: time- and temperature-sensitive pharmaceutical product.
- **Temperature-controlled:** Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise pre-defined limits.
- **Mapping:** Documented measurement of the temperature distribution within a storage area, including identification of hot and cold spots.
- **Standard Operating Procedure (SOP):** A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.
- **Maximum Temperature:** refers to the highest value recorded in the mapped space over the study period, and it may be outside the specified acceptance criteria for the store.
- **Minimum Temperature:** refers to the lowest temperature recorded in the mapped space over the study period, and it may be outside the specified acceptance criteria for the store.
- **Mean Kinetic Temperature:** If you have a set of temperature readings across a certain period of time, the Mean Kinetic Temperature across this period means the effective average thermal value for this period. This temperature value is what the stored goods effectively feel during the mentioned time. This is not the arithmetical average of the readings.
- **Hot Spot:** refers to the highest temperature(s) recorded in the area studied over the study period, but these highest temperature(s) remain within the specified temperature range.
- **Cold Spot:** refers to the lowest temperature(s) recorded in space over the study period, but these lowest temperature(s) remain within the specified temperature range.
- **Worst Locations:** It refers to hot and cold spots determined in the space over the study period during the thermal qualification study.

  Note: It is also important to look at the overall high and low trends rather than just the highest and lowest temperatures. Average values can be useful to help confirm true hot and cold spots.

3. Rationale

The rationale behind this protocol is to confirm that the Incubator located at LIPTIS functions as intended and produces reliable results essential for maintaining product quality. By conducting performance qualification, it becomes possible to identify any deviations from the desired temperature range, reduce risks of product degradation, and maintain quality assurance measures. we aim to minimize the risk of errors or inaccuracies in testing procedures, ensuring that the equipment operates within specified parameters.

Performance Qualification Protocol shall provide the methodology of qualification studies, formats for recording the observation, Criteria of qualification and a guideline for documentation of the study.

4. Protocol Scope

The scope of this protocol intends to cover the thermal qualification procedure of Incubator (EQ-QCM-026) located at LIPTIS with the following description:

Description	Incubator
Manufacturing	Binder
Model	KT053
S.N.	20190000006576
Code	EQ-QCM-026
Acceptance Criteria	(55 ~ 60) °C
Location	Micro Lab
Load Description	Empty
Key Operating Parameters	Temperature

5. Protocol Purposes

- To describe the followed procedure used to study the heat distribution throughout the Incubator (EQ-QCM-026) located at LIPTIS and to ensure uniformity and compliance with regulatory standards.
- To determine the hot and cold spots attained during thermal qualification of the specified Incubator to identify the locations where the monitoring sensors should preferentially be located.
- To demonstrate the air circulation profile throughout the system, when empty and in a normal loaded condition.
- To define zones which should not be used for storage or during routine use (for example areas in close proximity to cooling coils, cold air streams or heat sources).
- If required, to demonstrate the maximum time for door opening without affecting the heat distribution inside the Incubator and to determine the time taken for temperatures to attain the accepted limits after the door closing (if needed).
- If required, to demonstrate the time taken for temperatures to exceed the designated limits in the event of a power failure and to determine the time taken for temperatures to attain the accepted limits again after providing a power supply (if needed).

6. Signature Log

Each person records, review and approve the information in this document must complete the signature log (see Appendix No. (1)).

7. Roles and Responsibility

For the submission/approval, execution of this protocol and its final report, the responsibility of all personnel involved with the verification and documentation process are as follows:

7.1 LIPTIS

- Provide the necessary information needed for the protocol issue.
- Review the protocol for compliance before qualification execution and ensure that the protocol aligns with regulatory requirements and company policies.
- Approve the protocol before qualification execution.

7.2 TAG

- Design and prepare the qualification protocol, including all the recommendations and corrections that are required by LIPTIS.
- Review the protocol for compliance before qualification execution and ensure that the protocol aligns with regulatory requirements and company policies.
- Approve the protocol before qualification execution.
- Execute the qualification only after this protocol has been approved by LIPTIS.

8. Associated Materials and Equipment

A mapping operation requires a sufficient number of electronic data logging monitors (EDLMs) to ensure that the temperature distribution in the space to be mapped is adequately characterized. In addition, suitable computer equipment and software is needed to store and analyze the data. The selected EDLMs must:

- be technically suitable for the specific mapping task and for the intended operating environment.
- provide a reliable and continuous record of time-temperature data.
- have an appropriate temperature range so that all anticipated temperature extremes can be recorded.
- have a user-programmable data sampling period, allowing time intervals to be set in the range from 1 minute to 15 minutes (maximum) and sufficient memory for the intended length of the study and the chosen recording interval.
- have a US National Institute of Standards and Technology (NIST)- traceable 3-point calibration certificate with a guaranteed error of no more than ± 0.5 °C at each calibration point.
- enable the recorded time-temperature data to be downloaded to a computer system for subsequent analysis.
- have data storage and analytical software that complies with applicable regulatory requirements (for example: 21 CFR part 11).

Used Reference Equipment Description						
Description	No. of EDLMs	Location	Accuracy	Manufacturer	Model	Calibration Due Date
Data Logger	10	Inside Incubator	± 0.5 °C	Will be determined at the execution phase		

9. Locations and Rationale for Distributing Data Loggers

By distributing data loggers at various locations within the Incubator, we can ensure that temperature remains consistent throughout the unit, minimizing the risk of temperature differentials that could affect products integrity. As the heat goes up and cold down the data loggers shall be placed on top and bottom shelves of the equipment. Shelving and loads may create 'hot spots' by obstructing air circulation. Due to less circulation of air in corners the data loggers shall be placed near to each corner of the equipment. The exact location of data loggers in Incubator are specified in separate layout, see Annex No. (1).

- **Top Shelf:** Placing a data logger on the top shelf enables monitoring of temperature variations at the highest point within the Incubator, where heat distribution may differ from lower levels.
- **Bottom Shelf:** Monitoring temperature at the bottom shelf helps assess heat circulation and ensures uniformity throughout the entire Incubator space.
- **Near the Door:** Positioning a data logger near the door provides insights into temperature stability and potential impacts of external factors on the internal environment.
- **Centre:** Placing a data logger in the center of the Incubator helps evaluate overall temperature uniformity and ensures that critical samples receive consistent heat exposure.
- **Adjacent to the Heating Source:** Monitoring temperature close to the heating source allows for assessing the efficiency of heat distribution and the impact on temperature fluctuations.

10. Methodology

10.1 The following steps outline the methodology for conducting the thermal qualification study. It is important to note that Steps 1 to 5 must be completed before the mapping protocol can finally be approved.

STEP 1:

Select Data logger: Select the type of data logger to be used. Choose a device that has the required parameters, sufficient memory, suitable range and calibrated at points cover the working range with no deviation more than ± 0.5 °C.

STEP 2:

Designate the mapping team: Identify and list the team members. Record their signatures and initials so that signed records can be traced back to the person who prepared the document.

STEP 3:

Determine equipment specifications: The following information is required for each thermally separate area being mapped:

- Dimensions or volume of the equipment.
- Drawing of the equipment.
- The location of heating and cooling components.

STEP 4:

Establish acceptance criteria: The protocol should define the required acceptance criteria.

STEP 5:

Determine EDLM locations: Use the volume and drawing to mark the required locations of the EDLMs. A risk-based approach can be applied to define the location of EDLMs.

The number and location of the EDLMs required determined by the following instructions as per ISPE and IEC recommendations:

chambers less than 2000 L: minimum 9 EDLMs should be used and are located in each corner and in the center of the working space.

chambers more than 2000 L: minimum 15 EDLMs should be used and are located in each corner, in the center of the working space, and in front of the center of each wall.

The measuring system is to be arranged in such a way that the temperature distribution of the empty test chamber will not be affected. For a large capacity chamber, there may be a significant difference between the temperature control sensor(s) and the temperature at the center of the working space. It may be necessary to adjust the temperature setting to achieve the necessary tolerance.

STEP 6:

Record EDLM, monitoring sensors and thermostat locations: Record the EDLM locations on a temperature data logger location table. Also record the location identification and set point of the equipment controller.

STEP 7:

Label and program the EDLMs: Label each EDLM with a unique ID, taken from the temperature data logger location table. Enter the manufacturer's serial number on the temperature data logger location table. Recording the serial number ensures that the device can be traced to its calibration certificate. Program each device, ensuring that the recording interval is the same – typically this should be set between one and 15 minutes. Set the same start time for all units. This is essential; otherwise, the downloaded readings from the individual devices cannot be time-correlated.

Heat Distribution Study Design					
Controller Setting: @ °C (will be determined at the execution phase)					
Acceptance Criteria: (55 ~ 60) °C					
Cycle No.	Load Description	Start Date	Stop Date	Sampling Period	Sample Frequency
1.	Empty	*dd/mm/yyyy* hr:min AM/PM	*dd/mm/yyyy* hr:min AM/PM	01 Day	02 minutes

STEP 8:

Conduct the mapping exercise: Arrange the mapping study period with the customer.

STEP 9:

Download and consolidate the data:

- Download the EDLM readings and consolidate the data for the study analysis.
- Review the report and identify the hottest point, coolest point attained and calculation of mean kinetic temperature.
- Mark the area of hottest and coldest points.
- Review the report and note down the maximum, minimum temperature reached during the interventions (power failure, door opening) and the time required to regain the temperature.

10.2 Mean Kinetic Temperature Calculations

Mean kinetic temperature (MKT) is defined by the ICH as 'A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.' The Haynes formula can be used to calculate the MKT. It is higher than the arithmetic mean and takes into account the Arrhenius equation from which Haynes derived his formula. Thus, MKT is the single calculated temperature that stimulates the non-isothermal effects of storage temperature variations.

$$T_k = \frac{\Delta H / R}{-\ln \frac{e^{-\Delta H/RT}{}_{(1)} + e^{-\Delta H/RT}{}_{(2)} + \ldots + e^{-\Delta H/RT}{}_{(n)}}{n}}$$

Where:

T_k = MKT in °K
ΔH = Heat of activation/activation energy
R = Universal gas constant (8.3144 X 10^{-3} kJ.Mole^{-1}. °K^{-1})
T = Temperature in °K
n = Total number of equal time periods over which data are collected

10.3 Incubator Layout & Distribution of Data loggers

- 10 calibrated data loggers will be distributed inside the Incubator.
- The location of each data logger in the Incubator shown in the layout attached with this protocol (see Annex No. (1)).

10.4 The intervention Tests:

The purpose of the door open and blackout tests in thermal mapping is to simulate real-world scenarios that may impact temperature uniformity and stability within a storage environment. These tests help assess the resilience of the temperature control system and the effectiveness of the monitoring system in maintaining the required temperature conditions.

10.4.1 Power Failure (Blackout) and Recovery Test:

- The blackout test involves simulating a power outage or loss for a defined period. This test evaluates the system's response to sudden temperature fluctuations and its ability to maintain temperatures within acceptable limits during an emergency situation. By conducting these tests as part of thermal mapping, organizations can ensure that their storage facilities can withstand potential disruptions and maintain consistent temperature conditions critical for preserving product quality and compliance with regulatory standards.
- When the mapping exercise is in progress, shut-down the power for xx-minutes and record the shut-down time, then calculate the recovery time (the maximum time after shutting down the power & turning the power on for all data loggers to get back within the acceptance limits).

10.4.2 Door Opening and Recovery Test:

- This test evaluates how quickly the system can recover and stabilize temperatures after a disruption. This test simulates the impact of routine door openings during operational use and assesses the system's ability to maintain temperature integrity.
- During the mapping exercise open the door of room for xx-minutes and record time then close the door and calculate the recovery time (the maximum time after door opening & closing for data loggers to get back within the acceptance limits).
- The temperature should be maintained within the defined temperature limits except for a maximum of "30 minutes" following the door closing.

11. Acceptance Criteria

As per customer requirement, the temperature within Incubator will be recorded continuously for a period of 01 day as 1 cycle with recording interval of 02 minutes and the recorded temperature should be in this range (55 ~ 60) °C.

12. Requalification Frequency

- Thermal qualification will be repeated on annual basis as per LIPTIS qualification plan.
- Requalification will be performed if any significant modification to the premises, changes in stock layout or maintenance have been occurred before the annually planned qualification.

13. Results Evaluation

- After conducting the thermal mapping study, the results will be thoroughly evaluated to assess temperature distribution, uniformity, and stability within the storage environment. Key aspects to consider in the final report after the evaluation include:
  - Comparison of measured temperatures against set criteria and industry standards.
  - Analysis of data trends and patterns to understand the overall thermal performance of the facility.
  - Identification of temperature variations, and hot/cold spots would be identified for future monitoring (if needed).

14. Handling of Deviations (if needed)

Any observed deviations during thermal qualification study and their impact on the study results will be recorded in the deviation report to be reported to LIPTIS for taking and following up the corrective actions for those deviations.

15. Conclusion and Recommendations

- Based on the results of the thermal mapping study, a conclusion will be drawn regarding the effectiveness of the temperature control system and the overall thermal stability of the equipment. The conclusion will summarize the key findings of the study and address whether the equipment meets the required temperature specifications for intended use.
- Following the evaluation and conclusion of the thermal mapping study, recommendations will be provided to improve temperature management and enhance the overall efficiency of the equipment. By incorporating the following recommendations, organizations can optimize temperature control, mitigate risks of product degradation, and ensure compliance with regulatory requirements. These recommendations may include:
  - Implementing adjustments to the temperature control system to address identified hot/cold spots (if needed).
  - Upgrading controlling systems to improve temperature stability (if needed).
  - Enhancing monitoring and alarm systems for better temperature control (if needed).
  - Establishing protocols for door opening/closing procedures to minimize temperature fluctuations (if needed).
  - Conducting regular maintenance and calibration of temperature monitoring devices (if needed).

16. Appendices and Annexes

- **Appendix No. (1):** The signature log.
- **Annex No. (1):** General layout of the Incubator and the distribution of the data loggers.
- **Annex No. (2):** Performance qualification report in separate folder along with its annexes.

17. References

- WHO "Annex 9: Model guidance for the storage and transport of time and temperature–sensitive pharmaceutical products" Technical Supplement 7, May 2015.
- WHO "Annex 9: Model guidance for the storage and transport of time and temperature–sensitive pharmaceutical products" Technical Supplement 8, May 2015.
- ISPE Good Practice Guide – Controlled Temperature Chambers (2016).
- Health Products Regulatory Authority (HPRA): Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances
- USP (1079) Temperature Mapping for the Qualification of Storage Areas.
- USP (659) Packaging and storage requirement.
- USP (32) General Notice and requirements: Applying to standards, tests, assays, and other specifications of the United States Pharmacopeia.
- 21CFR 211.142 and 211.150: Storage and Distribution.

APPENDIX No. (1): Signature Log

Printed Name	Title	Company / Department	Initials	Signature
Mohamed Hassan	Technical Office Team Leader	TAG		
Noha Essam	Technical Office Senior	TAG		
Ahmed Adel	SR. QA Specialist	TAG		
Ahmed Tarek	Technical Manager	TAG		

ANNEX No. (1): Incubator Layout & Distribution of Data loggers

Freezer Layout & Distribution of Data loggers

No. of attached pages: 1

ANNEX No. (2): Performance Qualification Report for Incubator

Performance Qualification Report for Freezer (PQR-T-07025)

No. of attached folders: 1