Elements to Consider When Qualifying Control Environmental Chambers Used for CGMP Applications

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ABSTRACT

It is fundamental to ensure that all elements of thermo mapping of control environmental chambers (e.g., refrigerators, walk-in cold rooms, freezers, incubators, walk-in incubators, etc.) are properly designed and qualified with respect to user requirement specifications compliant with current good manufacturing practice (CGMP) standards.

As part of the installation, operational, and performance qualification (IQ, OQ, PQ) protocol of the control of environmental chambers, the thermo-mapping elements for testing are indicated as follows:

- Installation meeting the design specification
- Empty chamber thermo-mapping test
- Open-door study (for informational purposes only)
- Power failure (for informational purposes only)
- Full loaded chamber thermo-profile mapping.

This is a technical article on how to perform a specific validation function. This article aims to give guidance to the industry on utilizing one methodology for thermo-mapping profiling. The points to consider for each of the aforementioned testing elements shall be briefly discussed in this article. This article discusses the equipment necessary to qualify a control environmental chamber.

INSTALLATION MEETING THE DESIGN SPECIFICATION

It is recommended that the installation qualification (IQ) be conducted to meet the design specification as correlated with the user requirement specifications prior to any operational testing. The key elements to verify are as follows:

- Material of construction
- Major component installation
- Utility requirements (i.e., electrical)
- Calibrations of critical instruments
- Operation and maintenance standard operating procedures (SOPs)
- Location of unit
- Spare parts list
- Drawings.

EMPTY CHAMBER THERMO-MAPPING TEST

After the installation qualification has been successfully executed, the next step is to perform the functional testing (i.e., operational qualification), comprising of a sequence of operation and alarm testing followed by the empty chamber study. With respect to the emphasis of this article, only the empty chamber thermo-mapping study is discussed. The purpose of the empty chamber thermo-mapping study is to show that all geometrically placed thermocouples (see Figure 1) are capable of main-

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taining a specified temperature range for the entire duration of the test. For example in this case, a cold room is expected to maintain a range ≥2°C to ≤8°C during X amount of time. Depending on the design of the refrigerator or freezer and the advancement in the refrigeration systems, the defrost cycle normally has a negligible impact (i.e., very little temperature fluctuation-a tiny blip on the graph) on the overall study. This may not necessarily be the case for older refrigeration systems where adjustment of the programmable logic controller (PLC) or equipment analogue functions may be required to reduce the impact of the defrost cycle in order to ensure acceptable temperature profiling. Units that have a defrosted cycle that will have an impact on achieving uniform temperature profile over specific period of time may need to be replaced by a newer refrigerator. A product impact evaluation can be conducted prior to a final decision of accepting or not accepting the refrigerator or freezer (i.e., several thermocouples can be geometrically placed in product or solution for a 48-hour study, etc.).

The following is an example of how standard temperature mapping should be performed.

Requirements And Materials

Prior to performing any thermo-mapping studies, the environmental chamber (e.g., refrigerator) and monitoring testing equipment (e.g., Kaye 2000) must be calibrated. In addition, all installation and functional testing of the cold room, such as meeting design specifications, sequence of operations, alarms, must meet all the requirements of the qualification protocol's pre-defined acceptance criteria.

Procedure

Before the empty chamber study can be performed, it is important to verify that all aspects of the environmental chamber have been met by ensuring that all installation and operational tests (e.g., sequence of operation, alarms) have been satisfactorily completed. Once this has been achieved the second phase of the protocol execution can commence.

A procedure should be developed that clearly defines sequential steps necessary for the successful execution of the empty chamber thermo-mapping test for a cold room.

An example of a generic empty chamber thermo-mapping test procedure is indicated as follows:
- Prepare and calibrate 16 thermocouples using the setup parameters specified in Table I (Kaye setup parameters). The pre-calibration of all thermocouples must "Pass" the pre-defined specifications

Figure 1: Example of thermo-mapping placement locations.
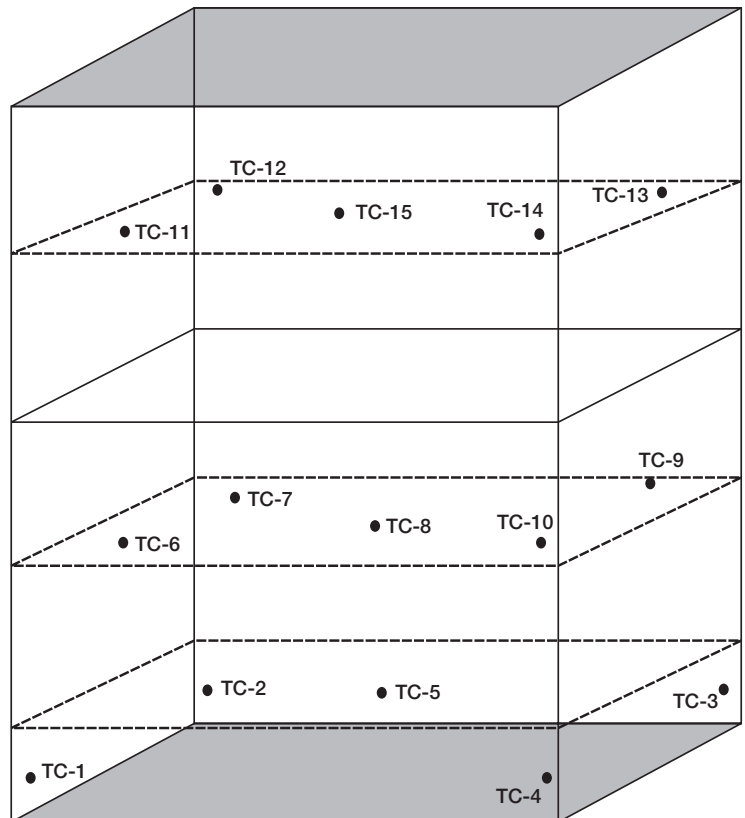
as stipulated in Table II (Kaye calibration requirements). For operation of the Kaye 2000, refer to the Kaye Validator 2000 operation manual and/or SOP XXXXXX.
- Distribute 16 calibrated thermocouples throughout the interior of the cold room in accordance with the drawing in Figure 1. Allow the temperature in the chamber to stabilize at set point prior to commencing the study.
- Once the chamber is in a state of equilibrium, initiate the Kaye data logging
- Continue recording data for a minimum of XX hours (user defined can be up to 72 hours)
  - The cold room door is to remain closed during data collection. A sign indicating not to open the door of the refrigerator is to be posted on the front door of the cold room.
- At the completion of the study, stop data collection
- Following the completion of the temperature uniformity study and the open door temperature profile and power failure studies, perform a post-study verification (i.e., post-calibration) of the thermocouples.

Table I: Setup parameters.

Type of study	Temperature distribution
Number of thermocouples	16 total
Type of thermocouple	T
Resolution	0.01°C
Validator hardware	
Printer intervals	N/A
PCMCIA intervals	N/A
File intervals	10 min

Table II: Kaye calibration points requirements.

Low	-5°C
High	15°C
Check	4°C
Sensor stability criteria	
Maximum temperature change	0.5°C
Duration	3 minutes
Sensor deviation criteria	
Maximum uncalibrated deviation from standard	1.0°C
Maximum calibrated deviation from standard	0.5°C
Log corrected results at 30-second intervals for 3 minutes	

Data Analysis

The following steps should be performed for data analysis:

- Record any thermocouples that are outside the 2°C to 8°C operating range and the duration they are out during defrost cycle
- Graph the data and interpret the results per SOP XXXX
- Verify that no more than 10% of the thermocouples malfunctioned during the study or failed post-study verification.

Acceptance Criteria

The following criteria should be obtained:

- Calibration verification readings (post-calibration of thermocouples) must be within ±0.5°C of the reference temperature standard. More than 85% of all thermocouples must be within ±0.5°C during post-use calibration verification.
- The temperature in every location during empty chamber distribution must be controlled within ≥2°C to ≤8°C. Attach all supporting data such as excel graphs, etc. (see Figure 2). During every defrost

cycle it is acceptable that the temperature (i.e., thermocouples measured in air) to go slightly out of 2°C or 8°C for a very short period of time. When the defrost cycle temperature fluctuation occurs it is recommended to perform an additional study by encompassing the geometric placement of the thermocouples in product or solution in support of this protocol and to subsequently ensure that the ≥2°C to ≤8°C are met.

OPEN-DOOR STUDY

This test is done to measure the time that it takes for the temperature controlling unit to recover from temperature fluctuation caused by opening the door.

An open-door study can be useful in explaining how the product can be affected or not affected to an auditor by the constant opening and closing of the door during a typical work schedule. To fully capture the range of the opening door data, four phases must be tested as follows:

- Prior–to-open-door phase
- Open door phase
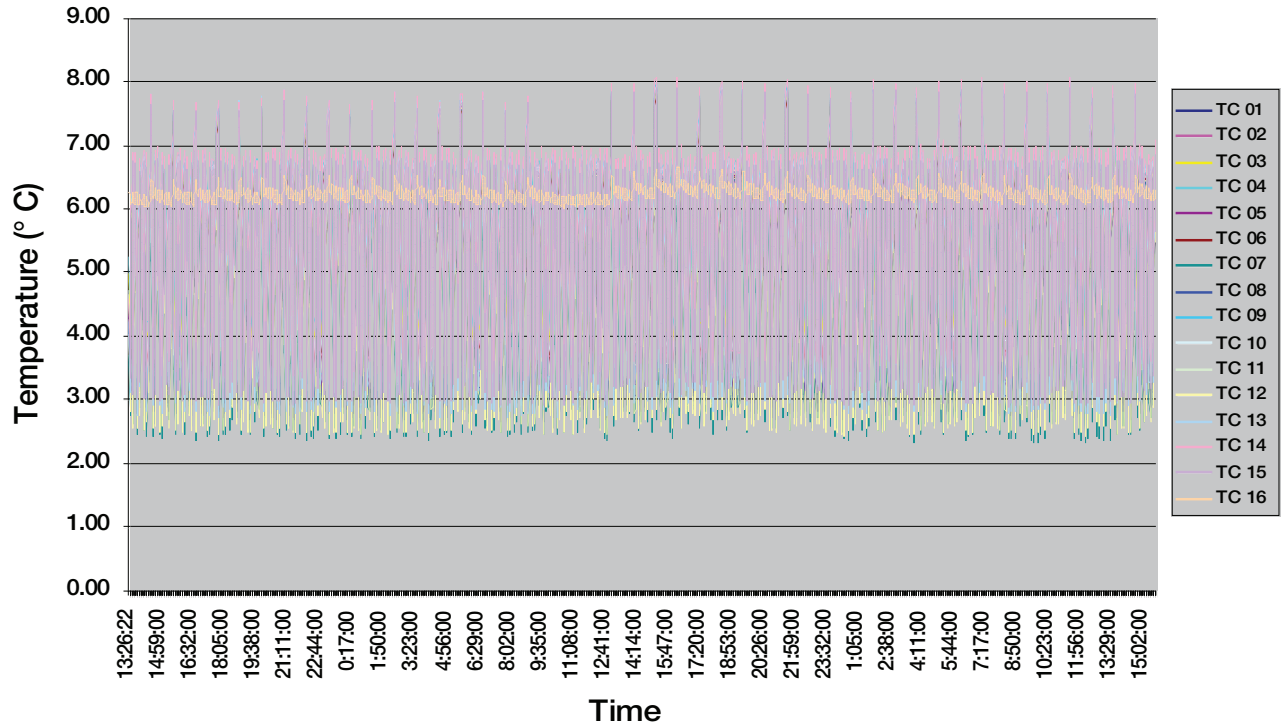- Close door phase
- Normal phase.

This test is performed in an empty chamber distribution profiling X amount of hours or the minimum time required to attain all four phases in condition that at least one hour in each of the prior–to-open-door phase and normal phase is attained.

Procedure

An example of a generic open-door study procedure is indicated as follows:

- Prepare and calibrate 16 thermocouples using the setup parameters specified in Table III. The pre-calibration of all thermocouples must "Pass" the pre-defined specifications as stipulated in Table IV. For operation of the Kaye 2000, refer to the Kaye Validator 2000 operation manual and/or SOP XXXXXX.
- Distribute 16 calibrated thermocouples throughout the interior of the cold room in accordance with Figure 1
- Allow the temperature in the chamber to stabilize at set point
- Initiate data logging and ensure data are captured in each of the identified phases specified as follows:
  - Prior to open door phase
  - Open door phase
  - Close door phase
  - Normal phase.

Figure 2: Empty chamber thermo-mapping test.

Data Analysis

The following steps should be performed for data analysis:

- Print the Kaye data logger report and the thermocouple calibration report. Attach all reports to the protocol.
- Interpret the results per SOP XXXX
- Verify that no more than 10% of the thermocouples malfunctioned during the study or failed post-study verification.

Acceptance Criteria

The following criteria should be obtained:

- Calibration verification readings (post-calibration of thermocouples) must be within ±0.5°C of the reference temperature standard. More than 85% of all thermocouples must be within ±0.5°C during post-use calibration verification.
- All four phases are captured as specified in the procedure section. Attach all supporting data such as Excel graphs. For example, refer to Figure 3. Note: The door was opened for a longer duration on the left side of Figure 3 compared to the right side (the second time the door was opened).

Table III: Setup parameters.

Type of study	Temperature distribution
Number of thermocouples	16 total
Type of thermocouple	T
Resolution	0.01°C
Validator hardware	
Printer intervals	N/A
PCMCIA intervals	N/A
File intervals	5 seconds

Table IV: Kaye calibration points requirements.

Low	-5°C
High	15°C
Check	4°C
Sensor stability criteria	
Maximum temperature change	0.5°C
Duration	3 minutes
Sensor deviation criteria	
Maximum uncalibrated deviation from standard	1.0°C
Maximum calibrated deviation from standard	0.5°C
Log corrected results at 30-second intervals for 30 seconds	

Figure 3: Open-door studies.
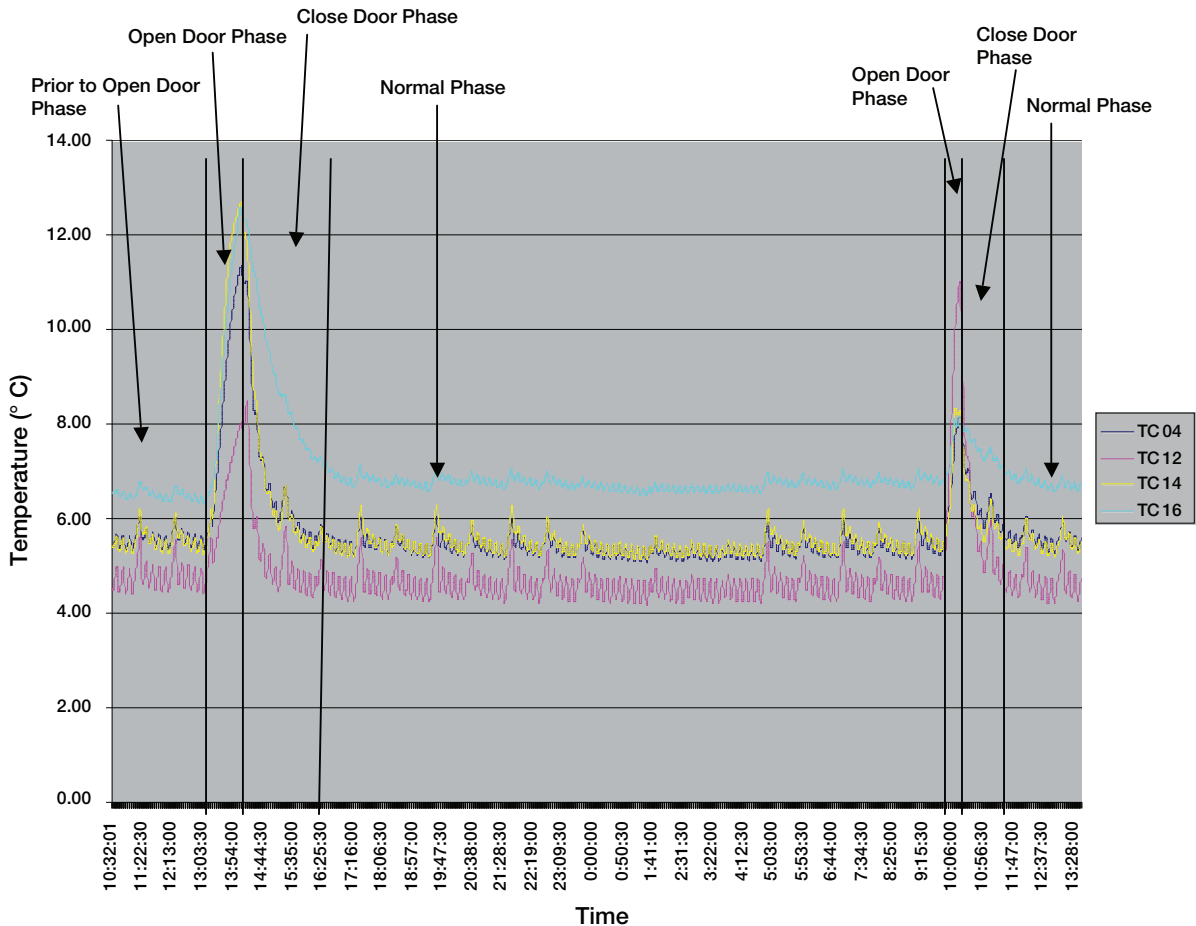
POWER FAILURE STUDY

This test is done in order to measure the time that it takes for the temperature-controlling unit to recover from a power failure.

A power failure study can be useful in explaining how the product can remain within acceptable range, how long the product was out of range, and how much time it takes to recover within specification during an actual power failure. To fully capture the range of the power failure data, the following four phases must be tested:

- Prior-to-power-failure phase
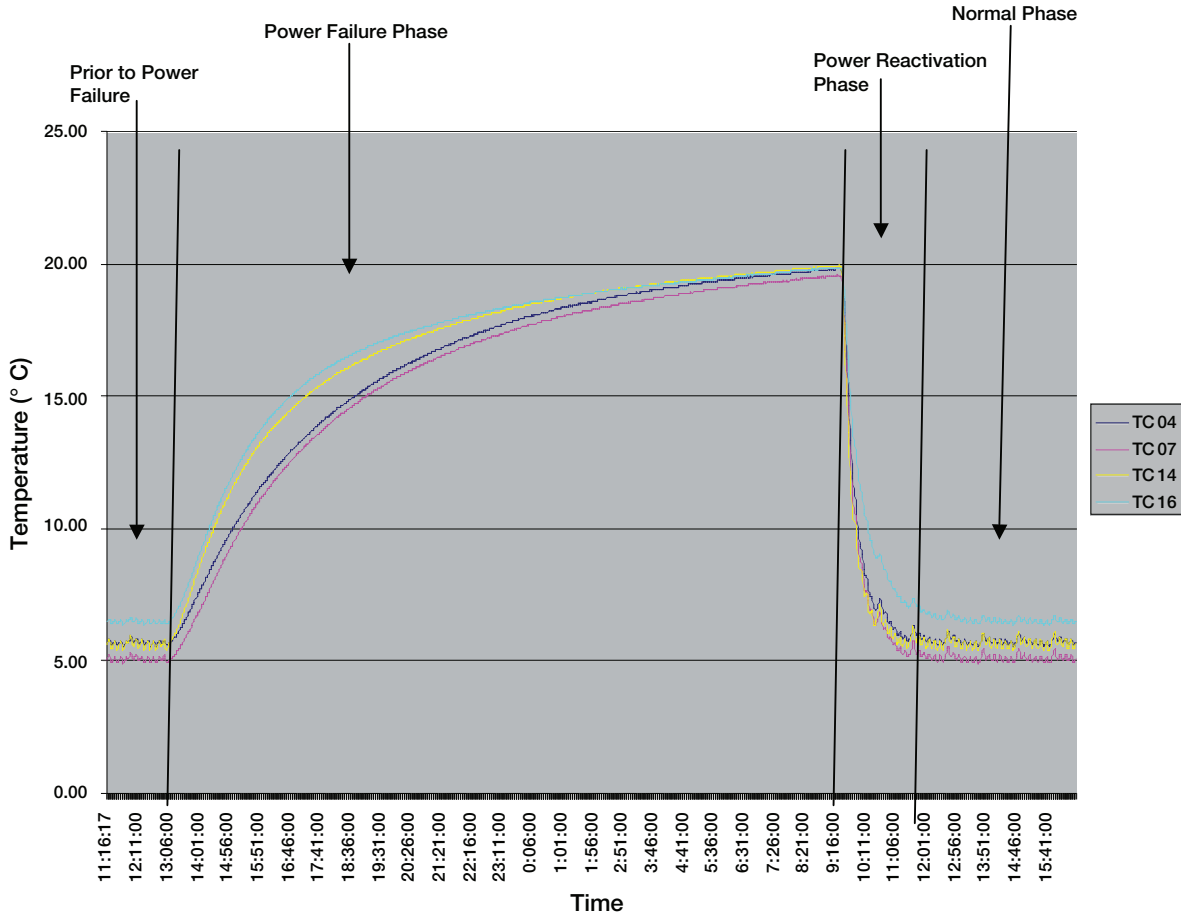- Power failure phase
- Power reactivation phase
- Normal phase.

This test is performed in an empty chamber distribution profiling at least 24 hours with the condition that data for at least one hour in both the prior-to-power-failure phase and the normal phase are attained.

Procedure

An example of a generic power failure study procedure is indicated as follows:

- Prepare and calibrate 16 thermocouples using the setup parameters specified in Table V. The pre-calibration of all thermocouples must "Pass" the pre-defined specifications as stipulated in Table VI. For operation of the Kaye 2000, refer to the Kaye Validator 2000 operation manual and/or SOP XXXXXX.
- Distribute 16 calibrated thermocouples throughout the interior of the cold room (see Figure 1)
- Allow the temperature in the chamber to stabilize at set point
- Initiate data logging and ensure data are captured in each of the identified phases specified as follows:
  - Prior-to-power-failure phase
  - Power failure phase
  - Power reactivation phase
  - Normal phase.

Figure 4: Power failure study.

- Following the completion of the power failure temperature profile study, perform a post-study verification of the thermocouples.

Data Analysis
The following steps should be performed for data analysis:
- Print the Kaye data logger report and the thermocouple calibration report. Attach all reports to the protocol.
- Interpret the results per SOP XXXX.
- Verify that no more than 10% of the thermocouples malfunctioned during the study or failed post-study verification.

Acceptance Criteria
The following criteria should be obtained:
- Calibration verification readings (post-calibration of thermocouples) must be within ±0.5°C of the

reference temperature standard. More than 85% of all thermocouples must be within ±0.5°C during post-use calibration verification.
- All four phases are captured as specified in the procedure section. Attach all supporting data such as excel graphs (see Figure 4).

Note: This test is to be used "For information only."

FULL-LOADED CHAMBER THERMO-PROFILE MAPPING (PQ)
The instruction for the empty chamber test is also applicable to the loaded chamber thermo-profile. The full-loaded chamber is defined as having at least 80% of surface area loaded with samples and containers in order to determine the effects and impact on the product. This will ensure both thermo profiling extremes are tested, empty versus loaded conditions. Consequently, a product impact assessment can be conducted and easily rationalized during an audit. Optionally, an

Table V: Setup parameters.

Type of study	Temperature distribution
Number of thermocouples	16 total
Type of thermocouple	T
Resolution	0.01°C
Validator hardware	
Printer intervals	N/A
PCMCIA intervals	N/A
File intervals	5 minutes

Table VI: Kaye calibration points requirements.

Low	-5°C
High	15°C
Check	4°C
Sensor stability criteria	
Maximum temperature change	0.5°C
Duration	3 minutes
Sensor deviation criteria	
Maximum uncalibrated deviation from standard	1.0°C
Maximum calibrated deviation from standard	0.5°C
Log corrected results at 30-second intervals for 30 seconds	

open-door/power failure study can be conducted as part of the full load testing in order to simulate the effects on the product and to subsequently evaluate the overall product impact.

CONCLUSION

The process presented in this article is one method that can be used to qualify a control environmental chamber. It can be concluded that all elements of thermo mapping of control units such as refrigerators, walk-in cold rooms, freezers, incubators, and walk-in incubators may include the following tests:

- Installation meeting the design specification
- Empty chamber thermo-mapping test
- Open-door study (for informational purposes only)
- Power failure (for informational purposes only)
- Full-loaded chamber thermo-profile mapping.

This article discusses just one methodology that can be used for performing temperature mapping. The aforementioned tests as stipulated in this paper can provide a roadmap leading to successful audits that can be defendable to US Food and Drug Administration inspections. **JVT**

ARTICLE ACRONYM LISTING

CGMP	Current Good Manufacturing Practice
IQ	Installation Qualification
OQ	Operational Qualification
PLC	Programmable Logic Controller
PQ	Performance Qualification
SOPs	Standard Operating Procedures