Supplement 7

Qualification of temperature-controlled storage areas

Technical supplement to WHO Technical Report Series, No. 961, 2011

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

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Abbreviations

CAPA	corrective and preventive action (procedures)
EDLM	electronic data logging monitor
IATA	International Air Transport Authority
IQ	installation qualification
OQ	operational qualification
PDA	Parenteral Drug Association
PQ	performance qualification
SMS	short message service
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
UPS	uninterrupted power supply

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Glossary

Auxiliary equipment: Equipment mostly used in conjunction with the equipment to be qualified but not included in the qualification package.

Component: Any major piece, part or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a stand-alone unit (e.g. valves and switches).

Controller, critical: A controller for which control has a direct impact on the quality of the product or proper operation of the equipment.

Controller, non-critical: A controller for which control has no direct impact on the quality of the product or 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.

Design qualification: The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[1]

Deviation: For installation qualification: any discrepancy between the installation specifications and the actual (as found) installation. For operational qualification: any discrepancy between the protocol and the actual performed test, test function methodology, testing equipment, and testing material.

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. These monitors have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Installation qualification (IQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

Main equipment: Major equipment to be qualified.

Operational qualification (OQ): The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

[1] World Health Organization. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 961).

Passive systems: Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Performance qualification (PQ): The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included.[2]

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

Qualified third party: An entity independent from the company that is mandated and involved in the preparation, execution or analysis of a quality assurance (QA) activity for the company. This third party should present the adequate professional qualification to perform QA activities.

Refrigeration equipment: The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Sensor: A mechanical device (pressure switch, or bimetal temperature switch, a digital or analogue transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates an electrical or mechanical signal to an instrument or a controller in order to be interpreted.

Spare parts: Parts that are available and may be used to replace or modify equipment components.

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to

[2] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.*

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.

Temperature excursion: An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

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 predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[3]

[3] Parenteral Drug Association (PDA). Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. Introduction

This Technical Supplement has been written to amplify the recommendations given in section 4.7 of WHO Technical Report Series No. 961, 2011, Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.[4] It covers the three stages of qualification needed before the release of a temperature-controlled storage area for routine use: installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Related topics are covered in the following Technical Supplements:

- *Checking the accuracy of temperature control and monitoring devices*
- *Qualification of shipping containers*
- *Qualification of temperature-controlled road vehicles*
- *Temperature and humidity monitoring systems for fixed storage areas*
- *Temperature mapping of storage areas.*

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

Stage 1 (for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is *design qualification*. Although design qualification demonstrates compliance with the URS and associated test protocols, it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Stage 1 (for installations): Establish by documented inspection and testing that an installation[5] that has been assembled in a specific location is fully in accordance with the URS and installation drawings. This is *installation qualification*.

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

[5] The installation will typically incorporate components that have a design qualification.

Stage 2: Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used. This is *operational qualification*.

Stage 3: Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions. This is *performance qualification*.

1.1 Requirements

Every new temperature-controlled store must be qualified before it is released for the routine storage of time- and temperature-sensitive pharmaceutical products (TTSPPs). As a minimum, the qualification procedure should:

- Establish that the installation, including all associated control, monitoring and alarm systems, has been carried out in accordance with the relevant drawings and specifications.
- Demonstrate, through temperature mapping, that air temperatures throughout the zone(s) designated for TTSPP storage are within the specified limits, both when empty and when in the normal loaded condition.
- Define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources).
- Demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure, and the time taken to re-establish these limits following power restoration.
- Demonstrate the time taken for temperatures to return to within the designated limits following a representative door opening event.

Further qualification exercises should be conducted whenever significant modifications are made to the installation, or to the way in which it is used. The qualification process must be fully documented in order to demonstrate compliance to management, clients and regulatory authorities.

Qualification activities should be planned and documented. The plan should set out the sequence of testing activities to be carried out. It should also describe the method(s) for ensuring traceability between the individual test activities and the specific design features being tested.

1.2 Objectives

This Technical Supplement applies to fixed storage locations used for TTSPP logistic operations. The objective is to provide guidance on how to carry out the three types of qualification needed to meet the requirements of good storage practice in temperature-controlled areas. These are IQ, OQ and PQ.

1.3 Target readership

This document is relevant to wholesalers, warehouse operators, distributors, dispatchers and third-poarty logistics (3PLs) who store TTSPPs. The specific target audience within these organizations includes those who have direct responsibility for quality management, for example, quality assurance (QA) managers and operations managers.

2. Guidance

The purpose of qualification in the pharmaceutical and medical sector is to ensure that equipment or ancillary systems are properly installed, work correctly, and produce the specified performance outcomes under routine operating conditions.

2.1 Associated materials and equipment

A qualification operation requires a sufficient number of electronic data logging monitors (EDLMs) to ensure that qualification activities can be carried out correctly. In addition, suitable computer equipment and software is needed to store and analyse the data. The chosen EDLMs should:

- be technically suitable for the specific task and the intended operating environment;
- provide a continuous and reliable record of time-temperature data;
- have an appropriate temperature range so that all anticipated temperature extremes can be recorded (e.g. from −30.0 °C to +60.0 °C);
- have a user-programmable data sampling period allowing time intervals to be set in the range from 1 minute to 15 minutes or more and with sufficient memory for the intended length of the study and the chosen recording interval;
- have a NIST-traceable 3-point calibration certificate and have a guaranteed error of no more than ±0.5 °C at each calibration point;
- allow for recorded time-temperature data to be downloaded to a computer system for subsequent analysis;
- have data storage and analytical software that comply with applicable regulatory requirements (e.g. FDA 21 CFR part 11).

2.2 Introduction to qualification

Qualification is part of *validation*, but the individual qualification steps do not in themselves constitute process validation. Validation is the entire process by which a product is obtained from a manufacturer or distributor and is examined and tested before it is formally approved for routine use.

A qualification exercise generally consists of four sequential phases: design qualification (DQ), IQ, OQ, and PQ.

a. *DQ:* The purpose of DQ is to ensure that the premises, supporting utilities, equipment and processes have been designed in accordance with the relevant requirements (user requirements and regulatory requirements).

b. *IQ:* The purpose of IQ is to ensure that the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications.

c. *OQ:* A successful OQ exercise provides assurance that the premises, supporting utilities and equipment operate in accordance with their design specifications. As a general rule, OQ is carried out on equipment when it is *empty*.

d. *PQ:* Following OQ, a PQ provides additional assurance through further testing that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. The outcome of a successful PQ exercise is a formal confirmation that the equipment, associated systems and operational processes can be "released" for routine use. In contrast to OQ, PQ is carried out on equipment that is *loaded* with product.

2.2.1 Qualification applied to temperature-controlled storage

Qualification is commonly used to validate pharmaceutical manufacturing processes but it can also be applied to the pharmaceutical supply chain in general, and to temperature-controlled storage processes and equipment in particular.

In this context, temperature-controlled storage covers any area where TTSPPs have to be stored within a controlled temperature range (e.g. 2.0 °C to 8.0 °C or 15.0 °C to 25.0 °C). This includes:

- active temperature-controlled storage equipment, including ultra-low freezers, freezers, freezer rooms, refrigerators, cold rooms and controlled-ambient stores;
- actively temperature-controlled transport equipment. This includes refrigerated and temperature-controlled trucks and vans, and refrigerated and temperature-controlled ocean containers. Refer to the companion Technical Supplement: *Qualification of temperature-controlled road vehicles*;
- passive temperature-controlled packaging systems (shipping containers). This includes insulated containers used to maintain product temperature during road and air transport. Refer to the companion Technical Supplement: *Qualification of shipping containers*.

All temperature-controlled equipment and systems used to handle, store and distribute TTSPPs should be qualified.

An integrated IQ, OQ and PQ procedure is commonly used to qualify temperature-controlled storage areas. Ideally the IQ, OQ and PQ procedures

should be applied in a progressive and coordinated way, from the installation up to the final performance verification. However, this may be more difficult if the storage areas and equipment are already in use.

2.2.2 Installation qualification

The IQ process should be completed first. Its purpose is to ensure that the storage area and all its associated equipment and systems are clearly identified and have been correctly installed. This step must be completed before any further functional or operational tests are carried out.

Specifically, an IQ process should:

- Identify the storage area and the equipment and systems required for it to operate correctly and establish that all systems are installed as specified.
- Ensure that an effective preventive maintenance programme is in place.

2.2.3 Operational and performance qualification

Once the IQ stage has been completed, the OQ and PQ can generally be carried out together as a single sequence of inspections and tests. These inspections and tests should be chosen to suit the specific characteristics, performance needs and operational conditions of the storage area being qualified.

OQ is carried out with the storage area or equipment empty. It typically involves the following assessments:

- Verify applicable standard operating procedures (SOPs) or work instructions.
- Verify that all measuring devices (e.g. controllers and sensors) have valid calibration certificates.
- Carry out control panel tests and checks.
- Carry out alarm system tests and checks.
- Assess temperature control and temperature distribution in the empty storage space or equipment.[6]
- Check temperature recovery following a door opening.
- Conduct power failure tests and checks.

[6] See Technical Supplement: *Temperature mapping of storage areas*.

Note: In this context "empty storage space or equipment" means that no products are being stored and normal operations have yet to begin.

PQ is carried out with the storage area or equipment fully operational, loaded and having been allowed to reach stabilized conditions. The following tests and checks should be carried out:

- temperature control and temperature distribution;
- temperature recovery following a door opening.

Note: In this context "loaded storage space or equipment" means that the store or equipment has begun to receive products and normal operations have commenced.

2.3 Qualification protocols

Prepare, review and approve a detailed and comprehensive protocol before the qualification process begins.

The qualification protocol should be a comprehensive document, which guides the user through the IQ, OQ and PQ processes and helps ensure that all temperature-controlled storage areas are correctly qualified. Each of the three protocols can be more or less generic. However generic documents should never be used unthinkingly; they should always be adapted to the specific type of temperature-controlled storage area. Each installation must be linked to and qualified against its own specific qualification protocol.

The qualification protocol should include the following sections:

a. Approval page and change control history
b. Acronyms and glossary
c. Description and rationale
d. Scope and objectives
e. Key parameters
f. Procedures
g. Qualification report template.

2.3.1 Approval page and change control history

Include a standard template for recording approvals and changes to the document. Table 1 shows an example.

Table 1
Example of a standard template for recording approvals and changes to a document

Approvals	Name	Date	Signature
Authorized by:			
Reviewed by:			
Revised by:			
Original author:			

Version history

No.	Date	Description of change	Reason for change
1		Original	
2			
3			
4			
5			

If the protocol has been prepared by a qualified third party, it should be authorized by the responsible person within the commissioning organization.

2.3.2 Acronyms and glossary

Define the acronyms and technical terms used in the protocol.

2.3.3 Description and rationale

Describe the installation to be qualified and the equipment and related systems to be included in the qualification exercise and outline the reasons for carrying out the exercise.

2.3.4 Scope and objectives

Clearly define the scope and objectives of the qualification exercise.

2.3.5 Key parameters

Describe the key parameters for the operation of the installation.

2.3.6 Procedures

The protocol for a specific installation should describe the procedure for every relevant test or check in detail, as follows:

a. *Title:* Briefly describe the test or check.
b. *Target:* Name the target system, subsystem or component.
c. *Procedure:* Clearly describe the test or check procedure as a step-by-step process. Specify any associated materials or test equipment required.
d. *Acceptance:* Define the acceptance criteria.
e. *Data collection:* Include templates for all the data collection and test sheets required.

A generic set of IQ, OQ and PQ tests and checks is outlined in sections 2.4 to 2.7.

2.3.7 Qualification report template

The protocol may contain a template for the qualification report. This should include everything needed to comply with internal rules and regulatory requirements, as follows:

a. *Introduction:* Describe the objectives of the qualification exercise.
b. *Summary:* Outline the results of the qualification exercise. Include a summary of all recorded deviations.
c. *Conclusions and recommendations:* State whether the installation can be used for routine operations. List all key recommendations that need to be acted upon; this should include a complete list of all changes that need to be made to the installation to correct reported failures recorded on the qualification inspection and test data sheets.
d. *Report annexes:* Append the following supporting material:
   – raw data as recorded on the appropriate inspection and test data sheets (see below) as well as all associated spreadsheets and graphs;
   – key documents and notes prepared during the qualification exercise, together with any other supporting material;
   – deviation reports, including corrective and preventive actions (CAPA) forms, if required;
   – calibration certificates for all EDLMs used;

- calibration certificates for the control and monitoring systems that form part of the installation;
- list of all members of the qualification team, and their designations.

All data sheets, results, spreadsheets and graphs must be reviewed by an independent person who was not involved in conducting the qualification exercise. The reviewer should confirm, approve and sign the results of the major tests and checks.

2.3.8 Approval process

If qualification is carried out as an in-house process, the IQ, OQ and PQ protocols and subsequent qualification reports must be authorized by the responsible manager(s) and quality assurance personnel within the organization.

If qualification is carried out by a qualified third party, both the IQ, OQ and PQ protocols and the subsequent qualification reports must be approved by the responsible person in the third-party organization.

2.4 Installation qualification

The purpose of IQ is to establish that all elements of the storage area, including building work, equipment, systems, subsystems and components are in accordance with the installation drawings and specifications. The first stage in the process is to itemize all these key elements. The next stage is to establish how each element should be inspected and tested to confirm compliance.

Once these preliminary stages have been completed, on-site inspection and testing can begin. The steps in the procedure are as follows:

- Carry out a detailed inspection of the storage area and all associated building works.
- Carry out a detailed inspection of the electrical services.
- Carry out a detailed inspection of the mechanical services.
- Carry out tests to confirm that the requirements for specified environmental conditions have been met.
- Identify, list and inspect the spare parts supplied as part of the installation.
- Identify, list and inspect any auxiliary equipment associated with, but not part of, the installation such as standby generators, security systems and the like.
- Confirm that satisfactory arrangements are in place to ensure an effective preventive maintenance programme for the entire installaton.

2.4.1 Identifying critical components

Although all parts of a temperature-controlled installation should be included in the IQ, there are certain critical elements that merit particularly close attention.

Refrigerators, freezers and other simple equipment: The critical parts of this type of equipment are the thermostat and its associated control sensor and the temperature monitoring device (thermometer or recorder) and its sensor; this may be a separate component such as a disposable 30-day temperature recorder.[7]

Complex equipment: This includes freezer rooms, cold rooms, pick coolers and more complex and specialized refrigerators and freezers, with a longer list of key components. Critical parts include the controller, sensor, cooling unit, condenser and evaporator. For freezer rooms and cold rooms, the room enclosure itself is also critical because these are sites assembled from separate panel elements.[8] All of these key components should be identified, listed, described and checked.

If the equipment has duplicates or multiples of any components or systems, each one should be checked. Critical components and systems that are directly involved in temperature control and measurement should also be checked for accuracy and calibration. Calibration certificates should be checked and copies included in the IQ report.

2.4.2 Checking installed systems, subsystems and components

Table 2 shows the type of record used to check and record installed systems and components. The example given here is for a cold room refrigeration unit.

Table 2
Example of an IQ inspection and test table

Subsystem or component inspection and test table	
Location:	South Warehouse
System:	Cold room #1
Subsystem/component:	Refrigeration unit #1
Inspection or test:	Inspection: ☒ Test: ☐
Type of inspection/test:	IQ protocol: visual check RFU-01

[7] See Technical Supplement: *Temperature and humidity monitoring systems for storage areas*.

[8] See Technical Supplement: *Refrigeration equipment maintenance* for a list of cold room enclosure checks.

Table 2 *continued*

Subsystem or component inspection and test table			
Details:	**Specified**	**As found**	**Pass or fail**
Manufacturer:	ABC refrigeration	ABC refrigeration	Pass
Model:	TTW50	TTW40	Fail
Serial number:	Not specified	TTW40-1310-025	Fail
Internal ID number:	CR1/RFU01	CR1/RFU01	Pass
Deviation report ref: Enter "none" if no deviation	DEV/001		
Inspected by:	AG	Date:	27 Oct 2013
Checked by:	JB	Date:	5 Nov 2013

For each system, subsystem or component, the table allows the IQ inspector to list the critical attributes of what was originally specified in the requirements specification or on the installation drawings (the "specified" column), what was actually installed (the "as found" column) and whether or not it complies (the "pass or fail" column).

a. *Specified conditions:* The entries for location, system, component and those in the "specified" column should be completed before the inspection begins. The same applies to the corresponding cells in Tables 3 and 4. Pre-filling in the table helps the IQ inspector to locate the listed item and check that it has been installed correctly. Where details are not available – in the above example the serial number of the refrigeration unit – enter "not specified". In addition, record whether an inspection and/or test(s) are to be carried out to assess compliance and describe the type of inspection and/or test(s) to be used. Key this back to the relevant section of the qualification protocol.

b. *As found column:* Use this column to record details of the item as found at the time of the inspection. To achieve a pass, the installed subsystem or component must meet or exceed the specified condition. In the example given in Table 2, although the refrigeration unit has been supplied by the specified manufacturer, the unit installed has a lower power rating than the one specified.

c. *Pass or fail column:* Compliance is achieved when an item fully meets or exceeds the specification or the specified performance conditions.

In the example in Table 2, the correct manufacturer has supplied the unit, so this is recorded as a pass. However, the refrigeration capacity of the installed unit is too small, so this is recorded as a fail.

d. *Deviation report:* Wherever a deviation is observed, this must be recorded on a separate deviation report form. Each inspection table should include a space to record a cross-reference to the relevant deviation report. If there are no deviations, enter "none". (For an example of a deviation report, see **Annex 1**.)

e. *Signatures:* The completed sheet should be signed or initialled by the inspector and checked by the designated reviewer.

Use drawings, photographs and other supporting material to expand and support the information recorded in the table.

2.4.3 Checking electrical systems and requirements

Because the installed electrical system typically connects to multiple components, it requires a separate inspection and qualification procedure. Table 3 can be used to record the overall compliance of the installed electrical system. Table 4 is used to identify and check the critical components of the system.

Table 3
Overall compliance check for electrical installation

Electrical installation: system compliance check sheet			
Location:	South Warehouse		
System:	Electrical installation		
Subsystem/component:	3-phase supply to cold room #1		
Inspection or test:	Inspection: ☒ Test: ☐		
Type of inspection/test:	IQ protocol: visual check ELEC-01		
Items	**Specified**	**As found**	**Pass or fail**
Main voltage (V):	415 V	415 V	Pass
Cycles (Hz):	50 Hz	50 Hz	Pass
Amperage (A):	100 A	100 A	Pass
Phase:	3	3	Pass
Inspected by:	*AG*	**Date:**	*27 Oct 2013*
Checked by:	JB	**Date:**	5 Nov 2013

Once the overall compliance check has been completed, the electrical supply to the individual critical components needs to be checked. The example below relates to the example in Table 2.

Table 4
Electrical installation: critical component checks

Electrical installation: critical component check sheet				
Location:	South Warehouse			
System:	Electrical installation			
Subsystem/component:	3-phase supply to refrigeration unit A			
Inspection or test:	Inspection: ☒ Test: ☐			
Type of inspection/test:	IQ protocol: visual check ELEC-05			
Electric supply	**Specified**	**As found**		**Pass or fail**
Breaker location/service panel	Panel A	Panel A		Pass
Circuit/breaker number	Not specified	RFU-1		Pass
Circuit voltage (V)	315	315		Pass
Circuit amperage (A)	30 A	20 A		Fail
Circuit phase	3	3		Pass
Emergency power?	Required	Yes ☒	No ☐	Pass
Isolating switch?	Required	Yes ☒	No ☐	Pass
Is the electrical supply compatible with electrical requirement?	Required	Yes ☐	No ☒	Fail
Grounded?	Required	Yes ☒	No ☐	Pass
Special isolation/ shielding?	Not required	Yes ☐	No ☒	Pass
Is the circuit-breaker properly identified?	Required	Yes ☒	No ☐	Pass
Inspected by:	*AG*	**Date:**		*27 Oct 2013*
Checked by:	JB	**Date:**		5 Nov 2013

The service panel and circuit-breakers that apply to the various critical components should be clearly labelled both at the service panel itself and at the component.

2.4.4 Checking environmental conditions

Check the environmental conditions in the storage area and check all installed equipment and components for cleanliness, fumes, and vibrations. Record the temperature and relative humidity conditions and determine whether these are within the limits designated in the IQ protocol (Table 5).

Table 5
Environmental conditions, control and monitoring checks

Environmental control and monitoring system check sheet			
Location:	South Warehouse		
System:	Cold room #1		
Subsystem/component:	As above		
Inspection or test:	Inspection: ☒ Test: ☐		
Type of inspection/test:	IQ protocol: visual check ENV-01 and instrumented measurement ENV-02		
Items	**Specified**	**As found**	**Pass or fail**
Cleanliness:	All surfaces clean	Floor dusty	Fail
Fumes:	None perceptible	None perceptible	Pass
Vibrations:	None perceptible	RFU #1 vibrating	Fail
Temperature control:	Single sensor	Single sensor	Pass
Humidity control:	No active control	No active control	Pass
Temperature monitoring:	3 sensors	3 sensors	Pass
Humidity monitoring:	None	None	Pass
Temperature (°C):	+2.0 °C to +8.0 °C	+5.5 °C (sensor 1) +6.1 °C (sensor 2) +4.9 °C (sensor 3)	Pass
Humidity (% RH):	60% to 75%	70%	Pass
Inspected by:	*AG*	**Date:**	*27 Oct 2013*
Checked by:	JB	**Date:**	5 Nov 2013

2.4.5 Checking spare parts

If applicable, include a section in the IQ report on change parts and list those that have been provided as part of the installation. These parts need to be checked for compliance as described above in section 2.4.1.

2.4.6 Checking auxiliary equipment

The installation may have auxiliary equipment associated with it, which is not directly included in the scope of the IQ inspection. An example might be a security and alarm system. This equipment should be identified and listed in the IQ report. The report should also include a description of the electrical, electronic or other interfaces between this equipment and the installation itself.

2.4.7 Checking information needed for the preventive maintenance programme

An effective preventive maintenance programme (PMP) cannot be implemented unless the relevant key elements are in place. The IQ inspector should check the following:

a. Are all the items of equipment and all key components listed in the equipment inventory?
b. Are all these items labelled in accordance with the organization's equipment management policies?
c. Is there an equipment inventory file, and where is it located?
d. Is there a maintenance logbook, and where is it located?

All relevant documentation, drawings and installation and commissioning records should be collected together in an equipment file and attached to the IQ report. Table 6 shows one way to index this information in tabular form.

Table 6
Equipment file index

Information available in the equipment file							
Equipment or component ID	Equipment or component name	TS	OI	MI	RS	Record type	Record number

TS, technical specifications; OI, operating instructions; MI, maintenance instructions; RS, recommended spare parts list.

2.4.8 Writing the IQ report

As soon as the IQ assessment has been completed, prepare a report as outlined above in section 2.3.1 Pay particular attention to the following points:

- Make sure that all of the sections included in the IQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the IQ protocol.
- Specify the actions that need to be taken to correct the reported deviations and state the name of the person or organization responsible for completing these actions.
- Merge any handwritten logbook notes made by the IQ team into the relevant sections of the report.
- List all members of the qualification team, and their designations.

2.5 Operational qualification

Do not begin the OQ stage until all relevant deviations recorded during the IQ inspection have been corrected.

The purpose of OQ is to establish that the installation and all its systems and subsystems operate effectively and consistently when the storage area is *empty*. As soon as the OQ process has been completed and the installation has been approved, the next step is the PQ stage, with the storage area *fully operational*. Once the entire OQ and PQ process has been successfully completed, the installation can be signed off and fully released for routine operation.

An OQ inspection should cover the following:

- Check the calibration of all temperature measuring and controlling systems and components.
- Test the installation's control systems and check that these systems function correctly. Check the system set points.
- If there is a temperature alarm system, set the low and high alarm limits and set-up and test the relevant alarm outputs such as email messages, short message service (SMS) text messages and telephone contacts. Record the results.
- Carry out a temperature mapping of the empty storage area and record the results. See Technical Supplement: *Temperature mapping of storage areas*.

- Ensure that all relevant SOPs are available, that the relevant personnel have been trained to follow these SOPs and that training records are kept.

2.5.1 Checking installed systems, subsystems and components

As with the IQ procedure described in section 2.4.2, the OQ inspection and test tables and report should record the specified condition and the as found conditions and whether the as found condition is a pass or a fail. All deviations should be recorded, and the assessment results should be signed by the inspector and checked by the independent reviewer.

2.5.2 Calibration of controllers and sensors

All the controllers and sensors that form part of the installation should operate correctly and have valid calibration certificates. These certificates should be attached to the OQ report. Controllers and sensors should be suitably tagged so that they can be identified. Each tag should record the component ID, the calibration date and the calibration expiry date.

The objectives of the inspection are to:

- Check that all critical controllers and sensors have been calibrated and that the calibration status is current.
- Ensure that all these controllers and sensors are added to a calibration and preventive maintenance programme.

In order to meet the acceptance criteria, every critical controller and sensor should have:

- a current calibration certificate, with the certificate available;
- a calibration that is traceable to national standards;
- an attached calibration tag;
- an individual record in the calibration section of the preventive maintenance programme.

2.5.3 Standard operating procedures

There should be a comprehensive set of SOPs which cover all relevant aspects of the installation, routine operation and maintenance of the installation. These should be reviewed as follows:

- Check that that all the requisite SOPs have been written.
- Check that their content relates to the actual installed equipment and the specific operational requirements of the installation.
- Check that a training programme is in place, based on the content of the SOPs.

The following acceptance criteria apply:

- All SOPs must be approved and available.
- All SOPs must be consistent with operational requirements.
- There must be a training record, directly associated with each SOP, to demonstrate that training has been provided.

2.5.4 Control panel

The objective of the control panel inspection is to establish that all temperature controls, indicators and other displays operate in accordance with the manufacturer's specifications. This inspection is equipment-specific and should be drawn up to suit the system that has been installed.

The acceptance criterion is that all these elements are fully operational.

2.5.5 Alarm tests

The purpose of the alarm tests is to confirm that the alarm system operates in accordance with the design specifications. For temperature alarm systems, there should be one high alarm test and one low alarm test. If the system also has an event alarm system – for example a door open alarm – this should also be tested.

For each test, record the alarm settings and trigger the desired alarm event. Confirm that the alarm system is activated. Activation may be indicated by an alarm sounder or alarm strobe, by a signal to an alarm company, which provides a remote monitoring service (solution as a service (SaaS), by SMS or telephone message or by any combination of these options – all relevant systems need to be tested.

Once the alarm tests have been completed, record the results on an alarm system test sheet. A simple example is shown in Table 7. More complex alarm systems will need a more complex test sheet.

Table 7
Alarm system test sheet

Alarm system test sheet						
Test	**Operation**	**Compliance**		**Deviation report number**	**Tested by**	**Date**
		Yes	**No**			
High temperature alarm	Alarm activated	☐	☐			
Low temperature alarm	Alarm activated	☐	☐			
High alarm setting:						
Low alarm setting:						
Checked by:		Date:				

2.5.6 Temperature mapping – empty

The objective of the temperature mapping test is to demonstrate that the installation is capable of controlling and maintaining a uniform temperature when the storage area is empty. The whole area should be monitored for a period of at least 24 hours using EDLMs. Table 8 shows how the data should be recorded for an OQ test.

Table 8
Test data sheet: temperature distribution

Data logger ID number	Min. temp. recorded (°C)	Max temp. recorded (°C)	Mean temp. (°C)	Within range?		Inspected by	Date
				Yes	No		
DL-001				☐	☐		
DL-002				☐	☐		
DL-003				☐	☐		
DL-004				☐	☐		
DL-005				☐	☐		
DL-006				☐	☐		
DL-007				☐	☐		
				☐	☐		
DL-XXX				☐	☐		
Mapping period starts at (date/hour):							
Mapping period ends at (date/hour):							
Checked by:				**Date:**			

Note: The mapping procedure is fully described in the companion Technical Supplement: Temperature mapping of storage areas. Table 8 is taken from Annex 1 of that supplement.[9]

[9] The temperature mapping supplement recommends that mapping should be carried out in both the hottest and coldest months. However, for the purpose of OQ, only one mapping exercise is required.

2.5.7 Power failure test

The power failure test relies on the same data logger set-up as the temperature mapping test. The objective of the test sequence is to establish and record:

- The length of time during which the installation can maintain the specified temperature range following a power failure – this is known as the *holdover* time.
- How long it takes the installation to recover within the specified range once power is restored.

The results of these tests are simply recorded – there is no deviation report. For cold rooms, freezer rooms and other large temperature-controlled stores[10] there are usually no set acceptance criteria to be met in this test. However, the test data are useful to the store operator for emergency planning and other purposes; for example, planning the installation and operation of standby generators.

Power failure test:

a. *Power Failure up to Temperature Excursion:* To do the Power Failure verification, the storage area and equipment is powered off, and the temperature inside the storage area is recorded continuously. When the temperature inside the storage area goes out of range, then the storage area and equipment can be powered back on, and the time period to recover within the specified temperature range is determined;
b. *Fixed power failure period:* In this version of the test the power is stopped for a predefined period – for example, two hours – regardless of whether or not the temperature inside the storage area exceeds the required temperature range. Power is then returned and the time taken for the storage area to recover within the specified temperature range is measured.

Because both these tests may trigger a temperature excursion, carrying them out when the store is full of TTSPPs can place stored products at risk. For this reason it is best carried out during OQ when the store is empty. Table 9 gives an example of a power failure test sheet.

[10] In settings with unreliable electricity supplies, holdover is an important performance feature of mains-powered freezers and refrigerators. For WHO prequalified vaccine refrigerators, the holdover time is laboratory tested and reported. See the WHO PQS website at: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

Table 9
Power failure test sheet

Data logger ID number	**Power off** Time temperature was within range (hh:mm)	**Power on** Time to recover to within range (hh:mm)	**Inspected by**	**Date**
DL-001				
DL-002				
DL-003				
DL-004				
DL-005				
DL-006				
DL-007				
DL-008				
DL-009				
DL-XXX				
Power turned off at (hh:mm):				
Power turned on at (hh:mm):				
Checked by:		**Date:**		

2.5.8 Writing the OQ report

As soon as the OQ assessment has been completed, prepare a report as outlined above in section 2.3.1. Pay particular attention to the following points:

- Make sure that all of the sections included in the OQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the OQ protocol.
- Transcribe any handwritten notes made by the OQ team into the relevant sections of the report.

- Specify the actions that need to be taken to correct the reported deviations and state the name of the person or organization responsible for completing these actions.
- List all members of the qualification team, and their designations.

2.6 Performance qualification

Do not begin the PQ stage until all of the deviations recorded during the OQ inspection have been corrected.

The purpose of PQ is to establish that the installation and all its systems and subsystems operate effectively and consistently when the storage area is *fully operational* (in use, loaded with TTSPPs). PQ is normally carried out immediately after satisfactory completion of the IQ and OQ stages. As previously noted, once the entire OQ and PQ process has been successfully completed and all deviations have been corrected, the installation can be signed off and fully released for routine operation.

A PQ inspection should:

- Check that all controllers and sensors are correctly calibrated.
- Carry out a temperature mapping of the storage area loaded as in normal operations. Record the results. See Technical Supplement: *Temperature mapping of storage areas*.
- Test and record temperature recovery following a door opening during normal operation.

2.6.1 Checking installed systems, subsystems and components

As with the IQ procedure described in section 2.4.2 and the OQ inspection in section 2.5.1, the PQ inspection and test tables and report should record the *specified condition* and the *as found* conditions and should confirm whether the as found condition is a *pass* or a *fail*. All *deviations* should be recorded, and the assessment results should be signed by the inspector and checked by the independent reviewer.

2.6.2 Temperature mapping – full

The temperature mapping exercise described in section 2.5.6 is repeated as for OQ, but with the storage area loaded normally with TTSPPs. The same arrangement of EDLMs should be used for the PQ mapping as for the OQ mapping.

2.6.3 Temperature recovery after door opening

The purpose of the door opening temperature recovery test is to establish that the temperature within the store can return to being within the specified temperature range within the specified time following a door opening event. The following test parameters should be observed:

- The same arrangement of EDLMs should be used as for the OQ and PQ mapping tests.
- The door-open period used for the test should represent actual door opening behaviour observed during routine operations. If there is a single door, the critical factor is the maximum observed length of opening. If there is more than one door, the critical factors are the length of opening, the sequence of opening, and whether more than one door needs to be kept open at the same time.

The acceptance criterion for this test is that the temperature recorded by all the EDLMs located inside the storage area should return to being within the specified temperature range (e.g. 2.0 °C to 8.0 °C within 30 minutes after the door(s) are closed at the end of the door opening test sequence). Table 10 shows an example of a door opening test sheet.

Table 10
Door opening test sheet

Data logger ID number	Time to return to within specified temperature range (min)	Compliance?		Inspected by	Date
		Yes	No		
DL-001		☐	☐		
DL-002		☐	☐		
DL-003		☐	☐		
DL-004		☐	☐		
DL-005		☐	☐		
DL-006		☐	☐		
DL-007		☐	☐		
		☐	☐		
DL-XXX		☐	☐		

Table 10 *continued*

Door(s) opened at (hh:mm):			
Door(s) closed at (hh:mm):			
Checked by:		**Date:**	

2.6.4 Writing the PQ report

As soon as the PQ assessment has been completed, prepare a report as outlined in section 2.2.1. Pay particular attention to doing the following:

- Make sure that all of the sections included in the PQ protocol have been completed, signed and dated.
- Record all deviations from the installation drawings and specifications in the deviation report section. Make sure that each deviation is cross-referenced to the relevant sections of the PQ protocol.
- Transcribe any handwritten notes made by the PQ team into the relevant sections of the report.
- Specify the actions that need to be taken to correct the reported deviations and state the person or organization responsible for completing these actions.
- List all members of the qualification team, and their designations.

The installation cannot be formally released for routine use until all of the deviations recorded during the PQ inspection have been corrected.

2.7 Specific requirements for small-scale equipment

Cabinet freezers and refrigerators are frequently used for storing TTSPPs in smaller facilities such as pharmacies and health-care facilities. This equipment may include domestic freezers and refrigerators,[11] vaccine freezers and refrigerators,[12] blood bank refrigerators and specialist pharmacy and laboratory refrigerators and freezers. Capacities can vary from as little as 10–15 litres up to 1000 litres or more for a large pharmacy refrigerator.

[11] Domestic refrigerators do not control temperature accurately and WHO specifically recommends that they should not be used for storing vaccines, many of which are damaged by freezing.

[12] See the WHO PQS website at: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

With the exception of domestic equipment, these products are thoroughly tested to meet the specific needs of the medical applications for which they were designed. However, the working environment in which such equipment is ultimately placed may expose it to operating conditions outside its design envelope – examples of such conditions include very high or very low ambient temperatures, humid tropical conditions, extended power cuts and the like.

Consequently it may be necessary to carry out an IQ,, OQ, PQ test sequence, or some subset of this process, to establish that a specific product is fit for purpose in the actual operating environment. In particular, some form of temperature mapping may be needed; this should definitely be done in the case of domestic equipment. In this case, EDLMs should be used to record temperatures at the top and bottom of the cabinet as well as at the rear and front. Door shelves should not be used to store TTSPPs because this zone is known to be subject to widely fluctuating temperatures.

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Revision history

Date	Change summary	Reason for change	Approved

Annex 1

Deviation and corrective action report form

Report number:	
DEVIATION DESCRIPTION	
Documented by:	Date:
IMPACT ASSESSMENT ON QUALIFICATION	
Does this deviation have sufficient impact on the qualification to require a corrective action?	Yes ☐ No ☐
Documented by:	Date:
RATIONALE FOR CORRECTIVE ACTION	
Documented by:	Date:
CORRECTIVE ACTION APPROVAL	

Name	Signature	Date

RATIONALE FOR CLOSING THE DEVIATION REPORT

Does corrective action resolve the deviation? (Attach all resulting test data sheets to this report)	Yes ☐ No ☐ Not applicable ☐
Can this deviation be closed?	Yes ☐ No ☐

Name	Signature	Date