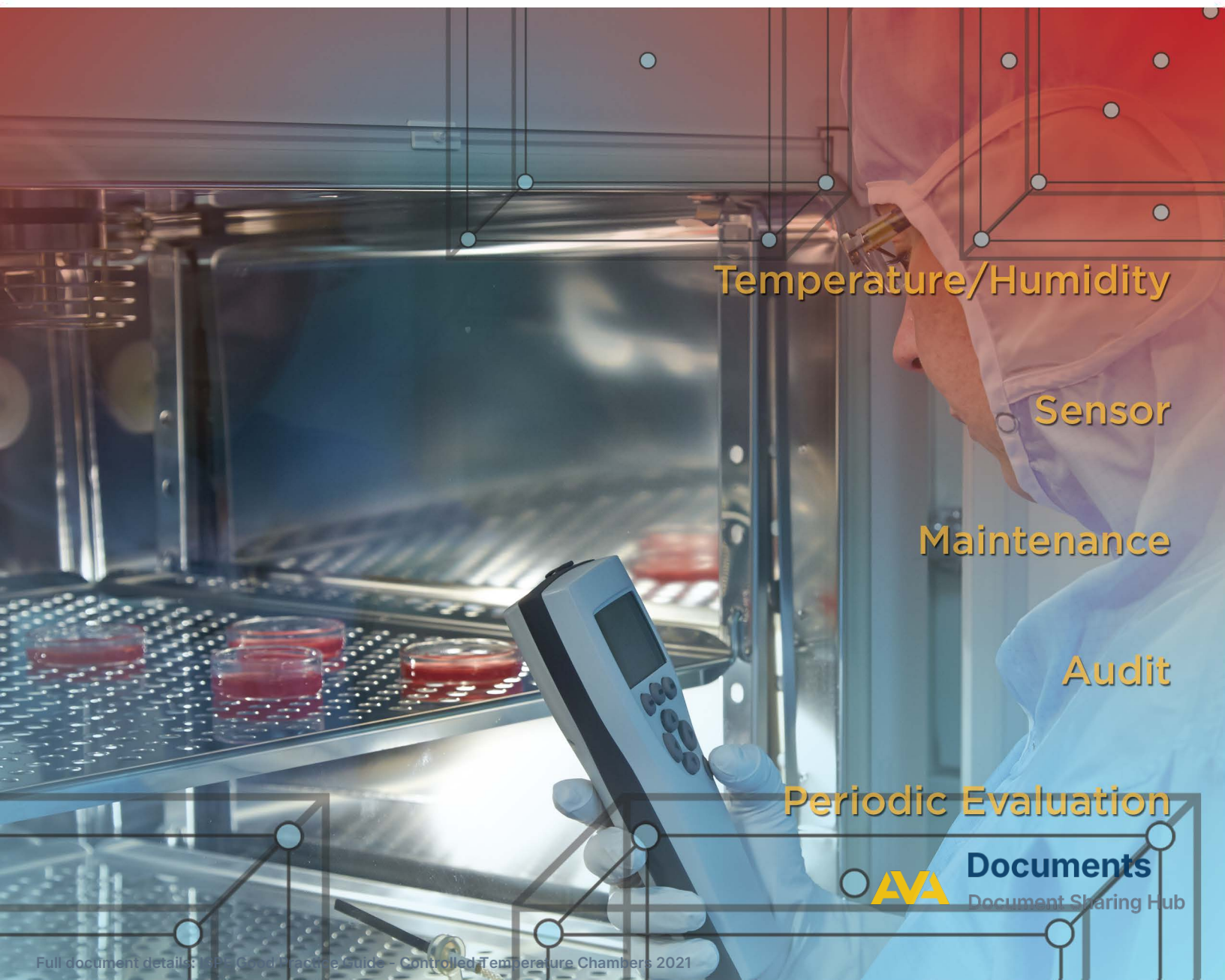


GOOD PRACTICE GUIDE:

Controlled Temperature Chambers

Commissioning and Qualification, Mapping and Monitoring

Second Edition



Temperature/Humidity

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Disclaimer:

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Preface

Global distribution of medicines requiring controlled temperatures has only increased in complexity since the first edition of this Guide was published. In order to meet changing industry practices, the second edition of this *ISPE Good Practice Guide: Controlled Temperature Chambers – Commissioning and Qualification, Mapping and Monitoring* was undertaken.

The primary purpose of this revision was to align with the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)*. Revising the Guide provided the opportunity to consider a periodic review frequency based on risk of failure to maintain uniform temperature and criticality of product stored rather than a standard, one-size-fits-all time span. In addition, the Guide was expanded to include ultra-low freezers, decommissioning a unit, and a discussion on using ocean reefers.

Together these improvements present a cost-effective way of demonstrating and maintaining compliance.

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Company affiliations are as of the final draft of the Guide.

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1 Introduction

A Controlled Temperature Chamber (CTC) is defined as a system, unit, equipment, or room in which the environmental conditions (typically temperature, sometimes temperature and humidity) of a chamber are controlled to meet specific user requirements.

ISPE Good Practice Guides are reviewed periodically to ensure alignment with industry best practices and other ISPE guidance documents. This *ISPE Good Practice Guide: Controlled Temperature Chamber – Commissioning and Qualification, Mapping and Monitoring* has been updated to align with the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [1].

The most significant changes are:

- Improvements to the commissioning and qualification activities resulting in more efficient processes
- Determining the periodic review frequency based on risk of failure to maintain uniform temperature and criticality of product stored

Additional revisions include:

- Expansion of freezer types to include ultra-low freezers and duration of storage needs
- Discussion on how materials of construction may impact cold rooms
- GxP storage facilities and warehouses descriptions
- Enhanced descriptions of monitoring systems
- High-level overview of decommissioning a unit
- Considerations for using ocean reefers (air-conditioned containers)

These revisions and other edits ensure that the Guide reflects current best practice and provides relevant guidance to industry, presenting a cost effective way of demonstrating and maintaining compliance.

Topics covered in this Guide include:

- Commissioning and Qualification
- Test Strategies
- Acceptance Criteria
- Qualification Approaches
- System Monitoring
- Periodic Evaluation
- Maintenance

- Decommissioning
- Packaged Transport Units

1.1 Purpose and Objectives

With the increasing complexity of global distribution for medicines requiring controlled temperatures, the *ISPE Good Practice Guide: Controlled Temperature Chamber – Commissioning and Qualification, Mapping and Monitoring* provides guidance on CTCs that operate under Good Manufacturing Practices (GMP). Topics include the definition of requirements (producing a user requirements document), design, purchase, commissioning (including temperature mapping), qualification, and maintenance of CTCs used to store and transport raw material, Active Pharmaceutical Ingredient (API), Work in Progress (WIP), and finished product. The approach presented is consistent with that described in the *ISPE Good Practice Guide: Cold Chain Management* [2].

1.2 Scope

This Guide provides guidance on CTCs operating under GMPs including:

- Purchased commercial off-the-shelf items, e.g., freezers, ultra-low freezers, refrigerators, refrigerated delivery vehicles, incubators, stability chambers, etc.
- Custom-built controlled temperature units, such as warehouses, walk-in cold rooms, walk-in freezers, etc.

This Guide does not include systems designed for heating/cooling of material such as blast freezers, although some of the concepts described may be useful when commissioning/qualifying these systems.

1.3 Benefits

There is an increased regulatory interest in cold chain driven by the growing number of products requiring controlled temperature shipping and storage, the complexity of the distribution network for the products, and governmental requirements for distribution of medicines.

This is reflected in the recent revisions to the related regulatory guidance (see Chapter 2). Utilizing this Guide provides a number of benefits in an area where there is little authoritative guidance, including:

- Provision of industry good practice for the temperature mapping of CTCs, considering the impact of load, and the use of the data to determine worst-case locations and number of monitoring sensors
- Development of test acceptance criteria
- A risk-based approach to practices for periodic review of system performance

1.4 Key Terms

Generally recognized temperature ranges are found in national codes such as USP <659> [3] and ICH Q1A [4].

Commissioning

A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end user, that results in a safe and functional environment that meets established design requirements and stakeholder expectations. [1]

Design Authority

Architect, engineering company, specialist supplier

Mapping versus Monitoring Probes

Mapping probes are located in the storage locations to confirm that all locations remain in the defined limits during operations.

Monitoring probes are the independent means of verifying that the system remains operating within the qualified range.

Qualification

Per the *ISPE Baseline Guide: C&Q (Second Edition)* [1], a process to demonstrate and document that the critical manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.

Rounding of Temperature Values

This Guide follows USP General Notices Section 7.20 Rounding Rules [5] when considering temperature values:

“When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1.”

Temperature Mapping

Temperature mapping is the process of measuring and documenting temperatures at multiple predefined locations within the storage location over a specified study duration to verify the capability of a controlled temperature chamber to maintain predetermined temperature specifications.

2 Regulatory and Industry Guidance and Standards

Regulatory guidance covering CTCs include:

- Health Products Regulatory Authority (HPRA)
 - Guide to Good Distribution Practice of Medicinal Products for Human Use [6]
 - Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances [7]
- European Medicines Agency (EMA), Guidelines of 5 November 2013 on Good Distribution practice of medicinal products for human use [8]
- Health Canada, Guidelines for environmental control of drug products during storage and transportation [9]

Information on calibration and traceability is available from national standards organizations.

Additional guidance includes:

- PIC/S Guide PE 011-1 to Good Distribution Practice for Medicinal Products [10]
- WHO:
 - WHO Technical Report Series No. 961 [11]
 - > Annex 9: Model guidance for the storage and transport of time and temperature-sensitive pharmaceutical products
 - > Annex 5: Technical supplements to Model guidance for the storage and transport of time and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9
 - > WHO Technical Supplement, Calibration of temperature control and monitoring devices
 - > WHO Technical Supplement, Qualification of temperature-controlled road vehicles
 - > WHO Technical Supplement, Qualification of temperature-controlled storage areas
 - > WHO Technical Supplement, Temperature and humidity monitoring systems for transport operations
 - WHO, How to Temperature Map Cold Chain Equipment and Storage Areas WHO/IVB/19.09 [12]
 - WHO Evidence Brief, Cold room temperature mapping studies [13]
- United States Pharmacopeia (USP):
 - <659> Packaging and Storage Requirements [3]
 - <1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products [14]
 - <1118> Monitoring Devices – Time, Temperature and Humidity [15]

- ISO 17025 – General requirements for the competence of testing and calibration laboratories [16]
- Taylor, J.L., Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products [17]
- Seevers, R. et al., The use of mean kinetic temperature (mkt) in the handling, storage and distribution of temperature sensitive pharmaceuticals [18]

Regulatory guidance for Good Distribution Practice (GDP)¹ is updated on a regular basis. There is normally a requirement to demonstrate that product is being stored in the appropriate conditions. This can be accomplished through mapping the parameters in the storage areas to confirm that all storage locations used in the CTC remain within the defined conditions for these parameters.

There are no standards written specifically for CTCs as used in the pharmaceutical and biotechnology industry. Available standards are written for environmental test chambers and stability chambers. Although the same principles may be applied, the details on how the systems are to be used in an operational environment should also be considered.

A list of the applicable standards known at the time of publication is provided below for reference:

Japan

- JTM K 01 Temperature and Humidity Chambers – Test and Indication Method for Performance [19]
- JTM K 03 Environmental Temperature and Humidity Rooms – Test and Indication Method for Performance [20]
- JTM K 05 High Temperature Chambers – Test and Indication Method for Performance [21]

France

- FD X15-140 Measurement of Air Moisture – Climatic and Thermostatic Chambers – Characterization and Verification [22]

Germany

- DIN 12880 Electrical Laboratory Devices – Heating Ovens and Incubators [23]

IEC

- IEC 60068 Environmental Testing Series [24]

CTCs used in the pharmaceutical and biotechnology industry are usually used for long-term storage (for testing, long-term environmental studies or stability) or for short-term Work in Progress (WIP)/distribution warehousing.

¹ China (PRC) and South Korea use Good Supply Practice (GSP) rather than GDP.

3 User Requirements Specification

A User Requirements Specification (URS) defines the user's functional requirements for equipment or systems. By specifying requirements in the URS but not how those requirements are met, the designer is given freedom to provide the optimum design solution to meet the requirements.

Aspects to consider in relation to stored material include:

- Unit capacity, i.e., quantity, nature of the material to be stored, and airflow within chamber
- Whether the unit is providing cooling or heating (i.e., preconditioning) of the stored material, and if so:
 - What criteria need to be met, e.g., maximum load size, specific heat capacity supply, temperature, heating/cooling time?
 - How long and how frequently is the door to load/unload the unit open?
 - Which environmental conditions are critical, e.g., light/temperature/humidity?
 - What is the condition the loading door is opening into, e.g., external conditions or conditioned space?

Qualification is intended to demonstrate through testing (verification) that the requirements specified in the URS have been met. Confirmation that the user requirements have been met should be traceable in the qualification documentation.

Appendix 1 provides a discussion of typical URS content and presents an example of a URS for a walk-in unit.

Note: Information included in specifications or the purchase order general requirements (such as manuals, training, spare parts) is not included in the URS to avoid duplication. The URS should be a simple concise definition of the user requirements supported by relevant company specifications and standards.

As stated in the *ISPE Baseline Guide: C&Q (Second Edition)* [1]:

"A statement of the URS may be contained in various forms, e.g., purchase request, functional specification, change request, or data sheet. For standard off-the-shelf or simple catalog systems, a statement of the URS may be a purchase order, vendor cut sheet, or catalog data."

It should be noted that if a purchase order or catalog cut sheet is used then compliance with company standards/specifications should be confirmed or deviations justified.

4 Types of Controlled Temperature Chambers

The equipment considered in this Guide is listed below and is not all inclusive:

- Refrigerators
- Freezers
- Ultra-low freezers
- Liquid nitrogen freezers
- Cold rooms
- Stability chambers
- Incubators
- Heated chambers

Transport reefer containers are discussed in Section 10.2.

Note: Generally recognized temperature ranges are found in national codes such as USP <659> [3] and ICH Q1A [4].

4.1 Freezers

Freezers are used, but not limited to, for the preservation of materials:

- Active Pharmaceutical Ingredients (APIs)
- Process intermediates
- Stability samples
- Laboratory materials
- Cell banks
- Vaccines
- Cell and gene materials

Freezers ranging from -25°C to -10°C [3] and ultra-low freezers with set points ranging from -20°C to -90°C are used. Lower values down to -140°C are required for cryopreservation.

Temperature uniformity in freezers is maintained within a qualified range to ensure product quality is preserved. Peak variation from set point could range from -7°C to +4°C but can vary from model to model.

Door opening recovery temperatures could be in the range of 10 to 30 minutes and are influenced by the provision of one or more additional inner doors, and physical configuration such as a chest freezer versus a front opening freezer. In general, the greater the difference between ambient temperature and the internal specified temperature, the longer the recovery time.

Peak temperature variation from set point, the door opening recovery temperature time, and temperature recovery time after a power failure should be defined in the user requirements.

Operation can be controlled via a temperature controller that maintains the locally configured temperature set point and provides a local audible/visual warning for out of range temperature excursions and power failures.

Chambers are usually equipped with the general freezer refrigeration components of:

- Compressor
- Receiver
- Condenser
- Evaporator
- Tubing
- Insulation
- Fan
- Control panel
- Structural support

The refrigerant compressors are usually hermetically sealed for integrity. The evaporator is typically a tube and fin design. The chamber control monitors interior temperature using a permanently installed thermocouple or Resistance Temperature Detector (RTD) (also known as a control probe). Typically, the RTD is adjusted at the factory based on the temperature at the geometric center of the chamber.

Temperature calibration requirements are specified in the user requirements so that the most suitable temperature detectors are selected.

The evaporator is usually located within the upper portion of the chamber interior and chamber temperature uniformity is obtained through natural (by convection or "passive") air circulation. There are several different designs available that include positive forced-air circulation to keep temperature uniformity stable in space and in time.

For units with an automatic defrost, the control actuates an automatic defrost cycle at a predetermined frequency (typically 6 to 72 hours) to minimize ice accumulation, or by activation of electrical heaters (in which case the evaporator fans are turned down).

The evaporator defrost generally occurs by redirecting the hot refrigerant gas into the evaporator coil for a short time to melt ice/frost accumulation. Depending on the manufacturer and model, the defrost cycle is terminated by:

- Elapsed time
- Evaporator coil temperature set point

- A combination of time and temperature

The timed defrost is adjustable to allow for the conditions of use (frequency of door opening, length of time for door opening, and exterior air humidity level at time of door opening), with the preference to have the defrost cycle occur outside of normal working hours. The defrost cycle can usually be adjusted.

Models with manual defrost are also available. The temperature uniformity in time offered by the two systems could be different.

The defrost cycle can also be initiated by a low suction pressure/super heating of the compressor.

These aspects relevant to defrosting apply also to equipment such as refrigerators and freezers.

For GMP applications these systems should be monitored. It can be difficult to calibrate the system control sensor, and the use of an independent system allows routine calibration and the flexibility to place the sensor in a location that measures the worst-case temperature. Location is determined from test results (see Section 5.4).

Remote connections could also be wireless.

Backup cooling systems using liquid nitrogen or carbon dioxide (CO₂) are available and could be included, if necessary, to increase the reliability of operation and mitigate temperature excursions during power failures.

4.1.1 Conditioning/Blast Freezers

Facilities may process large quantities of bulk product that need to be frozen from ambient conditions to a specified temperature, e.g., -70°C, prior to transfer into a -70°C storage unit. Dedicated conditioning freezers are needed to perform this function, as storage freezers are not capable of handling the large volume of product and significant temperature disparity without potentially compromising the temperature of the stored material. This type of equipment is outside the scope of this Guide.

4.1.2 Liquid Nitrogen Freezers

Liquid nitrogen freezers are used for storing material below -120°C, for example, cell banks. If materials are immersed into liquid nitrogen, they eventually assume the temperature of the liquid (-196°C). Materials stored in the vapor above the liquid become warmer as they are moved away from the liquid (up to -120°C).

It is thus important to define the purpose of the equipment. In the case of cryopreservation of animal cells or tissues, the required temperature will be lower than the glass transition temperature of water, that is, -130°C. The temperature of the vapor can be changed by varying the amount of liquid nitrogen in the chamber.

4.2 Refrigerators

Refrigerators are typically used to store material within a qualified range of 2°C to 8°C [3, 4]. The capability of the equipment to achieve temperature uniformity should be considered when assigning the chamber set point.

Operation is typically controlled via a temperature controller that is used to maintain the locally configured temperature set point, and may also provide a local alarm. The suggested set point is in the midrange at about +5°C to reduce the possibility of the refrigerator going out of range.

Refrigerators may be equipped with fans that cool via forced-air circulation and utilize a hermetically sealed compressor and refrigeration system. Alternatively, refrigerators may use a heat exchanger located in the storage space, relying on convection to maintain an even temperature. Refrigerators should have wire shelving or provisions to allow air circulation.

Refrigerators will usually automatically defrost the evaporator to maintain system performance. Evaporator defrost may be performed by redirecting the hot refrigerant gas into the evaporator coil for a short time to melt any ice/frost accumulation or by using electrical heaters.

4.3 Cold Rooms

Cold rooms are typically used for the storage of material within a qualified range of 2°C to 8°C [3]. Cold rooms should be equipped with a dedicated refrigeration compressor/condensing unit. The air-cooled condensing unit is usually located outside, for example, on the roof of the building. Building safety construction codes provide instructions and limitations when chillers are located indoors in mechanical rooms. Consider specifying redundant components (condensing units, compressors, etc.). Cold rooms may be provided with redundant condensing systems, each capable of handling the total system load.

There is a risk that water condensation may form on internal surfaces from the effect of air entering when the door is open. The level of risk is influenced by the amplitude of absolute humidity difference across the door and therefore, by the thermo-hygrometric conditions of the environment used to access to the cold room. In this case, the cold room could have, for example, a desiccant dehumidifier (usually based on a silica gel absorption process), or a low Relative Humidity (RH) airlock at the entry.

Walk-in cold rooms may be prefabricated, metal-clad structures with an insulated floor, walls, door, and roof panels, furnished and installed as self-contained units. These may include all essential refrigeration equipment, controls, air circulation, and other equipment necessary to reach the specified environmental conditions.

The interior of the system should be constructed of materials that are easily wiped down, will not shed, and are resistant to the cleaning chemicals used.

Depending how low the required temperature is inside the cold room and its location in the building (near exterior walls, slab on grade, adjacent to a walk-in freezer or walk-in incubator), the floor could range from an insulated concrete slab with urethane cement-based coating, with no slip, no porous properties to a floor with an insulation panel like the other five sides and a vapor barrier. The flooring could be required also to withstand loads of pallet traffic and portable cages.

The total thickness of the cold room floor could be an issue when revamping existing plants since access ramps may be needed. To mitigate this, solutions are available based on the use of high-density microporous insulation sealed under vacuum with optimized thermal performance, thus reducing the thickness of the floor required.

The water permeability of the floor and risk of frost heave under the floor can be solved by proper ventilation with heat using a low voltage electrical mat. A better option is to have a thin ventilation cavity (empty space) by PVC profiles or equivalent open to the cold room sides.

For negative temperature applications, to prevent the door seals from freezing due to air leaks from the external side, consider electrical tracing or equivalent methods.

Cold room control systems usually consist of a local Programmable Logic Controller (PLC) to monitor and control the temperature within the cold room. Within the main chamber, the temperature may be measured by temperature sensors placed in different locations. One sensor should be routed to the main controller for controlling interior temperature. The second sensor should be connected to a monitoring system for temperature trending and alarms; for larger units there may be multiple monitoring sensors.

Redundancy of temperature devices may be considered.

4.4 Stability Chambers, Incubators/Incubator Shakers

Stability chambers are designed to maintain a stable environment for incubating materials or holding samples by controlling air temperature near to ambient or warmer than ambient conditions [3, 4]. These may include cultures for microorganisms or cell culture and hybridization in production or quality control laboratories. The incubator may accommodate cell culture vessels from small tissue culture flasks to roller bottles and small spinner flasks.

A local controller should control system operation for process parameters such as temperature, humidity, and CO₂. Incubator shakers can also control shaker speed.

The technology adopted to obtain the heat transfer (refrigeration cycle, Peltier effect) will influence the temperature mapping criteria to adopt.

4.5 GxP Storage Facilities and Warehouses

This section refers to areas that may store API, bulk drug substance, bulk drug intermediate, bulk finished goods, combination products, packaged finished goods, and raw materials with temperature and/or humidity monitoring and control requirements. Long-term storage areas are where products or materials are stored continuously for 72 hours or longer.

Temperature and/or humidity mapping is performed to ensure that the facility can maintain the required temperature and humidity for the products/material being stored. Seasonal mapping is required for facilities that experience summer (hot) and winter (cold) temperatures affecting the room conditions or the operation of compressors/condensers if located outdoors.

For internal facilities that do not share walls or windows with external environments, seasonal mapping is not needed.

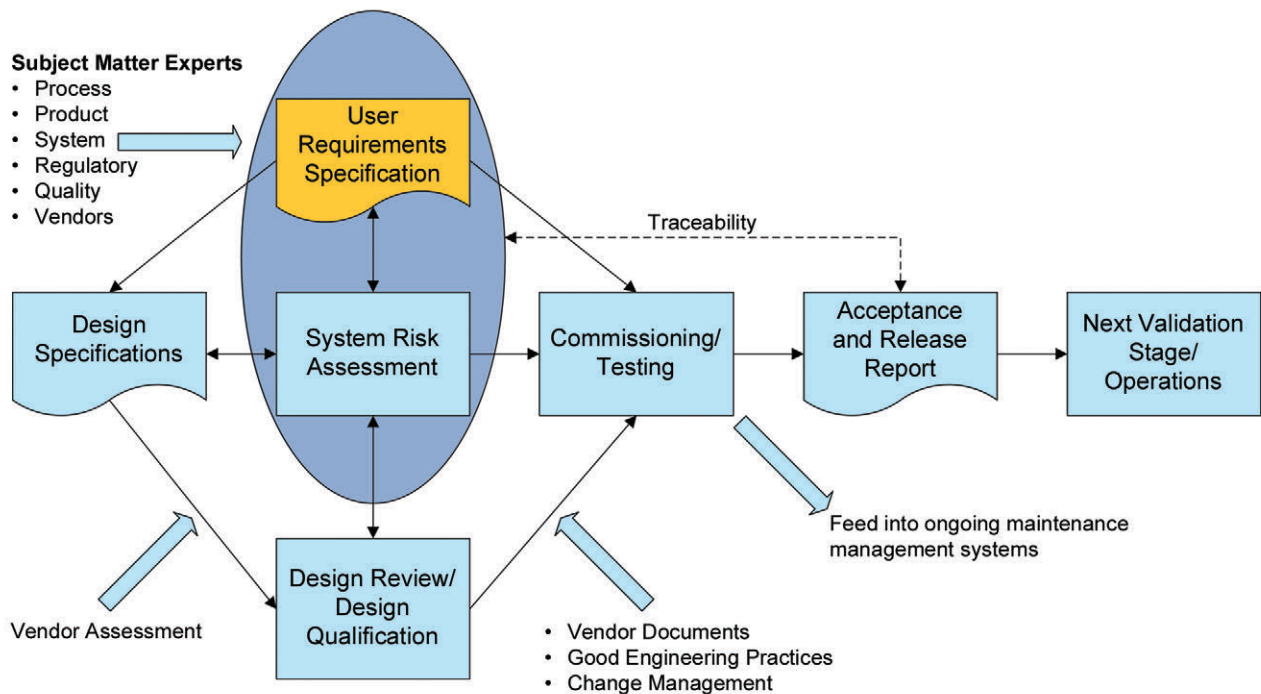
Facilities located in areas where the range of external temperatures is limited and the conditioning system provides only heating or cooling (so the air distribution pattern is consistent), mapping of only one season is necessary.

5 Commissioning and Qualification

This Guide describes a commissioning and qualification process aligned with the *ISPE Baseline Guide: C&Q (Second Edition)* [1]. This process is intended to be efficient, compliant, and ensures that the quality risks and risk controls associated with a system are understood. The process described (see Figure 5.1) is scalable to suit the complexity of the project and system.

Figure 5.1: Relational Overview of the Process [1]

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5.1 Commissioning Planning

The testing strategy and the acceptance criteria should be documented in a change control record, commissioning plan, or test strategy document prior to test execution. The objectives are to:

- Ensure consistency of approach and testing across the project
- Define the scope of the verification to be used to provide documented evidence that the system is installed and operates to meet specifications
- Provide clear and early definition of deliverables and handover requirements
- Ensure verification testing incorporates the Critical Design Elements (CDEs)/Critical Aspects (CAs) identified in the System Risk Assessment (SRA)
- Define roles and responsibilities
- Define safety considerations

- Describe the process to be used for the review and approval of test method statements
- Describe the process to be used to address test discrepancies
- Define the Engineering Change Management (ECM) system
- Define the acceptance criteria/expected results*
- Ensure full transparency on progress metrics (test execution and productivity)
- Define the progress reporting approach
- Define the training approach for maintenance users and end users
- Define witnessing requirements and associated test notification procedures
- Describe the process for handling and retaining raw data
- Describe the format and content of the commissioning report (e.g., is a particular documentation practice required?)
- Define responsibilities for operating and maintaining a facility during commissioning, until it is handed over/ released to the end user
- Identify who is responsible for maintaining the system and operating log from start-up to hand over/release to the end user
- Define how the system is handed over/released to the end user

* Acceptance criteria are “non-negotiable” test results. Expected results may be acceptable across a broader range, or are results taken for reference purposes.

CTCs typically use commercially available controllers, which are usually commissioned. The qualified independent monitoring system confirms the correct function of the system.

5.1.1 Roles and Responsibilities

Company structure, project size, and contract philosophy define the roles and responsibilities. It is important for a successful project that roles and responsibilities are discussed and defined with the final decisions documented and published to the team, usually through documents such as the commissioning or qualification plan.

Typical roles and the responsibilities involved in a small project are:

Construction Manager

The construction manager is responsible for delivering the project (which may be or include a CTC) usually to the stage of mechanical completion, meeting specifications and established quality standards. The scope may also include commissioning and qualification.

Commissioning Lead

The commissioning lead is responsible for coordinating and managing commissioning activities and allocating resources. This role takes ownership of the activity and ensures the supporting documentation is developed and completed to defined documentation standards to meet the schedule. The commissioning lead is responsible for the accuracy of the content. The commissioning lead is usually responsible for communication and coordination between functions, monitoring the walk down and punch list as well as the commissioning and qualification process.

System Owner

The system owner is responsible for the operation and maintenance of the system after commissioning and qualification. This role reviews and approves the commissioning and qualification plan, the verification documentation, qualification documentation, and associated summary reports. The system owner has decision-making authority and is accountable for compliance to the URS. During the design phase, the system owner should have oversight of the design process, and during construction they should determine the acceptance of the “as-built” system at mechanical completion, usually with the support of a technical lead.

The system owner may be a site representative, a member of the project team, or the role may be delegated to a Subject Matter Expert (SME).

Commissioning Staff

The commissioning staff are involved in the verification activities (execution, documentation, and expertise). Commissioning staff may be company employees or contractors. The work can be divided into two categories:

- Site activities: Verification of the completion of the systems presented by the construction team or manufacturer, and perform job safety analysis, installation and operational verification, submission of punch items, and training of the maintenance team
- Office activities: Preparation of the commissioning test documents, update construction documents as redlined during the commissioning phase, communicate executed protocols to the team, perform archiving

Owner Technical Services (SME) and/or Validation group

Technical support is provided to the system owner where necessary to ensure company specifications and standards are met, the design is robust, the installation is completed following specifications, and the technical content of the installation and operational verification are appropriate.

Validation Group

Although the role varies depending on the company organization, typically the validation group acts as a representative of Quality, ensuring compliance with company procedures, documentation standards, etc.

Training

This role trains the staff designated for specific roles who do not have the appropriate experience or training, based on the role requirements or specialist subcontractors used. Training may also be required for personnel conducting specific commissioning tests to ensure that the tests are carried out correctly and safely.

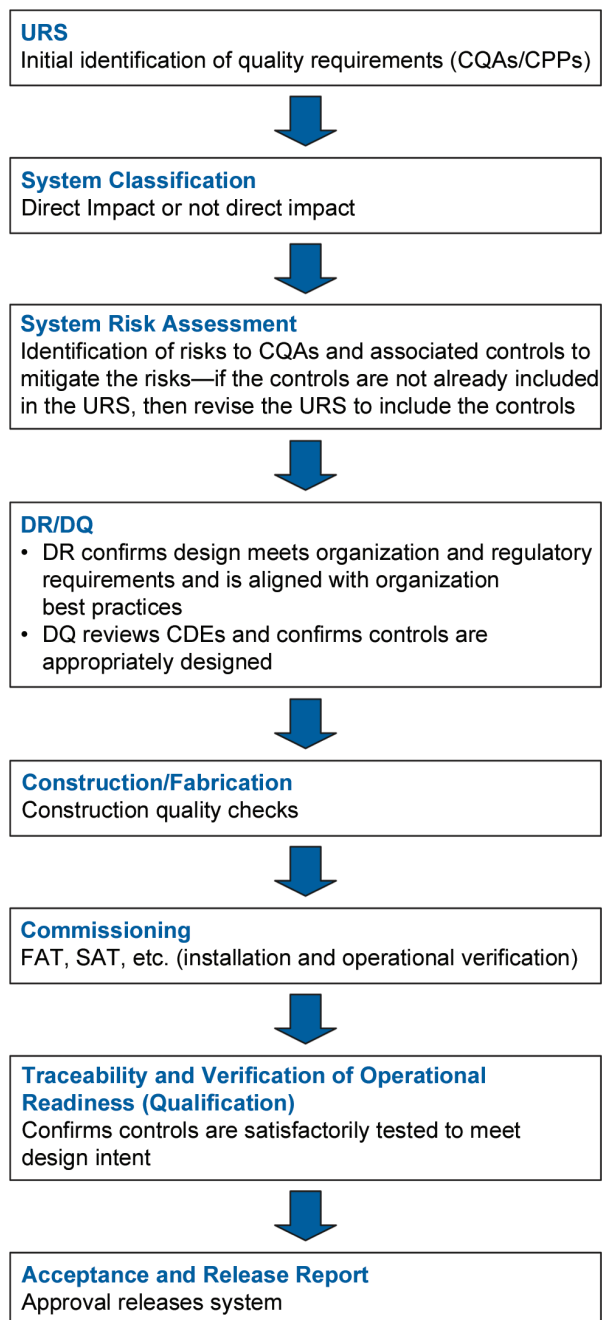
5.1.2 Process Overview

A diagram showing the process workflow is shown in Figure 5.2.

Notes:

- The construction/fabrication stage is not required for a standard off-the-shelf or catalog system, such as a freezer.
- The diagram is simplified and does not include ECM.

Figure 5.2: Process Workflow [1]



Improvements suggested in the *ISPE Baseline Guide: C&Q (Second Edition)* [1] have been incorporated into the process workflow descriptions in this Guide.

For a project the system boundaries should be defined, so that the scope of work for commissioning and qualification can be defined, together with the relationship of associated systems, such as independent monitoring systems, smoke detection, and fire protection systems.

5.1.2.1 User Requirement Specifications

The user must define their requirements (see Chapter 3). Typically, this requires collaboration of the user and the Quality Unit to produce a concise document that contains the requirements but does not repeat specification or contractual details.

The requirements may be defined in a URS – see the example in Appendix 1. The URS should be supported by relevant company specifications and standards.

For simpler systems a purchase order or catalog cut sheet may be used provided the quality critical aspects are defined with the associated acceptance criteria. When using a purchase order or catalog cut sheet, compliance with company standards/specifications should be confirmed or deviations accepted.

5.1.2.2 System Classification

Using the same terminology as the *ISPE Baseline Guide: C&Q (Second Edition)* [1], systems are classified as:

- Direct impact systems – are commissioned and qualified
- Not direct impact systems – are commissioned

The process descriptions in this CTC Guide are direct impact systems. How to determine the classification of a system is discussed in the *ISPE Baseline Guide: C&Q (Second Edition)* [1].

The same principles can be applied to not direct impact systems up to and including commissioning, except for Design Qualification (DQ). Usually a commissioning summary report is produced closing out the activities, confirming that the installation and operation meets the specifications, and closing out any engineering changes.

With an experienced project team, systems are often informally classified in order to help define the documentation strategy, and the classification formalized in a commissioning and qualification strategy and/or plan.

5.1.2.3 System Risk Assessment

For walk-in cold rooms, freezer systems, and warehouses, it is worth developing the SRA. Note that the independent monitoring system is typically qualified separately because it is not the same system as the CTC system. For simpler systems, such as off-the-shelf or catalog refrigerators and freezers, it may be appropriate to use a standardized approach.

The timing for the initial risk assessment can be defined by the project team. The assessment is used as an engineering tool until the final revision is completed based on the Issue for Construction (IFC) design. Then the assessment and summary report becomes a GMP document, and managed as such.

Companies may have their own risk assessment approach. The SRA process described below is the approach proposed in the *ISPE Baseline Guide: C&Q (Second Edition)* [1].

- “A small team develops an initial baseline draft that includes development of the process description and

- *identification of design and procedural controls*
- *A broader team reviews this initial baseline draft, making any necessary revisions to ensure the information is correct and no risks or controls have been omitted, and assigns the system risk profile*
- *As a general guide, the initial session by the small team and the review session by the broader team should not exceed more than a few hours each if the preparation work is complete and teams with the correct level of expertise are used.*

The initial draft can be completed at the time the project deems appropriate and is a Good Engineering Practice (GEP) document that can be used to assist design development. It becomes a GMP document when it is revised to reflect the final approved design.”

“Developing the Baseline Draft

The small team that develops the initial baseline draft should consist of the following:

- *Experienced facilitator to guide the process*
- *Quality Unit representative*
- *Process/system SME (may be one SME or could additionally include a system vendor representative)”*

“Performing the System Risk Assessment

After the initial baseline is completed, a broader team reviews the document and determines the risk profile. This review team generally consists of representatives from a broader group with different experiences to provide a balanced perspective; this team could include:

- *Operations (Production)*
- *Maintenance*
- *Engineering*
- *Process development*
- *Vendor representatives*

Note: *The time taken for the review generally increases with the number of people in the team, thus maintaining a balance between experience and the number of team members is important. Prior to determining the risk profile, the team identifies the sources of the risks (potential failure modes) along with design aspects and/or procedural controls that would mitigate or eliminate the risk. Risk profiles are assigned per definitions shown in Table [5.1].”*

Table 5.1: System Risk Level Definitions [1]

Risk Level	Definition
Low	Considered acceptable with no actions needed. The likelihood of the risk occurring with the defined controls operating is considered low, and the detection is robust.
Medium	Normally considered unacceptable and requires mitigation through design (CAs/CDEs) and/or procedural controls. However, the SME reviewers may consider a medium risk as acceptable for the specific process/system and decide to accept the risk.
High	Considered unacceptable and requires mitigation through design and/or procedural controls. In certain situations, the SME reviewers may determine that these controls are not appropriate, e.g., implementation costs outweigh the incurred costs if the risk occurred, operational challenges, or other reasons. The SMEs may recommend acceptance of the system with the high risk; in this case, the assessment needs to be accepted by high-level management.

Note: The risk level is defined considering the overall process; thus, if the process is changed, the System Risk Assessments may need to be reviewed/updated. This aspect should be addressed through change management.”

The *ISPE Baseline Guide: C&Q (Second Edition)* [1] adds:

“Determination of the risk profile should also be based on the SME’s experience with the process/system. While defining the risk of the failure or hazard occurring, the SME should consider that the controls listed are in place and operating as intended.”

The procedural and design controls (CAs and/or CDEs) defined during the SRA are considered part of the system requirements and should be included in the URS. If a URS is not being used, they can be added to the C&Q plan, or, if a traceability matrix is used as a tool to manage the C&Q execution process, the CDEs could be added to the traceability matrix only.

Use of the System Risk Assessment

The strategy using the SRA should be defined and incorporated into the relevant document, for example, change control or C&Q plan.

There are many ways that the SRA can be used, such as determining the lowest risk system as part of bid analysis, or as a tool to assist during design development, to ensure that the final design has an acceptable risk profile.

For standard systems there may be no value in completing a draft early in a project, apart from early use of available resources.

A typical process for a complex system is:

- Complete the initial SRA

As the design progresses the SRA can be reviewed and revised to suit the design, to ensure that it has an acceptable risk profile, and the design review process started.

Once the design is complete:

- Complete the design review/DQ

Completing the SRA ensures that the team understands how the system operates knowing the associated risks and risk controls (CDEs). The SRA ensures that the proposed system design has a suitable risk profile.

Completion of the alarm table using the data from the assessment helps define the system critical alarms/instruments. Note that the critical alarms typically come from the independent monitoring system.

A model risk assessment is described in Appendix 5.

5.1.2.4 *Design Review/Design Qualification*

Design Review

Based on the documents provided (for example, the URS and company standards/specifications), the design authority/supplier proposes a design or an off-the-shelf or catalog system that meets the requirements. The proposed design is reviewed by company SMEs to:

- Ensure that the user requirements and company design standards and specifications are understood and incorporated into the design documents
- Determine compliance to quality, business, health, safety and environmental, national and local codes, operations, maintenance, project, and technical requirements
- Incorporate lessons learned from previous projects into the proposed design to ensure that it is robust and will perform reliably, and that the performance can be documented
- Confirm appropriate integration with available utilities
- Ensure that CAs are met
- Ensure all stakeholders have the opportunity to review the design
- Ensure that preferred suppliers have been specified if applicable
- Ensure that the design proposed is cost effective, i.e., that design options, lifecycle costs, and risks have been identified and addressed

The process is typically iterative, with the reviews conducted as the design is developed from concept to detailed design. It is easier and more cost effective to change a design before it is constructed than during or after construction, and therefore, there is less impact on capital cost and schedule. As the design develops, input from all interested parties should be considered to avoid later changes.

For systems that may affect product quality, it is a recommended practice to split design reviews into two categories:

1. Engineering or technical reviews
2. Quality (GMP) focused reviews (DQ)

It is recommended that the review considers both aspects to improve understanding of the design for all parties.

To facilitate the process companies may develop and utilize knowledge capture systems such as:

- Design review checklists
- Design guides that define the preferred way of designing a given system type

These approaches should ensure that organizational experience and preferences are both captured and considered. They should be written so that they do not preclude novel concepts.

The review method used should be defined and agreed upon. The method and participants may vary depending on the system type. For complex systems such as a warehouse and the associated HVAC system, the use of a multidisciplinary team to ensure that key viewpoints are considered is recommended. For simpler systems such as an off-the-shelf or catalog freezer, a single review with the appropriate SMEs may be sufficient.

Actionable items from the design review should be implemented through drawing and specification changes. The means of tracking these should be defined, such as by an action items log or assigning the relevant SME with responsibility for tracking and confirming that the items have been addressed. This should be a formal process for a direct impact system.

Note: During the design review phase documents relevant to the areas surrounding the chamber and to the utilities serving it (e.g., hot water, chilled water, glycol (heat transfer fluids), electricity, floor loading limits based on fully loaded CTC with fork lift, the impact on HVAC and air balancing for the surrounding area) could be included in the review in order to properly understand the interaction between the CTC and the rest of the facility. This will help to ensure that the overall design is robust. From the commissioning perspective, the design review also allows the commissioning team to become familiar with the project and to verify that the design has adequate provision for the tests required, as defined in the equipment specification and URS.

Design Qualification

For direct impact systems, at a specific point in the design process (usually at the end of detailed design) DQ is performed to verify that the project design to date is fit for use. As with design review, DQ should focus on two main areas:

- GEP
 - Does the design satisfy user preferences as expressed in the user requirements?
 - Can the design be constructed, commissioned, operated, and maintained?
- GMP
 - Does the design meet the quality CAs/CDEs as expressed in the user requirements?
 - Is the design aligned with the SRA?
 - Does the design meet regulatory expectations?

This scope allows the conclusion that the design is fit for its intended use. This may be a very simple statement for an off-the-shelf or catalog type system, confirming that it addresses the quality CAs/CDEs. The GEP aspects are typically addressed through the design review process.

It should be noted that regulatory guidances expect a design review/DQ. ICH Q7 [25] suggests a design review and the EU Annex 15 [26] and PIC/S Annex 15 [27] state:

“Design qualification (DQ)

The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.”

5.1.2.5 Construction Documents and Construction Support

After the detailed design is finished, the design team should complete bid documentation, resolve construction questions, and perform on-site construction reviews. Engineers also may be involved in activities related to the receipt and installation of equipment and systems to verify that they were delivered and installed in a manner consistent with the design. This approach of integrating installation verification with construction is efficient, although it requires robust ECM to ensure that at the end of construction the documentation accurately reflects the installation.

System Risk Assessment Completion

Once the design is finalized and has been accepted (i.e., completed design review/DQ), the SRA can be finalized, as the design controls are defined. The risk assessment and summary report are typically approved by the system owner or SME representative and the Quality Unit.

Engineering Change Management

It is critical to ensure that:

- Any proposed changes to the approved (design review complete, DQ approved) design are acceptable to the design authority (as they are usually responsible for code compliance)
- The documentation at the completion of commissioning accurately represents the installation, and operation of the system.

In order to do this, an ECM system is required to ensure all proposed changes are considered and accepted where appropriate. It should cover the project from the approval of the design until qualification is complete, when the site change control process takes over:

- Site ECM for commissioned systems
- Site quality change control system for qualified systems

5.1.3 Commissioning

Note: This section considers the CTC. For guidance on commissioning and qualifying the independent monitoring system, refer to the appropriate ISPE GAMP guides [28].

The science and risk-based approach to commissioning and qualification uses the engineering documents to provide the documented evidence that the system is installed and operates to meet the design specification (i.e., is commissioned). The format and naming of these varies depending on company practice. The terminology used in this Guide is:

Installation Verification: Documentation of installation verification includes a record of the major components, confirmation that the system has been installed per manufacturer's recommendations, calibration has been conducted as required by the specifications, and confirmation that the specified utilities have been correctly connected.

Operational Verification: Documentation of operational verification provides evidence that the system operating temperature ranges (Critical Quality Attributes (CQAs)) meet the specifications during simulated operations.

As well as the temperature mapping and testing described below, the normal functions of the system automation should be verified, for example:

- Power failure recovery

- Refrigeration system failure operates the standby refrigeration system
- Engineering monitoring system alarm remote notification systems operate

Note that the operational verification of the independent monitoring system and the associated functions are covered in the documentation associated with that system.

5.1.3.1 *Challenging the Area with Operational Activities*

The area being mapped should be challenged with specific known operational activities during the thermal mapping process. These activities should simulate normal processes and functions that occur during routine operations, such as opening interior doors, opening exterior doors (receiving dock doors, shipping dock doors), running equipment (e.g., thermoformers, stretch wrappers, forklifts, conveyors), where there is a potential impact to the conditions. By performing these functions and operating equipment during the execution of the mapping studies, cause and effect relationships can be identified for the thermal profile.

- Quality-related alarms should be tested and captured in the calibration program, to ensure that the alarm function is tested on a periodic basis
- Perform open-door testing where applicable (simulating operations)

Open-Door Recovery Test

An example of a typical operational activity is to examine recovery time for the internal chamber temperature after opening the access door and simulating loading/unloading. It is recommended to determine the time that the chamber door may remain fully open before the monitoring sensors show that the conditions are no longer within the acceptable range. This test can also help to determine how quickly the temperatures recover and return to the normal operating temperature range. For an open-door recovery test for a new CTC, it is recommended to:

- Use a minimum (simulated) load with minimum thermal mass or no load in the storage unit (i.e., no thermal mass stored is the worst case for this test, as adding thermal mass slows the rate of temperature rise)
- Locate temperature sensors as recommended for thermal mapping (with special attention to the sensors located in proximity to the storage locations nearest the door being tested)

It is recommended to set the data acquisition rate to < 1 minute intervals on the mapping system for this test, because of uncertainty in the time that the test may take. Generally, there are no specific acceptance criteria for this test unless a recovery time is specified in the unit manufacturer's specifications. An open-door recovery test should be performed as an integral part of the mapping study to enable acquisition of the mapping data showing the potential impact of the loading/unloading activities.

Note: For larger walk-in CTCs fitted with vinyl curtains or an airlock, the units may be able to maintain the internal conditions (temperatures) indefinitely, as the impact of passing through the curtains is short term and has a negligible impact on the temperature. Vinyl curtains should be well-fitted, rest on the unit walls, and sit just clear of the floor.

- Temperature mapping should be conducted on an empty chamber for no less than 24 hours
- Where there are duty/standby systems, both should be tested
- Temperature study should be conducted on a "loaded" chamber for no less than 24 hours
- Mapping sensors should be located as defined in the test strategy document
- Test records should include a diagram showing the mapping sensor placement

- Perform power loss temperature rise/recovery testing where applicable (an engineering test)

Power Outage/Thermal Degradation Test (Recovery from Power Failure or Power Interruption)

Another type of test that may be helpful from a business continuity, disaster recovery, and operational perspective for a refrigerated unit is a simulated power outage test. This test measures the amount of time the CTC remained within the desired temperature range once electrical power is turned off.

Note: Although it is expected the CTC will have redundant and backup power supplies, the results from this test provide data to define how quickly materials need to be moved to another location if the backup power systems failed, or if maintenance requires shutting off all power supplies. Doors to the storage chamber should remain closed during this test.

For a power outage/rate of temperature rise (and subsequent recovery) test for a refrigerated CTC, it is recommended to use a minimum (simulated) load with the minimum thermal mass or no load in the CTC.

There is another test that is recommended as a commissioning activity before the storage unit is put into use, if possible, with the mapping sensors in place, and the data acquisition rate to ≤ 1 minute intervals for this test, because of uncertainty in the time that the test may take.

Once power is restored to the CTC, the amount of time required for the unit to return to the required temperature can be of value for operational considerations for recovery from a disaster, or after a maintenance activity (i.e., elapsed time for recovery of temperature sensor(s) from the time when power is restored until the last temperature sensor(s) returned to the acceptable range). If recorded from an ambient temperature condition, this time can be a useful overall reference of the system's cooling capacity.

Generally, there are no specific acceptance criteria for this test unless a recovery time is specified in the unit manufacturer's specifications.

- Cover system defrost where applicable – it is typical to cover multiple defrosts, usually three to ensure the worst case is included (typically with clean coils so that there is a maximum heat loss to the surrounding space; where there are duty/standby systems both should be tested)
- There should be a record of all adjustable set points

Note: The level of liquid nitrogen or CO₂ is maintained at its set point (liquid nitrogen or CO₂ freezers)

The tests may be in different document or sections of a single commissioning document, and as part of Factory Acceptance Testing (FAT) or the Site Acceptance Testing (SAT).

Note: The test record should include a list of the settings used for any adjustable set points.

These tests will commission the system, as shown in Figure 5.2. The additional activities required to qualify the system are also shown.

5.1.3.2 Preoperational Safety Checks

This phase is intended to eliminate as many risks as possible regarding the safety of personnel during commissioning and operation.

A section of the commissioning report (or site acceptance test) should describe and document the appropriate procedures.

Procedures such as the “lock out/tag out” can determine that utilities, e.g., chilled water, gas, steam, and electrical power, are provided to the system once the following are available and documented:

- Conformity of the electrical system included in the CTC system and correct settings, e.g., earthing (grounding), overloads/fuse ratings
- Evidence of pressure test of utilities lines
- Testing/certification of safety devices, e.g., pressure release valves, emergency lighting
- Door release mechanisms
- Freezer heated air vents
- Presence of pressure/temperature safety release devices (with right settings)
- Emergency escape routes
- Required personal protective equipment

5.1.3.3 Safety during Commissioning

There may be a separate project safety plan for a project or a job safety analysis covering all phases of commissioning that should be prepared by the personnel who will execute the site activities. The analysis should describe the potential risks, their probability, and should identify protection devices. Operators or technical personnel should be informed about the outcome of this analysis when receiving permission to execute commissioning activities. Information about scheduled activities and related risks should be provided to other personnel that may be in the area at the same time.

The job safety analysis should be reviewed by the personnel responsible for safety. An example job hazard analysis template is provided in Appendix 7.

When judged appropriate, the testing area or room should have signs informing personnel of risks or forbidding access.

Additionally, the project typically has a waste handling strategy or plan. [29]

5.1.4 Documentation Standards

The documentation practices used for engineering documentation (preoperational documentation) should follow a specified standard, which typically is not as detailed as the requirements for a GMP record (such as a batch record).

The *ISPE Baseline Guide: C&Q (Second Edition)* [1] states:

“Testing and verification documentation are usually written in the local language. Summary documents are generally in English to facilitate regulatory review.

The use of forms/templates is encouraged to promote consistency. Forms/templates can be approved once when created and then utilized multiple times without pre-approval if the relevant content is not changed. Where this approach is used, there should be a procedure to ensure that the form/template used for data entry is current at the time of use.

When forms/templates are used, the SME should review the form to ensure that it includes all of the required testing for the system being verified; if additional tests are required, the form/template should be supplemented with additional testing.

Test scripts may be approved individually and assembled into a test plan/report. If test data sheets are used to supplement test scripts, they should be approved in accordance with the requirements defined in the test plan.

The test procedures should be clear and unambiguous such that the results are repeatable and reproducible, as explained below:

- *Repeatable: The same result would be achieved if the same procedure is repeated by the same trained and qualified personnel.*
- *Reproducible: The test procedures should be performed the same way each time and the same result would be achieved by different trained and qualified personnel.*

The test document should indicate the order that the cases are to be executed. Acceptance criteria needs to be established and it should be clear that the tests demonstrate that the acceptance criteria have been met.”

Documentation should be completed following the ALCOA+ principles so that the test and inspection records are:

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate
- Complete
- Consistent
- Enduring
- Available

5.1.5 Discrepancy Resolution Process

Commissioning test failures that can be corrected through adjusting the equipment may be addressed in the commissioning test document, with an explanation and a retest record added for approval by the assigned SME.

Commissioning test failures that require system modifications should be noted as discrepancies and addressed using ECM. Impacted documentation should be revised to reflect the installed system.

5.1.6 System Risk Assessment

The SRA records the system CQAs, process parameters, and the associated CDEs (design risk controls) and procedural risk controls for hazards that could impact them. The scope of the Installation Verification (IV)/Operational Verification (OV) is determined by GEP. The SRA defines the CDEs and related acceptance criteria that are tested during commissioning.

Note that for simple systems an SRA may not be required.

5.2 Qualification

The traditional approach delivers the following C&Q documents (note the list only includes documents that would be impacted by the change in strategy).

By Engineering:

- Commissioning test, inspection and set up documents (documented evidence that the installation and operation meets the specifications)
- Commissioning summary report

By Validation:

- Installation Qualification (IQ) – documented evidence that the installation meets the specifications
- Operational Qualification (OQ) – documented evidence that the system operation meets the specifications
- Performance Qualification (PQ) where applicable
- Qualification Summary Report

Adopting a science and risk-based approach provides benefits not only in terms of reducing the number of documents, but also results in a risk assessment that provides an understanding of the quality risks associated with the system.

By Engineering:

- IV – documented evidence that the installation meets the specifications
- OV – documented evidence that the system operation meets the specifications

By Validation:

- SRA
- Commissioning and Qualification Summary Report

The commissioning and qualification summary report includes:

- Verification that installation and operation meets specifications
- Verification that the CDEs (design controls) identified in the SRA are installed and operate in accordance with the specifications by cross-referencing the relevant commissioning test documents
- Verification that the procedural risk controls described in the SRA are implemented in the operational SOPs
- Verification that the system is incorporated into the maintenance and calibration system
- Verification that staff are trained on the operational, maintenance, and calibration SOPs
- Verification that a spare parts list and associated consumables are available as appropriate

5.3 Handover and Release

Handover/release usually represents turnover of the system to the end user, with the handover of operation and maintenance. C&Q activities are usually completed. (The timing of the handover may be defined differently on a case-by-case basis according to specific contract stipulations).

There should be a documented record confirming that the functionality and operation of the system is acceptable and commissioning can be considered complete. The *ISPE Baseline Guide: C&Q (Second Edition)* [1] suggests that handover/release of the system to the end user is through the approval of the C&Q summary report.

A punch list (snag list) is typically used to manage completion of the system to meet the specifications. Major items on this list would prohibit handover; however, other items that can be resolved following handover are generally accepted. These items should be included on an action list to facilitate tracking to completion after handover. Typical categories used for a punch list include:

- Items that affect performance – to be addressed prior to handover
- Items that affect safe operation of the equipment – to be addressed prior to handover
- Items that block next activities/verifications – to be addressed prior to handover
- Minor items that do not impact operation – to be addressed after handover
- Desirable changes/improvements – to be addressed after system handover/release through the change control system

Following handover, responsibility for operation and maintenance of the system is transferred to the end user and the maintenance team. Appropriate operation and maintenance procedures should be established.

5.4 Calibration Strategy

The calibration strategy needs to be defined to ensure the requirements are met before testing is completed in operational verification.

There are operational benefits to be derived from a considered calibration strategy, for example:

- Many of the instruments on the refrigeration system can only be calibrated when the system is emptied for major maintenance; therefore, they are calibrated following the manufacturer's recommendations.
- The control sensor can be verified at a single point, as the control functions are usually based on whether the system is above or below the operating set point. If variable set points are used, for example in an incubator, then the sensor calibration needs to cover the working range.
- Calibration of the monitoring sensors should encompass the operating range and ambient conditions. For example, if the storage condition is 2°C–8°C, the calibration low point should be lower, for example below 0°C, and the high point must be above ambient room temperature, for example above 25°C. This is necessary to ensure that any excursions from the storage condition can be properly investigated. Excursions below the storage condition may present a different risk to those excursions above the storage condition. For example, freezing the load may represent a catastrophic risk to the product. The calibration strategy needs to account for this; otherwise temperature excursions may not be adequately investigated. This system provides the quality record of the storage conditions.
- Ensures that quality-related alarms are tested on a periodic basis; every 2 years is suggested.

5.5 Test Strategy

5.5.1 Outcomes

Testing is intended to:

- Confirm that the storage space remains within the defined limits with respect to temperature uniformity and stability over time across usable storage space
- Determine locations representing operating temperature extremes to establish the strategy for monitoring and alarming the space used for storage and/or processing

Note: It is assumed that temperature is quality critical. If there are other parameters, such as humidity or light, they should be considered using the same approach.

The operational temperature limits should be defined, together with any allowable excursions (acceptable limits, time periods).

Note: Some companies apply MKT to the acceptable operation of long-term storage areas such as warehouses. MKT is not used for refrigerators, cold rooms, or stability chambers.

There are many variable factors to consider when planning temperature mapping for a system. It is recommended that they are considered and the approach to be used put into a test strategy document for the Quality Unit to approve.

5.5.2 Risk Assessment

Prior to developing the test strategy, evaluate potential sources of excursions by considering the following factors:

Note: A company may use Computational Fluid Dynamics (CFD) modeling to evaluate the impact of these factors but the results still need some level of confirmation through actual testing.

- Purpose of the facility: storage, process cooling, transportation preconditioning
- Size: speed and magnitude of changes are impacted by the footprint as well as the height (Note: Pay attention to potential stratification with heights over 4.6 m.)
- Layout/configuration: wall and obstructions, fixed racks, temporary racks, pallets on floors, duct supply and return locations, door location
- Geographic location of facility: to define ambient conditions and seasonal variation
- Facility layout: physical location within a facility, location of windows, skylights, doors, traffic and access frequency
- Operating characteristics of the HVAC/refrigeration system: defrost cycles, redundant systems, number of units supporting storage space and how they interact with each other.

For example, a cold room may have duty standby systems that both operate in the event of a high temperature. This could impact temperature distribution compared to a simpler design that disables the duty system and starts the standby system in the event of a duty system failure or high temperature.

Additionally, there should be a clear definition of the acceptance criteria/expected results. Typically, this is provided in the URS, change record, C&Q plan, or equivalent document.

Temperature mapping is used to confirm that the system is operating to meet specifications, that is, the temperature range within the unit is acceptable.

It is a standard practice in the pharmaceutical industry to provide permanent monitoring of critical parameters using an independent system. Advantages of this practice include:

- Calibration of the monitoring sensors can be carried out without impacting the system operation
- The independent system becomes the Quality “system of record”
- The data can be used to provide continuous verification of acceptable system performance

Mapping results may be used to define the number and location of the permanent monitoring sensors for a warehouse, cold room, or chamber.

Note: While MKT may be used for the temperature monitoring for a controlled room temperature warehouse, the Guide authors recommend using this only for abnormal situations (i.e., do not use during testing to justify poor performance). Commissioning should be used to confirm that the room maintains the normal operating range.

A company can use multiple sensors in the area to provide continuous verification of the CTC performance. This can be used as justification for not conducting periodic mapping. (See Chapter 7.)

5.5.3 When to Perform Temperature Mapping

Temperature mapping should start as early as possible during commissioning. This allows the early detection and resolution of any performance issues. It also allows potential operational constraints to be identified and discussed with end users, to determine if the constraints are acceptable or require resolution.

Where there are systems that support operation of a CTC such as the refrigeration system for a cold room, HVAC system for a warehouse, or a condenser water cooling system for a refrigeration system, these systems should be identified and commissioned or in a known (and monitored) state prior to temperature mapping, to help ensure complete and representative testing, and facilitate investigation in the event of performance problems. For example:

“It can be acceptable to temperature map an area served by an HVAC system where a chilled water system which supports HVAC system operation has not been fully balanced, if:

- *the chilled water system is known to provide an adequate supply of chilled water at a constant temperature*

Note: the Building Management System (BMS)/Building Automation System (BAS) could be used to provide supporting data that:

- *the chilled water supply temperature remains within the operating limits*
- *the HVAC system cooling control valve does not open completely – indicating that an adequate supply of chilled water has been available for the duration of the test” [30]*

5.5.3.1 Prior to Temperature Mapping

Before temperature mapping begins, the commissioning plan/temperature mapping strategy should be approved by the system owner or SME representative and the Quality Unit.

The level of detail, number of personnel, or number of suppliers involved in temperature mapping can vary depending on the type of project. For example, commissioning of an air-conditioned warehouse in a new facility can involve several groups (e.g., construction manager, system installation contractors, and commissioning contractors). For a custom-built refrigerated storage room purchased through a design/build qualify contract, the requirements and responsibilities may lie with one company.

Roles and responsibilities should be clearly defined. *ISPE Baseline Guide: C&Q (Second Edition)* Section 6.4 contains an example document approval matrix [1].

Temperature mapping equipment requirements should be defined and the system calibrated.

Documents that should be available from the supplier/construction company (as applicable), include:

- Control system functional description
- Control system I/O list
- Calibration certificates as applicable
- Control system drawings (e.g., control panel layout, wiring diagram)
- Equipment and instrument lists
- Instrument and equipment data sheets
- Materials receiving and inspection reports/material certifications
- Equipment receipt and/or installation verification records
- Cable tests (continuity, insulation)
- Grounding (earth) tests
- Motor insulation “megger” and direction of rotation tests
- Fuse and breaker ratings/overload settings
- Control loop wiring checks
- Piping leak (hydrostatic) and evacuation tests
- Pipework cleaning/flushing records
- Record of cleaning for ductwork
- Ductwork and Air Handling Unit (AHU) leakage tests
- Operation and maintenance manuals
- Spare parts list
- Consumable parts list
- List of fluids/lubricants