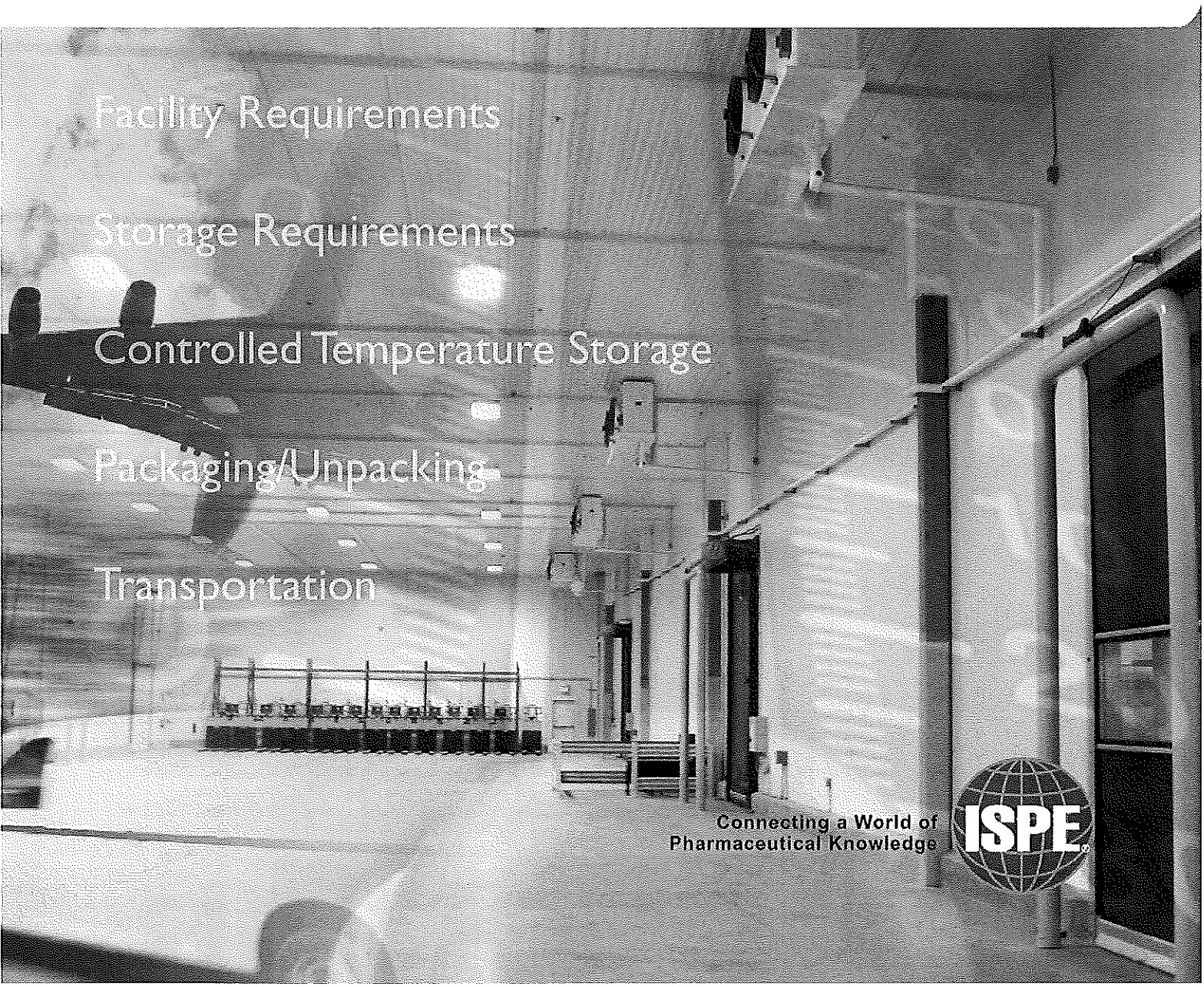
Good Practice Guide

Cold Chain Management



Connecting a World of Pharmaceutical Knowledge

ISPE

Good Practice Guide

Cold Chain Management

Disclaimer:
This Guide is intended to provide practical guidance to assist in the specification, design, commissioning and verification of the fixed and passive systems within the pharmaceutical and biopharmaceutical cold chain. The ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

Cold chain management is the specialist area of the pharmaceutical and biopharmaceutical distribution system dealing with product that is required to be held and distributed in a temperature controlled environment with the objective of providing safe and effective product to the patient.

The design, development, testing, and monitoring of the systems required to support this endeavor utilize a blend of Good Manufacturing Practice (GMP) and Good Engineering Practice (GEP) together with advanced technology to help provide a safe and reliable distribution system.

This Guide aims to define current good practices in this area, providing information to allow organizations to benchmark their practices and improve on them. The Guide also considers some of the issues relating to sustainability and economics.

The intended audience for this Guide is global with particular focus on US (FDA) and European (EMEA) regulated facilities.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers with input from members of the ISPE Packaging and HVAC Communities of Practice (COP). There is no single approach to satisfy every situation, but this Guide attempts to provide the background to help readers make an educated choice.

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Section Writers and Reviewers

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This Guide was produced by a dedicated team of subject matter experts from across the industry. The leaders of this Guide would like to recognize the following participants who took lead roles in the authoring of this document (organization affiliations are as of the final draft of the Guide.)

Luca Arrighi	Foster Wheeler Italiana Srl	Italy
Dr. Jean-Pierre Emond	University of South Florida Polytechnic	USA
Geoffrey Glauser	Health & Human Services – BARDA	USA
Paul Harber	Lilly	USA
Nicholas Haycocks	Amgen	USA
Brian Lee	Schering-Plough	USA
Elizabeth Martinez	Terra Farma S.A De C.V.	Mexico
Matthew McMenamin	GlaxoSmithKline	USA
Neritan Mustafa	Biogen Idec	USA
John Oliver	Clarion Construction, Inc.	USA
Karen Oliver	World Courier Inc.	USA
Douwe Rijpkema	Quality in Maintenance BV	Netherlands
Brian Saxton	Sunovion Pharmaceuticals Inc.	USA
Ted N. Schnipper, P.E.	SLAC National Accelerator Laboratory	USA
Jeff Seeley	Merck & Co., Inc.	USA
Walt Spendley	Intervet/Schering-Plough	USA
Carol Susla	Cangene Corporation	Canada
Brian Venturi	Merck & Co., Inc.	USA
Jean Vezina		USA
Brian Wallin	Amgen	USA
Guy Wingate	GlaxoSmithKline	United Kingdom
Graham Wrigley	Pfizer	USA

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Connecting a World of Pharmaceutical Knowledge

ISPE Headquarters
600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office
73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office
Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

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1 Introduction

1.1 Background

Cold chain management is the specialist area of the pharmaceutical and biopharmaceutical distribution system dealing with product that is required to be held and distributed in a temperature controlled environment. Concerns over having adequate control in cold chain is increasing, mainly because of:

- increasing volumes of cold products in the supply chain (demand)
- complexity of cold product (e.g., new types of product, patient specific products)
- complexity of the supply chain (worldwide supply)

Therefore, it is considered critical to have adequate control of all steps and procedures involved, both in manufacturing and quality control and in storage and distribution, to ensure that product quality is maintained.

Understanding the requirements of the cold chain process will help to focus efforts to ensure that activities and development programs add value, are based on robust science, undergo appropriate risk assessment, and meet the expectations of the regulators.

1.2 Purpose

This ISPE Good Practice Guide (GPG): Cold Chain Management is intended to provide practical guidance to assist organizations in developing, establishing, documenting, implementing, improving, and maintaining industry good practice for product requiring controlled cold conditions to maintain its safety, efficacy, and quality. These practices include:

- transferring
- packing
- storing
- distributing
- receiving
- unpacking

This Guide is intended to supplement published ISPE Baseline® Guides for facilities (Reference 24, Appendix 5) by providing detailed information and by recommending practices for implementation of cold chain management.

The information provided in this Guide reflects the cumulative knowledge and experience of the authors and reviewers with input primarily from members of the Packaging and HVAC ISPE Communities of Practice (COP).

This Guide defines:

- the application of risk assessment to cold chain management
- a standardized approach to temperature mapping of cold rooms

This Guide also provides:

- a primer on traceability
- a review of the relevant sections of the USP (Reference 8, Appendix 5)

1.3 Scope

This Guide is intended to cover the facility and practices from the point at which temperature becomes critical (generally considered to be entry into the controlled storage area after filling and packaging) through delivery to the distributor or customer premises. This includes the areas that lie within the manufacturers' scope of responsibility.

Approaches suggested by this Guide have been aligned with:

- ICH Q8, Product Development (Reference 3, Appendix 5)
- ICH Q9, Quality Risk Management (Reference 4, Appendix 5)
- ICH Q10, Pharmaceutical Quality Systems (Reference 5, Appendix 5)
- US Pharmacopeia (Reference 8, Appendix 5)
- ASTM E2500 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment" (Reference 19, Appendix 5)

It uses science- and risk based management and verification of GEP practices, rather than independent qualification activities.

The concepts included in ASTM E2537 "Standard Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing" (Reference 19, Appendix 5) are used; equipment performance is continuously monitored, evaluated, and adjusted (as necessary).

1.4 Benefits

Cold chain management is part of the life cycle of a regulated organization and ISPE and technical representatives have recognized a need for practical guidance in this topic area.

This Guide provides practical guidance for cold chain management, either to assist those new to this area of work or to allow those currently operating in this area to benchmark themselves against other organizations.

This Guide intends to provide tools and strategies for cold chain management and to complement work by the PDA including the Technical Report 39, Guidance for Temperature Controlled Medicinal Products, (Reference 32, Appendix 5) which provides details on the definition of cold chain management.

2 Regulatory Requirements

This Guide provides a list (see Section 13 (Appendix 2) of this Guide (current for the countries included at the time of publication) of the applicable regulations for several countries. It suggests an approach that may be used to:

- develop appropriate practices
- perform an internal audit of an organization's supply cold chain
- help organizations that contract warehousing and distribution services in cold chain to know what issues should be taken into account when assessing potential suppliers

It should be noted that the information provided in this Guide can be used to confirm compliance with the regulations and organization's internal requirements; it also provides a method to overview the quality systems applied in this area and ensure best practices are being consistently applied.

2.1 Defining the Relevant Regulations

Organizations should have a clear understanding of the regulatory requirements of all markets that a facility serves, locally and overseas, and any relevant guidance issued by the relevant regulatory authorities. These should be clearly defined and the relevant sections of the regulations understood.

Organizations should have a process for monitoring revisions to regulations and ensuring that the relevant internal departments are aware of these changes, so that revised requirements can be anticipated and met in a planned, integrated manner.

A suggested way of achieving this is included in Section 13 of this Guide.

3 Quality Plan

It is considered a good practice for an organization to have an established Quality Plan (or Quality Manual), as outlined in ICH Q10 (Reference 5, Appendix 5), describing the overall quality system approach used for the storage and distribution of pharmaceutical products.

A Quality Plan also provides a vehicle for communication between the key stakeholders, such as:

- Package Engineering
- Marketing
- Logistics/Supply Chain
- Validation
- Quality Assurance
- Operations
- Purchasing
- Shipping
- Clients
- Regulatory Authorities

The scope and content of the Quality Plan can vary from one organization to another, depending on the role definitions within the cold chain process and the structure of the quality management system. An example of a typical table of contents is suggested below:

Facility

- Specification and Standards
- Governing Procedures
  - Training
  - Cleaning
  - Maintenance
  - Pest Control
  - Security
- Roles and Responsibilities

Storage Requirements

- Packaging Materials
- Gel Packs
- Printed materials
- Product potentially including, controlled substances, narcotics, bio hazardous materials, cytotoxins
- Quarantine Materials
- Returns
- Reject Material
- Inventory Control/Records – first expired/first out
- Governing Procedures
  - Training
  - Receipt
  - Dispatch
- Roles and Responsibilities

Controlled Temperature Storage

- Specification and Standards
- Product Data
- Procedures
  - Cleaning
  - Maintenance and Calibration
  - Qualification
  - Monitoring
  - Action in the event of an alarm/excursion
- Roles and Responsibilities

Packaging/Unpacking

- Receipt/Storage
- Waste Handling/Management

- Procedures
  - Re-Packing
  - Pack Development and Testing
  - Qualification
  - Controls
  - Records
- Roles and Responsibilities

Transportation

- Selection of shipping method/service supplier
- Technical agreements with contractors (to include associated subcontractors)
- Auditing of suppliers
- Service supplier performance monitoring/qualification
- Shipment monitoring/performance monitoring
- Roles and Responsibilities

General

- Procedures
  - Training
  - Gowning
  - Change control
  - Recall
  - Complaints
- Policies
- Vendor Assessment/Approval
- Validation Planning
- Deviation and Investigation Handling
- Data Management Document Storage
- Procurement (Materials and Services)

- Environmental Roles and Responsibilities
- Self Inspection
- Business Continuity Plan

4 Product Considerations

4.1 Introduction

Robust stability data should be used to drive appropriate decisions based on the potential impact of the storage and shipping environments on a product/drug substance.

The stability testing of product should provide data on the ability of that specific product to withstand excursions from the defined storage temperature through the use of the testing at the designated storage conditions, accelerated testing, and/or from testing at an intermediate condition. ICH provides standard definitions for these conditions in ICH Q1a (Reference 1, Appendix 5).

Accelerated testing may be performed at conditions defined by a manufacturer to address conditions likely to be experienced during shipping, e.g., freezing (or short term exposure to high temperatures due to out-of-time issues resulting from pallet holding on a packaging line, in transit from the lines, or while waiting to go into cold storage).

The EU provides guidance on labeling to define the acceptable storage conditions based on supporting stability test data in 'CPMP/QWP/609/96/Rev2 Guideline on Declaration of Storage Conditions A – in the product information of medicinal products B – for active substances' (Reference 21, Appendix 5).

Note that for product supplied for clinical trials unique testing may be required to cover anticipated ranges of temperature excursion that could be encountered during shipping.

The USP<1046> (Reference 8, Appendix 5) provides the following information:

"In all cases, the stability study should be designed on the basis of scientifically sound principles and approaches and a comprehensive understanding of the final therapeutic product and its intended use. Stability of in-process hold steps, cell and virus banks, critical raw materials, and reference standards also needs to be assessed. A well-designed and executed stability program will provide a high degree of assurance that the product is stable within the specified shelf life.

The stability-indicating profile of a cell or gene therapy product may vary with time under the influence of a wide variety of environmental conditions, including temperature, extremes in physiological storage conditions, and light. Multifactorial degradation pathways must be considered in the development of a program investigating the effects of these parameters on the stability of the products. Studies should include conditions that are outside of the specified storage ranges, that is, challenge conditions such as those encountered during periods of abnormal storage, shipping, or handling. Examples include brief incubator malfunctions, incubator, or cold storage failure, periods of extreme temperature fluctuation due to shipping to hot or cold climates, hypobaric conditions experienced in the cargo hold of a commercial airliner, or temperatures likely to be encountered in the surgical suite."

The data gathered from accelerated testing or from testing at an intermediate condition may be used to evaluate the effect of short-term excursions outside the label storage conditions, such as those that might occur during shipping.

The manufacturer is responsible for defining acceptable conditions, e.g., Mean Kinetic Temperature (MKT) should be used where acceptable, there may be temperature limits outside of which the product degrades (e.g., the product is not allowed to freeze).

The responsibility for temperature monitoring during storage and shipping should be clearly defined with a quality system to ensure regular review of associated data.

The responsibilities for monitoring conditions may be split depending on the organization with storage the responsibility of one department and shipping under another department.

As the product is usually stored in conditions controlled by the manufacturer for as short a time as possible (to minimize stock levels), it is desirable to minimize the risk of any excursions from the defined storage conditions within that time.

The USP <1079> (Reference 8, Appendix 5) states:

"A procedure should be in place in the warehouse to define the action that should be taken in the event of deviation from required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action that is taken. The product in question should then be placed in a quarantine status. Advice on the suitability of the product for use should be sought from the manufacturer or supplier of the product. The manufacturer's response should be documented prior to issuing the product to the customer, if that product is to be issued to the customer."

GUI-0069, Health Canada (Reference 22, Appendix 5) states:

"Written procedures should be available describing the actions to be taken in the event of temperature excursions outside the labeled storage conditions. All excursions outside the labeled storage conditions must be appropriately investigated and the disposition of the stock in question must be evidence-based."

4.2 Related Definitions

The definitions for storage and shipping conditions for the market served should be clearly understood. The USP in Chapter 10 of the General Notices defines the following conditions:

Freezer

"Freezer" indicates a place in which the temperature is maintained thermostatically between -25° and -10°C (-13° and 14°F).

Note: the freezing point is defined as the temperature at which a liquid substance turns to a solid. The term frozen is applied to the solid product.

Cold

Any temperature not exceeding 8° (46°F) is "cold." A "refrigerator" is a cold place in which the temperature is maintained thermostatically between 2° and 8°C (36° and 46°F).

Cool

Any temperature between 8° and 15°C (46° and 59°F) is "cool." An article for which storage in a cool place is directed may, alternatively, be stored and distributed in a refrigerator, unless otherwise specified by the individual monograph.

Controlled Cold Temperature (CCT)

"Controlled cold temperature" is defined as temperature maintained thermostatically between 2° and 8°C (36° and 46°F), that allows for excursions in temperature between 0° and 15°C (32° and 59°F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8°C (46°F). Transient spikes up to 25°C (77°F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.

Room Temperature

"Room temperature" indicates the temperature prevailing in a working area.

Controlled Room Temperature (CRT)

"Controlled room temperature" indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°C," or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations. (See also Pharmaceutical Stability <1150>.)[1]

An article for which storage at *controlled room temperature* is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.

Warm

Any temperature between 30° and 40°C (86° and 104°F) is "warm."

Excessive Heat

"Excessive heat" means any temperature above 40°C (104°F).

The current storage temperature guidance in the USP allows for the MKT to be considered for CRT and CTC storage areas – this allows there to be temperature excursions and calculates the MKT considering a year of data – as long as this lies within the acceptable range then the product is considered fit for sale.

Protection from Freezing

Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place

The term "dry place" denotes a place that does not exceed 40% average relative humidity at Controlled Room Temperature or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered storage in a dry place."

[1] Note <1150> refers to the paragraph in the US Pharmacopeia.

Mean Kinetic Temperature (MKT) is Defined in <1150>

"Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation. It is not a simple arithmetic mean. MKT is calculated from temperatures in a storage facility. The temperatures for calculating MKT can be conveniently collected using electronic devices that measure temperatures at frequent intervals (e.g., every 15 minutes). MKT can be calculated directly or the data can be downloaded to a computer for processing. For dispensing sites, such as pharmacies and hospitals, where the use of such instruments may not be feasible, devices such as high-low thermometers capable of indicating weekly high and low temperatures over a 52-week period may be employed. The arithmetic mean of the weekly high and low temperatures is then used in the calculation of MKT. MKT is calculated by the following equation (derived from the Arrhenius equation):

$$T_k = \frac{\Delta H/R}{-\ln\left(\frac{e^{-\Delta H/R_1} + e^{-\Delta H/R_2} + \ldots + e^{-\Delta H/R_n}}{n}\right)}$$

in which Tk is the mean kinetic temperature; ΔH is the heat of activation, 83.144 kJ•mole-1 (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144 × 10-3 kJ•mole-1•degree-1; T1 is the value for the temperature recorded during the first time period, e.g., the first week; T2 is the value for the temperature recorded during the second time period, e.g., second week; and Tn is the value for the temperature recorded during the nth time period, e.g., nth week, n being the total number of storage temperatures recorded (minimum of 52 weekly entries) during the annual observation period. [**Note:** all temperatures, T, are absolute temperatures in degrees Kelvin (K).]

The following is an example of a typical storage and distribution temperature range in Kelvin degrees and the conversion factors used to convert this range into degrees Fahrenheit and Celsius.

Kelvin (K)	Fahrenheit (°F)	Celsius (°C)
288.1 to 303.1	59 to 86	15 to 30

Conversion Factors:
Fahrenheit to Kelvin = {[(°F -32) × 5/9] + 273.1}
Celsius to Kelvin = 273.1 + °C
Fahrenheit to Celsius = [(°F -32) × 5/9]

Note: when calculating the MKT where there are less than 12 months data, a rolling calculation may be developed, based on available data, for the time that data are available. Once there are 12 months of data, the calculation can be maintained, based on the previous 12 months data.

Freezers are also commonly used with operating set points of -30°C and -80°C (-22°F and -112°F). (**Note:** this is not addressed in the USP.)

5 Facility Design Considerations

This section describes factors that should be considered in temperature controlled facility design, including:

- engineering
- scientific
- quality
- regulatory
- logistical
- personnel

Review of storage conditions, including freezing and refrigerated temperatures, and their placement within a physical facility should be considered when evaluating an operating environment.

Design parameters should incorporate financial risk policy and loss control at a local and organizational level, consistent with the products being manufactured and stored.

5.1 Work Flow Considerations

The scale of temperature controlled pick, pack, and ship operations should be based upon unit volume.

The throughput specification and complexity of operations should have a direct correlation to forecasted mid and long range product volumes. The scale of temperature controlled handling operations can then be determined using a capacity analysis. The core functions of the facility should be included in the analysis, including controlled room temperature products and the handling of defined temperature conditions, e.g.:

- 2°C to 8°C (36°F to 46°F)
- -20°C (-4°F)
- -40°C (-40°F)
- -80°C (-112°F)

Aspects of pharmaceutical, biological, veterinary, consumer product, scheduled drugs, and clinical cold chain should be incorporated into the overall facility layout and work flow considerations.

Automation may be present, in the form of conveyors and barcode container sorters. The level of automation and information systems should be commensurate with the volume, risk tolerance, and control level desired, along with market regulations.

Materials to be handled in the facility should be considered, including:

- raw materials
- bulk intermediate product

- final bulk product
- primary product containers
- secondary finished packages
- printed components
- insulated packaging materials
- temperature monitors
- controlled materials
- returned goods
- damaged goods for return
- supporting manufacturing components

5.1.1 *Receiving*

Receiving areas should provide space and operating systems that incorporate product accountability, identification, and quality screening for inbound materials.

Receiving is the point at which determinations should be made to decide whether further processing should take place or materials should be segregated for further evaluation.

Adequate temperature controlled (and monitored where required) space should be established for sampling, disposition, control, and release processes.

Isolation systems and/or physical areas should be established for materials designated as quarantined. The concepts of material segregation and virtual control should be considered.

If strict out-of-temperature-control product parameters apply, then further levels of facility engineering may be required (e.g., refrigerated loading dock space). The handling of materials in receiving and throughout the facility should be in accordance with the known stability profile. Alternatively, a worst-case handling methodology may be adopted.

Space should be identified for the control of incoming insulated packaging materials for later use, as well as components to be re-used, recycled, or discarded.

5.1.2 *Hold or Quarantine Area*

A designated area should be identified for inbound materials to be reviewed for quality status prior to further movement within the facility. Space should allow for complete physical visibility of the materials.

5.1.3 *Put Away*

Inventory control systems should be sensitive to time and temperature materials requirements. Standard inventory classification practices such as First-Expired-First-Out (FEFO), First-In-First-Out (FIFO), Last-In-First-Out (LIFO) and warehousing material velocity (ABC classification) should be part of these systems.

5.1.4 Stock to Stock

The time out of temperature control is the critical factor in stock-to-stock or stores-to-stores movements. Cold or freezer storage areas should incorporate staging areas for material movement consistent with expected volumes and product flows.

5.1.5 Stock to Manufacturing

Temperature controlled materials should follow restrictions in accordance with the product stability profile for staging and time-out-of-control in accordance with the manufacturing production schedule as determined and documented during process validation. Product control should include all transfers to and from production areas and during any time within production areas.

5.1.6 Manufacturing to Storage

Materials returned from production areas should follow good inventory practices for Work-In-Process (WIP) and Finished Goods (FG) again, in accordance with process validation guidance.

5.1.7 Stock to Shipping

The pick, pack, and ship processes should focus on adhering to time-out-of-control standards in order to preserve the efficacy and safety of materials.

5.1.8 Distribution

Schedule creation and conformance for outbound goods should focus on systems that incorporate packing, staging, and shipping throughput standards. All queues for temperature controlled goods should be limited to the capacity of the outbound packing and staging areas.

Individual packing requirements should be established through separate package qualification studies.

5.1.9 Ingress and Egress

Loading dock doors, door seals, dock levelers, lights, and safety systems should conform to the materials temperature requirements. Door features should minimize the exposure of materials to undesired temperatures. Pest control, dirt ingress, and security should be considered during design activities.

5.1.10 Storage Racking and Materials Handling Equipment

Racking materials should be appropriate for continuous use in the controlled environment. Organic materials (e.g., wood slats) should not be used as permanent structural elements in cold or freezer vaults, in order to limit microbial load.

Physical storage location sizes and warehouse inventory management systems should be adaptable to accommodate lot sizes (pallet, less-than-pallet) of temperature controlled materials.

Each storage location should be independently identified with a unique identifier that is acceptable for use in the controlled environment.

Material handling lifting equipment and associated electronic scanners should be suitable for extended operations within the controlled environments.

5.1.11 Pallets

Pallet selection should be appropriate for the materials to be stored. Plastic, metal, or composite pallets may help to limit surface mold. To limit bioburden, procedures for discarding, inspection, or cleaning of pallets should be established. Pallet safety and flammability concerns should be examined as part of a facility risk assessment. Where appropriate, pallet change equipment may be used to transfer from "external" to "internal" pallets.

5.1.12 Personnel Flow

Within a facility, personnel flow should be limited to personnel necessary for the operation of that facility.

Individuals working within a facility should receiving operational and safety training for tasks, prior to being assigned those tasks. Access points should be controlled for security as well as temperature control purposes. Third parties (e.g., drivers, delivery personnel) should be restricted to specific areas and have minimal access to temperature controlled areas. This may be accomplished by segregating trucker areas from the warehouse common areas through limited access doorways. Windows also may be used to communicate with third parties to remove requirements for third parties to access a facility.

5.1.13 Information Systems

Within temperature controlled areas, automated systems (e.g., Radio Frequency (RF) and pick-to-light equipment) should be able to operate within the designed temperature conditions, as well as support the technical requirements of the inventory operating system. Automated systems should conform to transaction accountability standards and should have the ability to apply a quality status to materials.

5.2 Surface Finishes

Warehouse or distribution floor and wall surfaces should be finished such that they are favorable to good housekeeping and sanitation practices. Temperature controlled vault surfaces should be impervious to external penetration. Floor construction materials, such as concrete should be able to function in the designated temperature environment (e.g., freezer vault).

5.3 Layout

Facility design should focus on:

- minimizing travel
- proximity to materials entrance and exit points
- limitation of out-of-temperature handling times

Storage of packing components should be in close proximity to the refrigerated storage areas for material. Throughput and material flows should be considered for all warehousing and distribution processes.

5.4 Facility Systems

5.4.1 HVAC – Air Flow Considerations

Warehouse controlled room temperature airflow design and corresponding validation should support individual cold storage requirements, including documentation and good monitoring and alarm practices. It should incorporate, as necessary, pre-treatment, filtration, and humidity controls.

Temperature controlled storage areas used to contain pharmaceutical and biological materials should be validated. Validation of these areas should include:

- three dimensional mapping
- identification of maximum temperature fluctuation points
- recovery capabilities
- maximum warm load implications
- system sizing
- equipment redundancy
- calibration
- alarming systems
- modification documentation
- back-up power systems
- planned maintenance
- integration with monitoring systems such as BAS/BMS

Internal condensation lines within cold and freezer vaults should be properly protected from freezing, dead legs, and the potential for mold growth. Condensate pumps or drains should be clear of interferences with condensate piped to drain. See Section 6 of this Guide for more information.

5.4.2 Fire Control

Installed fire control systems should be compatible with the temperature controlled environment in which they are installed. Local fire code should be reviewed prior to installation as it may vary from region to region. The concept of zonal systems may be incorporated in order to limit maximum foreseeable loss.

5.4.3 Electrical

System installation and backup power systems should be approved in accordance with Maximum Foreseeable Loss (MFL) policy. MFL, safety, and business continuation policy and issues may override any GMP/GDP considerations in electrical system design. Uninterrupted Power Supply (UPS) may be incorporated as necessary for data acquisition devices in accordance with regulatory principles.

5.4.4 Labeling and Package Identification

If primary or secondary package labeling is performed within the confines of a warehouse or distribution center then all GMP/GDP requirements for a packaging facility should be followed. See the ISPE Good Practice Guide on Packaging, Labeling, and Warehousing for more information (under development at time of publication, Reference 26, Appendix 5).

For application of package identification information of pharmaceutical tertiary or shipping containers, bar code, Radio Frequency Identification (RFID), track and trace, or product pedigree principles should be followed, as applicable.

5.4.5 Pest Control

Warehouse and distribution areas should have established pest control programs with associated documentation and training. These programs should be associated with the control of insects and small mammals that may find a way to enter an operating facility, including, but not limited to:

- standard operating procedures
- inspections
- controls
- use of pesticides
- historical incursions
- preventative measures

5.4.6 Returns

The processing of pharmaceutical returns should be accomplished in a restricted control area isolated from released finished goods. Returned goods designated for destruction should not be stored with released materials.

Return of product requiring temperature control should take place only when there is a full temperature history available with an established relationship with the returning parties that is supported by quality management systems. Material returns should be handled independently to other released materials to maintain separation and integrity.

5.4.7 Material/Product Destruction

There should be physical and systemic segregation of materials designated for destruction. Materials should be handled in compliance with local and regulatory authority expectations. Inventory management systems should be designed to handle materials designated for destruction.

5.4.8 Training

Proper handling of temperature controlled materials should be adequately covered through instruction, documentation, and proficiency demonstrations according to GMP/GDP requirements. Records for such training should be readily available for review by regulatory authorities. Third party personnel involved in operational activities should receive appropriate training prior to performing functions within a facility.

5.4.9 Safety

Local government safety Licenses and Inspections (L&I) may apply. Principles of safe material handling within temperature controlled facilities should focus on personnel temperature exposure limitations, associated vault alarms, and Personal Protective Equipment (PPE). Doors to cold and freezer vaults should be tested for excessive vacuum prior to activation. Heater strips on door seals normally serve two purposes: protecting from accidental door locking and door frame operability.

Other safety programs that may be evaluated during the facility design and implementation phase of operations include:

- material safety data sheets
- international hazardous materials guidances
- the Five S program for workplace organization (sorting, straighten, sweep, standardize, and sustain)
- hazard and operability studies (HAZOPs)

5.4.10 Construction

The physical space calculations should be based upon volume and throughput needs, taking into account both vertical and horizontal considerations. Total building insulation characteristics should support the interior specific temperature controlled spaces allowing for the optimum energy consumption profile for the building. Maximum foreseeable loss considerations should be based upon insurance requirements, organization policy, and incorporated into fire barriers and storage parameters for flammable materials.

For further information, see Section 6 of this Guide.

5.5 Security (Layered Design)

5.5.1 Alarming Systems

The alarm strategy should be defined – there may be a single set of alarms or two alarm categories:

- engineering alarms
- quality alarms

Alarms for temperature controlled storage areas should provide both audible and visual alarms and connect with site security systems. Adequate individual monitoring points should be present in each storage area. Backup alarm systems may be required dependent upon material risk tolerance. Reporting and response methodologies and responsibilities should be documented and agreed upon by operational management. Alarm systems should be linked to electrical power and backup circuits in order to protect high valued materials. The routing of alarms to destinations should be evaluated for purposes of timely responses by engineering, operations, and security. Standard operating procedures should define contact persons or departments and courses of action under each alarm condition.

5.5.2 *Information Systems*

Security for Information Technology (IT) systems should be hierarchical and in accordance with GMP/GDP inventory control regulations. Compliance and documentation of IT systems, as well as user procedures and training should be considered. UPS usage should be considered based upon need, and if incorporated, should be included in regular maintenance procedures. Procedural controls for access and operability should be in place in accordance with both regulatory and risk assessments. Any information systems to be utilized for handling GMP/GDP data may potentially be subject to and should be assessed against 21 CFR Part 11 (Reference 7, Appendix 5), as well as relevant EU Annex 11 requirements (Reference 9, Appendix 5) for compliance to electronic systems parameters.

An integrated retention and recovery plan for critical records should be inclusive of backup activities, monitoring strategy in case of system failure, offsite storage, and emergency recovery plans.

For further guidance on computerized system compliance, see GAMP 5 (Reference 28, Appendix 5) and the GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures (Reference 29, Appendix 5).

5.5.3 *Quarantine*

Virtual or physical isolation areas for materials in quarantine should be designed following GMP/GDP and inventory control principles.

5.5.4 *Power Supply*

Primary and backup power supplies should conform to local and regional regulations for the handling of temperature controlled materials. Implementation of alternate power sources, dual power sources, and independent backup power should be based upon business continuity and MFL policy.

5.5.5 *Access*

Personnel access to general warehouse and distribution areas as well as temperature controlled locations should be controlled and monitored based upon pre-approved access. Positive control principles should be applied for granting approval for ingress/egress.

5.5.6 *Physical Security*

Levels of physical security should correspond with physical building characteristics. For stand-alone warehouses and distribution centers, more complete physical security systems may be appropriate. Where a facility is co-located with other manufacturing buildings, site security procedures may incorporate warehouse/controlled temperature storage requirements. Contact with external security support would be dependent upon local requirements.

Consideration should be given to isolating individual operating areas from personnel that are not required to be in those areas.

Operational support spaces such as locker rooms, dining spaces, and rest rooms should be appropriately segregated from material handling and storage areas. Personal items should be kept out of operating areas.

Video cameras may be considered for additional levels of monitoring and documentation in material critical areas. Video data should be securely stored for a defined time.

5.5.7 Alarm Sensor Locations

Alarm sensor locations should mirror the alarming task to be addressed, e.g., door and window security, temperature controlled location outside monitoring, motion sensors, heat sensors, or other critical points. For individual cold or freezer vaults, the sensors should be placed in immediate proximity to the controlling sensors where possible. Each sensor should be installed such that it is accessible for regular testing for ease of use.

5.6 Specialized Equipment

Equipment that is unique to temperature controlled material handling should be able to withstand design conditions. Specialized equipment examples include:

- powered conveying equipment
- material flow racks
- accumulators
- carousels

Where availability is critical, consideration of facilities to ease maintenance may be considered when specifying equipment, e.g., plug and sockets for motors, quick release connections, and additional isolating valves.

5.7 Sustainability

Facility design should include adequate space for the accumulation of materials designated for reuse and recycling. Reuse and recycling of temperature controlled packing supplies should be considered. Prior to implementation, recycle and reuse programs should undergo technical scrutiny from operations, the original manufacturer, the relevant quality area, and risk analysis (considering, e.g., process risk, increased fire hazard).

5.8 Controlled Substances

Adequate provision should be made for the storage and handling of controlled substances in accordance with local regulatory requirements. Engineering design specifications are usually specific for scheduled drugs, and therefore, need to conform to government regulations.

6 Fixed Equipment

This section covers fixed equipment, including walk in cold rooms and freezers, as well as standalone equipment used for storing product that requires controlled temperature storage conditions below ambient conditions. This section is intended to provide a list of considerations for use when reviewing a proposed design for a new system or specifying a new system. It is not intended to be a complete design guide.

There are typically 5 types of cold room:

1. for storing material at refrigerated temperature, normally between 2°C to 8°C (36°F to 46°F) (see the WHO guideline of 2°C to 8°C (Reference 33, Appendix 5))
2. for storing frozen material; usually between -15°C to -25°C (5°F to -13°F)
3. can operate as either a freezer or a refrigerated cold room
4. walk in freezer to -40°C (-40°F) (e.g., for blood plasma)
5. walk-in freezer usually built inside or accessed via a walk-in cold room (to reduce the humidity in the freezer)

User requirements should be considered based on current and potential future requirements, considering the conditions required; temperature, humidity, lighting levels, room classification, the volume of product to be stored, and how the facility is intended be used, i.e., loaded and unloaded.

6.1 Procurement Processes

There are three main methods that can be used to obtain a new piece of equipment:

- use of a specialist supplier
- using the traditional "architect and engineer" model
- a hybrid approach
- The approach chosen will influence the type and detail of information that is provided.

Use of a Specialist Supplier

A specialist supplier is appointed to help develop a design or performance specification which may be put out for tender from the user requirements.

Using the Traditional Architect and Engineer Model

A user requirements document is developed and a designer appointed to develop an associated design specification. The design specification may then be put out for tender.

A Hybrid Approach

A user requirements document is developed and used as a system "performance specification" that is put out for tender to appropriate specialist suppliers.

Note that in all cases the industry requirements for detailed documented commissioning and acceptance testing should be included in the documents put out for tender.

6.2 General Considerations

6.2.1 Specified Internal Conditions

The acceptable temperature range should be clearly specified. The acceptable humidity range also should be specified; it is becoming more common to control humidity in cold rooms to minimize risk of any microbial or fungal growth, and in freezers to reduce ice buildup, improve safety, and reduce the need to defrost the cooling coils. This may increase the life of the equipment (by reducing the number of heating/cooling cycles to which the unit coolers are subjected).

6.2.2 Envelope

Use of the appropriate materials of construction, with high quality standards for the erection and sealing of the storage area is considered vital to providing a mechanically robust construction and a stable environment for product.

Insulation material, thickness, and vapor barrier should be adequate for the "insulated box" (i.e., walls, floor, and ceiling), equipment, ductwork, and piping to compensate for heat gain or loss and to avoid either internal or external condensation, especially through service penetrations in the envelope.

Sufficient thermal break should be provided to avoid sweating on surfaces of the cold store structure. This should help to eliminate the potential for mold formation and corrosion.

The design of the floor interface should be considered to ensure that potential for condensation on the floor immediately outside the cold room/freezer is controlled.

Energy conservation should be considered when deciding the final insulation thickness; local legislation may require minimum thermal resistance values. Legislation on energy usage and carbon footprint also should be considered.

The selection of the insulation material should comply with local fire protection and health codes and with the organization's insurance company requirements.

Joints of an insulated box (walls, floor, and ceiling) and any penetrations through the box (for piping, conduit, instrumentation, etc.) should be properly sealed to prevent heat loss and to avoid either internal or external condensation.

Wall finishes and other interior surfaces should be selected based on the materials used by the owner for cleaning or sanitizing the spaces. A common form of construction used comprises "foamed-in-place" panels with urethane or polyisocyanurate insulation; these provide an R -value of between R-30 (typically used for walls) and R-40, used for roofs. (Roofs are often thicker to provide walk on capability and be sufficiently robust to prevent potential leakage if sprinkler protection is provided to the environment above the cold room.)

Panels should be at least 102 mm (4 in) thick and should be Underwriters Laboratory (UL) approved by the organization's insurer meeting the relevant US National Fire Protection Association (NFPA) codes/local regulations for the application.

Ground floor heat transmission of cold rooms operating below 0°C (32°F) should be reduced to avoid both heat transfer to the cold room and potential ice formation on the surrounding floor. Under floor heating may be provided to an insulated section of a floor slab for this type of equipment. The heating should be designed such that it can be maintained.

During start up, commissioning, and subsequent maintenance and operation care should be taken when passing through the freezing temperature range to prevent any damage to a floor slab; it is usual to allow a period of time for this transition to occur, advice from the supplier should be sought on this.

6.2.3 *Location of Refrigeration Equipment*

Refrigeration equipment should be located in a secured and protected location to avoid adjustment by unauthorized personnel, physical damage, and potential vandalism.

The availability and access to required utilities, operating and maintenance space requirements, and ventilation requirements for equipment should be considered.

Where there are multiple systems, the local airflow should be considered to ensure that there is no risk of "short circuiting," i.e., rejects heat flow from one unit entering another as the "cooling" air supply.

Refrigerant leakage detection systems may be required by local or organization regulations for safety reasons, depending on the location and refrigerant used.

6.2.4 *Refrigeration System Controls*

Refrigeration system controls available range from simple proprietary systems to sophisticated computerized systems.

Simple "standard" systems may use a temperature sensor to turn off and on the refrigeration system, and operate a standby system if the duty system cannot maintain conditions.

Sophisticated systems can monitor the status of the duty system and turn on a standby system in the event of any alarm signal from the duty system, or any significant temperature excursion within the conditioned space.

Control can be based on a single temperature sensor in a controlled space or a number of sensors located throughout a conditioned space.

If redundant conditioning systems are required (when the loss of product due to system failure or service interruption may have a significant business impact), the redundancy of the controls as well as the mechanical components for each conditioning system should be considered to ensure that each system will be capable of operating totally independent of each other and be able to handle all cooling load requirements.

Each system should be capable of being programmed to perform automatic switch over on a time base to the stand by redundant unit(s) on a programmable cycle timer to assure that both systems are given equal run time and are periodically tested to be functioning properly. (Manufacturers' recommendations for this time interval should be sought – typically a maximum interval of one week is used.) Upon failure of one of the systems or deviation of environmental parameters, the standby system should automatically come on line to maintain room conditions.

Temperature/humidity control instrument installation should be designed to facilitate routine calibration without generating a swing of ambient parameters.

6.2.5 *Monitoring Systems*

The monitoring system is usually independent from the control system; it can comprise min/max temperature thermometer, a simple chart recorder, with single or multiple sensors, a data-logging chart recorder, or a more sophisticated SCADA system.

The physical configuration considerations (storage heights, racking layout, number of doors, etc.) of a cold room, the cooling system type, user preference, and the results of the system mapping should determine the number and the location for the temperature monitoring points. The number and location of monitoring points may be supported by a risk assessment or mapping data. The rationale for selecting the number and location of the monitoring points should be recorded and approved by the Quality Unit, as the data from this system will be used as the "system of record" providing a record of the conditions in which the product has been stored.

The requirement to have remote temperature monitoring and alarm management in addition to local alarm facilities should be assessed to ensure that the response time to an alarm is acceptable in a given situation.

Temperature recording readouts should be regularly reviewed and saved for trending audit purposes (for an appropriate time period).

The monitoring system used for the critical environmental parameters should be qualified.

The monitoring system should have an independent back up power supply/UPS.

It is common practice to use the monitoring system to provide an alarm if the temperature probes read above or below a preset value. An alarm time delay may be used to avoid nuisance alarms from momentary excursions because of the presence of personnel or door openings. Alternatively, the probe may be mounted in a container of thermal fluid to mimic the time it takes for stored product to be impacted by an external temperature changes (because of the thermal lag created by the packaging).

The control system may be used to provide equipment or temperature alarms for engineering use at conditions within those used by the monitoring (quality) system in order to give an early indication of possible problems to engineering staff. For example, a cold room that is designed to provide an operating range of 2°C to 8°C (36°F to 46°F), and normally operates at 4°C to 6°C (39°F to 43°F), may give an engineering alarm if it goes outside the 3.5°C to 6.5°C (38.3°F to 43.7°F), range. If there is an alarm from the conditioning system, the monitoring system may give an alarm if the conditions go outside the 2.5°C to 7.5°C (36.5°F to 45.5°F), range.

Similar design consideration should be made for calibration of the monitoring sensors as is made for the control sensors.

6.2.6 *Compressor Types*

Each compressor type has its advantages and disadvantages. The scroll type unit typically has a higher efficiency than a reciprocating unit, is less costly to operate, and has less moving parts which could fail. The semi-hermetic reciprocating unit can be field serviced.

As the capacity increases, larger reciprocating units are normally used, usually progressing to rotary units for higher capacities.

Noise and vibration levels should be considered in the selection and location of equipment. The rotary units usually have the advantage of quieter operation with less vibration.

When selecting a compressor, it should be noted that the system will have to modulate capacity to balance the process load and provide continuous compressor operation for the different loads, from loading the room, to extended periods without activity. Continuous cycling (start/stop) of the compressor is not recommended as it will lead to a reduction of compressor life.

A compressor will typically have the following components:

- low/high pressure safety control
- automatic head pressure valve control for units operating within low ambient conditions
- vibration eliminating devices on suction and discharge lines
- re-seatable safety pressure relief valve
- liquid line dryer

- moisture indicating sight glass
- suction line filter and accumulator
- discharge oil separator
- low voltage safety protection on 3 phase motors
- low ambient protection where appropriate

The impact of compressor or sensor failure should be considered. The design may include additional isolation valves and flexible couplings to facilitate use of standby equipment, wiring may include plug and socket connections to facilitate speedy replacement of faulty equipment, redundant systems may be specified, holding a stock of spare parts or skid mounted standby units. An organization may have emergency arrangements with other organizations/ cold storage contractors.

6.2.7 *Unit Coolers – Types, Locations, and Airflow*

A common design is to use ceiling mounted horizontal discharge units. An alternative arrangement is to use down flow units mounted in the aisles of the conditioned space.

When considering the racking system layout, it is important to look at airflow direction.

A computer airflow analysis can be performed considering the:

- conditioned space
- specified (minimum and maximum utilization (amount of stored product) assumptions)
- use conditions – loading/unloading volumes and frequencies
- door location/type
- racking locations

The impact on the stored product of the cold air leaving the space and warm air entering to replace it during loading and unloading through the door opening should be considered.

The need for a defrost cycle should be investigated and a determination made if defrost will be required. If so, then careful selection of a defrost cycle is required to prevent the conditioned chamber temperature from exceeding the upper temperature limit during defrost.

A typical defrost cycle for a system using an electrical defrost heater could include the following sequence:

- the fan shuts down
- liquid line solenoid shuts down
- system runs for a defined pump down time
- heater operates for a defined defrost time (heater operational)
- the system solenoid valve opens for a coil pre-cool time

- the fan re-starts

Other options are available, e.g., there are unit coolers that, during the defrost time are isolated from the conditioned environment by motorized shutters (these operate to close off the front and rear of the coil and fan assembly), improving the efficiency and limiting the heat loss into the conditioned space.

The use of exposed heating elements in the coil and condensate tray can lead to generation of water vapor, that will condense on surrounding cool material forming ice and frost; this needs to be removed periodically to prevent build up.

The condensate should be drained out through an insulated traced heated pipe to the outside.

An important consideration in the design specification of a cold room or freezer is the acceptable humidity level inside the space; this may not be a product requirement, but may be a safety or engineering requirement.

Low humidity will require the provision of additional components, such as chemical dehumidifiers, but may reduce the defrost requirement for a freezer, extending equipment life (less thermal cycling) and reduce potential ice formation on the floor; for a cold room, it may reduce the risk of microbial/mold growth within the room.

6.2.8 Heat Rejection Systems

- Air cooled units, which are the norm in the pharmaceutical industry, typically cost more to operate than water cooled units. Multiple units should be spaced so that they do not short circuit the air flow between units. Provide cleaning equipment locally – efficiency drops off rapidly if the coils get dirty.

- Water cooled units normally reduce the electrical demand from the compressor while keeping the refrigeration output capability high and stable. The need to chemically dose the cooling water to keep the heat exchanger units clean should be considered. For open circuits, any local regulations regarding bioburden monitoring (e.g., for *Legionella*) should be considered. Total loss use of city water should be considered as a possible emergency back-up for these systems

Adequate space should be allowed for maintenance equipment, this may include providing sufficient maneuverability space for equipment removal vehicles.

The condenser will typically have the following associated components:

- moisture indicating sight glass
- suction line filter and accumulator
- discharge oil separator
- low voltage safety protection on 3 phase motors
- low ambient protection where appropriate

The design of the interconnecting pipework should be considered. It should be adequately protected from any likely damage, mounted so that it is secure when the system's automatic valves operate – often these are fast acting solenoid valves that give rapid pressure changes in the system. Maintenance and inspection access should be considered.

6.2.9 *Door Types and Locations*

Door types range from basic single manual doors to sliding doors, automated sliding doors, and automated bi-parting doors. Doors should be:

- Flush mounted with the materials of construction to allow for longevity of operation with little deterioration, due to use, temperature, and humidity variations with minimal maintenance, usually constructed in a similar manner as the wall panels.
- Self closing with a safety release mechanism on the inside of the room preventing personnel from being locked in and compliant with local codes.
- Fitted with multi-layer, heated thermal pane windows to prevent condensation and freezing, where applicable.

The addition of an emergency button located within a room to notify security in the event that a person is trapped within a room and is unable to open the door(s) should be considered. An illuminated light switch should be provided on the inside near the door.

An automatic door closer that closes a door after a preset time or a door open alarm that operates after a preset time, may be considered to ensure that doors are not accidentally left open. Doors should be capable of high speed operation to minimize heat loss.

Door panels should be flexible and be constructed to withstand impact from a forklift or provided with internal and external protection using a bollard. Seal edges should incorporate dual-interlocking to minimize warm air infiltration, and coupled with heated header and jamb seals (heaters are often provided to prevent a door seal from freezing to the frame and reduce external condensation) to provide an effective full-perimeter closure.

Gaskets, where applicable, should have sufficient magnetic force to form a positive airtight seal. An adjustable rubber wiper gasket should be provided on the bottom of a door. Latches and frames should be designed to allow actuation under all design conditions, such as freezing.

To minimize the heat and humidity ingress to a cold room box when a door is open the following solutions may be considered:

- Air curtains: vertical and horizontal flow air curtains are available, usually activated by a door opening. Determination of whether the air is to be warm or cooled will depend upon the type of cold room and location of the air curtain, the manufacturer's advice should be sought.
- Vinyl strip curtains inside doors provide a common solution; these should be heavy duty, and seal against the structure to minimize air leakage.
- An ante-room, operated like an airlock, so that only one pair of doors is open at a given time.

The main goal of the airlock is to reduce the room temperature recovery time. In the case of a low humidity cold room or freezer, the airlock also can minimize the ingress of moisture, helping reduce the defrost frequency required, or could be used indirectly to control the humidity in the conditioned space if the airlock is maintained at low humidity.

6.2.10 *Electrical Systems*

Redundancy in electrical systems that provide power for refrigeration equipment and control systems is considered vital.

Cold rooms should have a backup power supply able to handle 100% of demand to protect from power failures. Control and monitoring systems also should have UPS back-up.

6.2.11 Lighting

Lighting design should be appropriate for the area served and should not adversely impact the stored product quality. The lighting construction materials, gasketing, illumination levels, glare, switching, and energy conservation should be considered. Lighting fixtures should be fluorescent, shatter/moisture-proof types with high efficiency solid state electronic ballasts and tubes for rooms operating below -10°C (14°F). Alternatively High Intensity Discharge (HID) lighting can be used, but should be evaluated by the design team for proper application. Sufficient quantity of light fixtures should be installed to provide for a uniform intensity level throughout the cold room. The lighting design should consider energy management system and may include an on/off timer and presence detectors such that the lights are off when no personnel are present. Emergency lighting should be of the non-maintained battery back-up type with running man symbols and be provided above each personnel entrance/exit doors to meet local regulations.

6.2.12 Racking Selection and Layout

Racking in a cold room or freezer should not interfere with air distribution (e.g., block air inlets or exhausts). The use of perforated shelves to allow for increased air flow should be considered.

The layout of the racking should be considered in relation with the location of the doors and access space requirement to minimize the impact on stored product of incoming air when the doors are used.

Racking may be subject to regular cleaning; therefore, the design should be easily cleanable with a finish that will be resistant to the specified cleaning agents.

6.2.13 Freezer under Floor Heating System

Under floor heat cable systems may be considered as the last of the possible available alternatives to adopt to prevent frost build-up. The system should be thermostatically controlled and be ground-fault protected. The heat cable should be installed in rigid conduit so that it can be replaced if necessary. An alarm is recommended to detect a faulty heating cable.

6.2.14 Refrigerant Selection

Refrigerants are the fluids that, in the cooling systems based on the vapor compression cycle (reverse type), will absorb the heat from one area through evaporation and will discharge it to another through condensation.

Other approaches to achieve refrigeration are available, but are considered to be of minor importance for this application and included for the sake of completeness:

1. the Peltier effect (or thermoelectric effect) used for systems operating at temperatures less than -160°C (-256°F)
2. lithium bromide/water and ammonia/water solutions used for absorption refrigeration systems

Aspects to consider when selecting a refrigerant include:

1. the safety aspects
2. the environmental impact
3. the thermodynamics
4. the chemical stability on the operating conditions
5. the compatibility with the materials used for the plant components

6. the compatibility with the lubricants

7. availability

8. cost

Safety and the environmental aspects are considered vital.

6.2.14.1 Safety Aspects

Safety aspects include toxicity and flammability. If the refrigerant is denser than air, it can replace the air in a room giving a potentially dangerous low oxygen environment.

ANSI/ASHRAE Standard 34 "Designation and Safety Classifications of Refrigerants" (Reference18, Appendix 5) has classified fluids in regard to these two issues.

The toxicity level is defined according to the: Threshold Limit Value – Time Weighted Average (TLV-TWA). It can define the maximum charge of refrigerant in a specific application and introduce one other selecting criterion, providing the capability to detect a leakage from the system.

6.2.14.2 Environmental Considerations

Traditionally, many refrigerants were chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), as they were considered very safe and efficient. After the finding that they contribute to ozone depletion, concern on their use lead to the inclusion of CFCs and HCFCs in the Montreal Protocol, which came into force in 1989. The Montreal Protocol defined a phase out of such substances.

The phase out for HCFCs is less stringent than that for CFCs and will mean a progressive reduction of production until to the 2025 for some countries and 2040 for all the others.

Hydrofluorocarbons (HFCs) were not regulated.

The Kyoto protocol of 2005 focused on global warming and defined HFCs as greenhouse gases. HFCs are still in use, but new solutions with less impact on the environment are in development.

In the future, these studies could result in a 4th generation of new fluids or encourage the use of natural fluids such as Ammonia, Hydrocarbons (HCs) or CO_2.

Currently, refrigerants are selected according to:

- low Ozone Depletion Potential (ODP)
- low Global Warming Potential (GWP)
- low Total Equivalent Warming Impact (TEWI)
- atmospheric lifetime

Once these criteria have been considered, the fluids will be evaluated according their thermodynamic properties. These properties will directly influence the efficiency of the cycle and hence the energy consumption of the system, which has its own environmental impact.

6.2.14.3 Refrigerants

This section discusses industry acceptable refrigerants that can be considered for producing the cooling effect needed for cold rooms. The temperature storage range of the products and the compressor manufacturer will determine which refrigerant is best suited for a given operation.

(The refrigerants are numbered according to the internationally accepted ASHRAE nomenclature).

6.2.14.4 R-134a

This is a high pressure HFC (1,1,1,2-Tetrafluoroethane) without chlorine:

- The ODP is equivalent to 0.
- The Global Warming Potential (GWP) is significant (about 1400).
- The atmospheric lifetime in air is 14 years.
- The toxicity is very low.
- It is not flammable.
- The compatibility with the materials used for the circuits is high.
- Applicable for use in large and small plants down to approximately 0°C (32°F).

6.2.14.5 R-600a

This is a high pressure HFC (Isobutane):

- The ODP is equivalent to 0.
- The GWP is negligible.
- Applicable for use in small size cold rooms operating at temperatures close to or above 0°C (32°F) requiring low quantities of refrigerant.
- The atmospheric lifetime in air is lower than R-134a.
- The toxicity is very low.
- It is highly flammable.

6.2.14.6 R-404a

This is a near azeotropic blend of HFC refrigerants R-125, 143a and134a without chlorine:

- The ODP is equivalent to 0.
- The GWP is high (about 3800).
- The toxicity is very low.
- It is not flammable.

- Applicable for use in low temperature freezers from -15°C to -35°C (5°F to -31°F).

6.2.14.7 R-507

This is an azeotropic blend of HFC refrigerants R-125 and R-143 without chlorine:

- The ODP is equivalent to 0.
- The GWP is high (about 3900).
- The toxicity is very low.
- It is not flammable.
- Applicable for use in low temperature freezers from -15°C to -35°C (5°F to -31°F).

6.2.14.8 R-508

This is an azeotropic blend of HFC refrigerants R- 23 and R-116 without chlorine:

- The ODP is equivalent to 0.
- The GWP is very high (about 12000).
- It is considered when the required temperature is -35°C to -80°C (-31°F to -112°F).
- The toxicity is very low.
- It is not flammable.
- Applicable for use in very low temperature freezers below -35°C (-31°F).

6.2.14.9 R-508B

- The ODP is equivalent to 0.
- The GWP is very high (about 12000).
- The toxicity is very low.
- It is not flammable.
- This is an azeotropic blend of HFC refrigerants R- 23 and R-116.
- Applicable for use in very low temperature freezers below -35°C. (-31°F).

6.2.14.10 R-717

R-717 (Ammonia) is a natural gas and is the most energy efficient of the refrigerants listed it is commonly used in Europe, with increasing usage in the US.

- It has an ODP equivalent to 0.
- The GWP is 0.

- The toxicity is very high.
- Use for low temperature warehouses down to -35°C.

6.2.15 *Fire Protection and Fire Detection*

System design should comply with the relevant local and national codes.

There are unique considerations for cold rooms and freezers due to their operating conditions. Cold rooms and freezers usually use dry systems, as the potential impact of a faulty sprinkler on stored product would be significant. The air used to pressurize the pipe work also should be dry (low pressure dew point), so that there is no risk of condensation forming on the inside of the pipe work, causing corrosion. The advice of the insurer should be sought when designing, installing, maintaining, and testing systems for these applications.

Carbon dioxide (CO_2) systems may be used for some applications.

Aspirated fire detection systems are commonly used for large spaces. When installing these units in a freezer, the potential impact on the system during a unit cooler defrost should be considered; the water vapor that may be released during the defrost will condense on any local cold surface, such as the aspiration system pipework, and may impede airflow through the system.

6.3 Pre-requisites to Commissioning

During the design phase, engineering design reviews should be performed to verify that critical aspects have been addressed in terms of equipment performance specifications, and that efficiency and reliability aspects (e.g., standby systems, maintainability, alarms, and equipment failure detection) are adequately addressed. The approved design will then be constructed, ready for commissioning.

Related systems needed to operate the unit under test should be previously commissioned to allow for complete and representative testing.

Commissioning and calibration of any supporting mapping/monitoring systems should be complete although the final sensor locations for the monitoring system may not yet be defined. The data obtained from the mapping results may be used to help define the final locations for the monitoring system sensors.

The local surrounding environment should, where possible/applicable, be kept or simulated at the worst case conditions to challenge the unit during commissioning.

The following aspects also should have been considered and responsibilities defined (typically in a commissioning plan) before work commences:

- review and approval of test method statements
- progress reporting
- problem reporting (punch list)
- handling of test discrepancies
- definition of drawings to be used for commissioning (and subsequent qualification)
- location and marking of mapping points

- expected range of test results
- test witness requirements and test notification procedures
- handling/retention of raw data
- provision of operational consumables and commissioning spares
- format of the commissioning report
- defined responsibility for operating the plant during commissioning until it is handed over to the user
- formal operating log for the system covering start up to handover

(**Note:** the level of detail will vary considerably depending on the type of unit, e.g., a packaged standard unit may have less detailed information than a specialist refrigerated storage room.)

The following aspects also should be included in a commissioning plan unless they have been covered elsewhere, e.g., in a project execution plan:

- tagging and labeling requirements for ductwork, pipe-work, equipment, instruments, and valves
- responsibilities for installing and checking tags, directional arrows, and labeling
- how drawings will be managed to ensure they reflect approved changes
- document control
- management of change control

A construction or field turnover package should be maintained for inclusion with the commissioning documents in the final turnover package. Contents of the construction or field turnover package may include:

- equipment and instrument lists
- materials receiving and inspection reports/material certifications
- equipment receipt and/or installation verification records
- cable tests (continuity, insulation)
- grounding (earth) tests
- motor "megger" (resistance) and direction of rotation tests
- fuse and breaker ratings/overload settings
- control loop checks
- instrument calibration records/certificates
- alarm checks
- piping leakage (hydrostatic) tests

- pipework cleaning/flushing records
- record of cleaning for ductwork
- ductwork and Air Handling Unit (AHU) leakage tests
- cold room integrity test (small open penetrations may result in large condensation issues)
- operation and maintenance manuals
- as built drawings/specifications
- refrigerant logbook

6.4 Commissioning

The level of testing and the specific test requirements for commissioning will depend on the type of system and how critical performance is to the product and or business.

The scope of work required for commissioning should include confirmation that equipment and materials have been received, checked, and documented, and that they have been installed per specification. These activities will usually be assigned to a construction manager and are included in the list below for completeness. The required commissioning activities and tests will then be completed and documented on test record sheets.

Commissioning activities usually fall into four broad categories:

1. inspection of the physical installation (e.g., field verification of installation drawings) and documentation (test) verification (e.g., pipework pressure/leakage tests)
2. setting to work, defined as setting a static system into motion or "shake down"
3. regulation and adjustment
4. functional and performance testing

Personnel performing commissioning also may be employed to oversee construction quality.

6.4.1 Inspection of the Physical Installation and Documentation Verification

The first stage of commissioning confirms that:

- the system is installed in accordance with the specifications
- as built or record drawings are available
- instruments are calibrated
- engineering quality tests are completed per specification, e.g., pipework leak tests, ductwork cleaning/leak testing

6.4.2 Setting to Work

The second stage of commissioning then checks the utilities supplied to the system are as specified with any safety settings correctly adjusted, e.g., overloads, pressure relieve valves, fuses installed have the correct ratings. A formal inspection of the system may be performed prior to start up to ensure that the installation is safe (emergency egress is available, fire detection/protection systems are in place operating, refrigerant leakage systems available, etc.); then the system is started. Where cooling tower water is used, the commissioned status of the water should be checked. Commissioning should have been satisfactorily completed, otherwise a strategy may be developed to allow system commissioning to continue, e.g., through monitoring of the cooling water flow and temperature – to ensure that it remains within specification during testing.

6.4.3 Regulation and Adjustment

During this stage, the system should be tested and adjustments made to ensure that it operates in accordance with the specification.

Note: the generation and approval of specific test method statements is considered necessary prior to commencing commissioning activities to ensure that personnel performing commissioning has an understanding of how the system operates and any potential interactions with other systems for the final two stages of commissioning. In this stage:

- Control loops should be properly tuned and tested to ensure that they operate as specified.
- Alarms and interlocks function should be tested to ensure that they operate as specified if this has not been done previously. (**Note:** set points may be defined and checked here or defined as a result of the testing, then documented.)
- Sequences of operation should be tested to ensure that they operate as specified (including start-up, shutdown, and power failure tests).
- System components should be tested to ensure that they perform the specified duties (e.g., fans, coils, humidification, and de-humidification equipment).

6.5 Mapping Sensor Locations – Number of Sensors Required

It is normal practice to put the mapping system in place prior to carrying out the testing of the system – the data confirms satisfactory operation and can be useful in analyzing and performance issues.

This Guide focuses on the environmental conditions as the primary control philosophy.

Because of the diversity of product formulations (e.g., aqueous and non-aqueous, lyophilized, solid, semi-solid) the location of monitoring probes inside the container that will house the product should be considered when it can be demonstrated to provide significant data.

Cold rooms and freezers within the scope of this Guide are typically used to maintain pre-cooled product at temperature; as the temperature fluctuation reported by sensors located outside the container will be wider than any fluctuation reported by a sensors located inside the product. It is normal practice to use the air temperature as the reference source for the stored temperature/hence the worst case representation of the stored product temperatures.

Although there is little guidance on the mapping of controlled temperature chambers, the following may provide useful information:

- The French Standard (NF X15-140 October 2002 Measurement of Air Moisture – Climatic and Thermostatic Chambers – Characterization and Verification) (Reference 12, Appendix 5)

- The German Standard DIN 12880 Electrical Laboratory Devices – Heating Ovens and Incubators (Reference 13, Appendix 5)
- The Australian Standard AS2853-1986: Enclosures – Temperature Controlled – Performance Testing and Grading (Reference11, Appendix 5)

Key factors to consider when determining the number and location of temperature sensors required to map a chamber are:

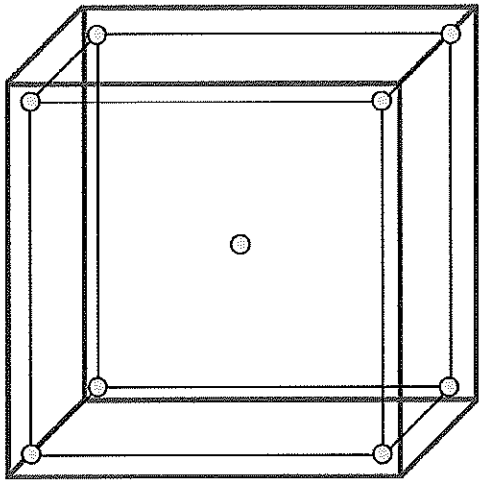
- Where will the product be stored?
- What is the layout of the racking?
- Where are the cooling units situated?
- What direction is the airflow – in duty and standby operation?
- How big is the unit?
- How many doors are there, and what is the normal usage pattern for the door?
- Where are the doors located?
- Will the mapping arrangement proposed detect air flow due to door opening on the product stored nearest the door?

Example Sensor Locations

The first example, which is relevant to chambers of up to 2 cubic meters (70 ft^3), represents the minimum locations that could be required for an open area (locating the sensors at the four corners (top and bottom) of the storage area perimeter and a center), but additional points may be needed depending on airflow sources/characteristics, shelving (storage locations), external temperature sources, and previous experience with similar units and their thermal behavior.

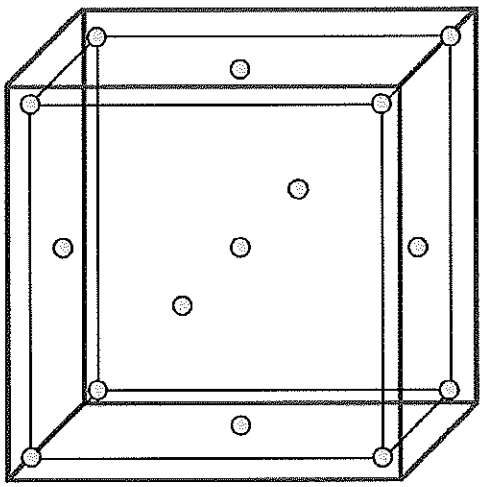
(**Note:** the inner box represents the working area (where product is stored), the circles represent the sensor locations).

Figure 6.1



For bigger volumes, up to 20 cubic meters (700 ft³) it would be appropriate to use a minimum number of sensors shown in Figure 6.2.

Figure 6.2



For reference purposes, it is normal practice to keep a record of the external conditions; both outside the chamber and the outdoor conditions during any tests.

Where there are multiple cooling units, it may be possible to divide the chamber and treat each as a conditioned zone within the cold room and duplicate the mapping arrangement for each zone.

The sensor type should be investigated, a thermocouple, e.g., has a low thermal inertia, and will respond very quickly to a change in temperature, showing the air temperature.

Where relative humidity is a critical factor, then humidity sensors could be located in the same locations – or fewer locations used with the impact of the temperature considered for the other locations – as the absolute humidity will be very similar throughout the space.

Where a system is being qualified, the test method, acceptance criteria, location and number of temperature monitoring sensors should be pre-defined and pre-approved by the Quality Unit.

6.5.1 Functional and Performance Testing, including Load Testing

The final stage of commissioning should test the equipment to ensure that system performance during simulated use meets specifications. There are a number of approaches regarding how this testing is conducted.

Key factors to consider include:

- the load mass
- the air flow patterns
- the incoming load volumes/temperature
- outgoing load volumes
- frequency and duration of loading/unloading
- the door opening
- the defrosting cycle (if any)

The load has an important influence on the cold chamber temperature distribution for two reasons:

1. the load mass/temperature will impact the system performance
2. the load volume will influence the air flow patterns

Temperature distribution studies should consider normal use, i.e.:

1. temperature mapping with chamber at low load (or empty) and door in use
2. temperature mapping with chamber with simulated full load and door in use

The effect of the defrost cycle should be included in the testing where applicable.

The potential for performance of a simulation of the full load scenario can be influenced by the size of the chamber. When defining a full load test, the variability of the mass/thermal data of the several products stored should be considered if the unit is being used to cool the load. This may require a specific test, which monitors the product temperature.

Where the unit is not being used to cool the load, the potential impact of the load on the system airflow should be considered.

The temperature mapping with door in use should demonstrate the system "in use" performance, showing the temperature reached, the area affected, and the recovery time needed. The testing procedure should be defined according to the User Requirements that should specify how often the door will be used and how long it may be kept open.

According to the location and the type of cold chamber, the need of seasonal (summer and winter) temperature mapping should be considered.

The following tests are suggested.

6.5.1.1 Control Loop Tuning

Where PID loops are used to control the system, their tuning should be demonstrated by the supplier, e.g., challenge the control loop by adjusting set points, and observe the system response – confirm that the system performance is satisfactory or retune the appropriate control loop and repeat the test.

6.5.1.2 Normal Operation

The performance of the unit should be monitored for a defined period of time.

The unit that provides the widest temperature variation and the one that may provide the in operation worst case results should be determined. For example, if the system has standby and duty cooling systems with one system having a unit cooler nearer the door opening than the other, the cooling system with the unit cooler furthest from the door will usually give worst case conditions for the stored product because the incoming warm air will be subject to normal convection, not mixed with the cold room air using a fan until it is further into the room. The rationale for selecting which system should be used to continue testing should be documented. (This approach is considered simpler than duplicating tests with both cooling systems.)

6.5.1.3 System Recovery

Cooling systems should be turned off and the unit allowed to stabilize to a predefined temperature – usually this is above the maximum allowable operating temperature and below the external conditions with the door open. The door should be closed and the cooling system started, allowing the room to return to normal operation.

The test should be repeated with the worst case thermal load in the unit, operating the unit until stable operating conditions are established.

These tests should confirm the worst case room heat up times (i.e., the unit operating with no stored thermal mass – this data can be useful for maintenance purposes (it can be used to define the maximum time the system can be shut down for).

6.5.1.4 Load Test

The worst case conditions of internal load with the doors open should be simulated for the specified maximum time if this is specified. The unit should be allowed to operate until stable conditions are obtained. Data should be reviewed and compared to the requirements of the User Requirements to ensure that the requirements have been met.

If the test results have not met the requirements, the designer/supplier should be asked to review the data and make recommendations for corrective action to ensure that once commissioning has been completed, the system complies with the design specification.

If the system is to be challenged to determine how it would perform in the event of any equipment failures, these tests can be performed at this stage to provide information that may be useful to operations, e.g., the potential impact of a failure of a unit cooler.

Specialized system components, such as dehumidifiers, may have a separate commissioning report from the specialist supplier. It is considered permissible to use this as a reference with the "proof of performance" extracted from the report and inserted as a single summary sheet within the body of the commissioning report (to simplify review).

6.6 Qualification/Verification

There is a wide range of approaches to the qualification of equipment including:

- utilizing the guidance provided in the ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5)
- the science- and risk-based approach based on ICH Q9 (Reference 4, Appendix 5)

In addition, there are potential approaches between these two models.

The approach described in ISPE Baseline® Guide on Commissioning and Qualification is addressed in this section. An example of a risk-based approach is described in Section 12 (Appendix 1) of this Guide.

6.6.1 Commissioning and Qualification

In this approach, the qualification of the system is performed as a separate and distinct activity to the commissioning although the test results from commissioning tests may be used to support qualification.

The use of commissioning tests requires a robust engineering change management system to be in place so that the impact of any changes to the system carried out during the commissioning process on previous tests or documents are understood, the validity of the test/document confirmed, or revisions retests carried out as required.

A typical structure for the qualification documents is as follows:

6.6.1.1 Design Qualification

For off the shelf equipment, the design will be standard, "qualification" of the design would usually be limited to ensuring that the equipment will operate in accordance with the user requirements.

For a bespoke or custom system, the qualification of the design may involve a detailed review of the equipment design and layout using the appropriate SMEs to ensure that it will meet the user requirements.

6.6.1.2 Installation Qualification

The documented verification that the facilities, systems, and equipment as installed or modified comply with the approved design and the manufacturer's recommendations. (Annex 15 to the EU Guide to Good Manufacturing Practice (Reference 9, Appendix 5)). IQ is also used to confirm that the correct data is available to populate the instrument calibration and maintenance management systems and that installed instrumentation is calibrated as specified.

6.6.1.3 Operational Qualification

The documented verification that the facilities, systems, and equipment as connected together can perform effectively and reproducibly, based upon the approved process method and product specification. (Annex 15 to the EU Guide to Good Manufacturing Practice (Reference 9, Appendix 5)). Factory Acceptance Test (FAT) and Site Acceptance Test (SAT) results are often used to confirm satisfactory operation of the equipment as part of this activity.

6.6.1.4 Performance Qualification

The documented verification that the facilities, systems, and equipment as installed or modified perform as intended throughout the anticipated ranges. (Annex 15 to the EU Guide to Good Manufacturing Practice (Reference 9, Appendix 5)).

Where used this should confirm that the system operates to meet specification over the normal operating range – for a cold room this could include:

- open door tests:
  - to determine the impact of an open door on the temperatures in the designated storage areas
  - This test should consider different load configurations/test conditions. The worst case scenario may be with the chamber empty, i.e., no internal thermal mass.
  - The test result may be used to define the maximum door open time or to demonstrate that conditions remain within the specified limits with the door left open.
- load test:
  - testing to determine the impact of the worst case operational load (usually integrated with a door test)
  - This may include a cooling load – to bring the stored material down to the storage temperature or just the impact of the stored product volume on the airflow in the chamber.
  - The qualification tests should be used to show that the results shown by the monitoring system are representative of the conditions seen by the stored product.

Organizations may choose to combine IQ and OQ into one document.

Organizations may carry out all the testing in OQ with no PQ stage.

Combining documents may reduce the cost of document generation, approval, execution, and storage.

7 Portable Packaging or Shipping Systems

Portable packaging or shipping systems have a more demanding role than fixed systems. In addition to protecting the product from fluctuations in the external conditions, (in the same way as a fixed system) they also should retain both their integrity and the product conditions during transit.

There are two main equipment categories of portable systems:

1. active

2. passive: those systems that use a phase change material to provide the heat sink or cooling source

The choice of portable system depends on an analysis of the product requirements, shipping routes, and transit methods and durations.

Where several portable systems are acceptable on a technical basis, an analysis of costs may be applied to determine which portable system is used. The costs of qualifying a new portable system should be included in this analysis.

7.1 Active Systems

Active systems are those systems that employ a container including a powered conditioning system, e.g., refrigeration system (i.e., requiring an internal or external power source).

- Systems that are used to transport foodstuffs may be covered by the ATP "Agreement on the International Carriage of Perishable Foodstuffs and on the Special Equipment" to be used for such carriage. This provides specifications for the equipment, and the internal temperatures – provided these align with the acceptance criteria for the product. Systems meeting these requirements are considered fit for purpose (Reference 20, Appendix 5).

(**Note:** for pharmaceutical products, it is more common to see refrigeration systems, rather than heating systems):

For an active system the specifications should be defined in a user requirement specification and may include:

- the modes of transport to be used. (It should be noted that some aircraft are restricted in the size/shape of containers they can handle.)
- the methods of handling available during transit, e.g., pallet trucks/fork lift trucks
- the available power sources (utilities) and connection types available or required en route
- the conditions required for the product (temperature, humidity, light, etc.)
- the range of potential shipment sizes and weights
- the environmental conditions in which the unit should be capable of operating (where known)
- the total transit time and durations of each stage (minimum and maximum expected)

Where this information is not available initially, it should be developed as the shipping options are reviewed and evaluated. User requirements can be developed as more information becomes available.

7.2 Passive Systems

Passive systems are those systems that use a non-mechanical refrigeration or heating sources. Cooling is the more common requirement. The energy required for cooling is usually provided by the energy given out as a material goes through a phase change (e.g., ice to water). This maintains the product at specified conditions through conduction and/or convection.

7.2.1 Phase Change Materials

These materials can be natural, such as ice or dry ice, or engineered. The engineered materials can be specified to change phase at a precise temperature to suit the product or package, e.g., -40°C (-40 °F). The phase change materials may be contained within hollow panels providing re-usable sections that fit together to form a box. The box may be placed in an insulated outer container.

At the time of publication, there is rapid development in this technology.

7.2.2 Dry/Vapor Shippers

A dry shipper, also called a vapor shipper, is an insulated vessel constructed of materials compatible with the different temperature extremes and pressures associated with the application of cryogenics.

The low-temperature environments required can be maintained with cryogens (liquefied gases). The temperature provided by a cryogen ranges from its triple point to slightly below its critical point. Commonly used cryogens include:

- liquid ethane
- liquid helium
- liquid hydrogen
- liquid nitrogen
- liquid propane

The walls of dry shippers are usually porous, allowing absorption of cryogenic liquids. The walls absorb all free flowing liquid and prevent fluid entering the product storage vessel during transit. Primary container closure testing conducted during product development should cover all aspects of long term storage as well as any transport temperature exposure.

It should be noted that the use of these units requires preparation time to charge the vessel prior to shipping (typically 6 to 12 hours).

This technology can maintain conditions for up to 10 days (depending on the unit size and conditions).

7.3 Insulation Materials

Both active and passive systems rely on good insulation from the environment. Most materials used are non porous. If porous materials are considered, they should be fully sealed, as any moisture ingress will significantly impair the performance of the material.

The efficiency of the thermal insulation is measured as thermal conductivity (K or U value) or more usually for this application, as thermal resistance (R-value):

- The R-value is the ratio of the temperature difference across the material and the heat flux (heat flow per unit area) through it; the bigger the number, the better the insulation.
- R-values are given in units of ft2•°F, h/Btu in Imperial units or m2•K/W square or (equivalently to m2•°C/W) in the SI system.
- R-values may be cited without their units, e.g., R-3.5. The correct units can usually be inferred from the context and from the magnitudes of the values.

Materials may be used in two ways:

- molded packages that can be supplied in standard sizes or custom made
- sheet material that may be cut (or pre-cut) for a specific application

Commonly used insulation materials include:

- Expanded Polystyrene (EPS)
- Polyurethane (PUR)
- Vacuum Insulated Panels (VIPs)

7.3.1 Expanded Polystyrene

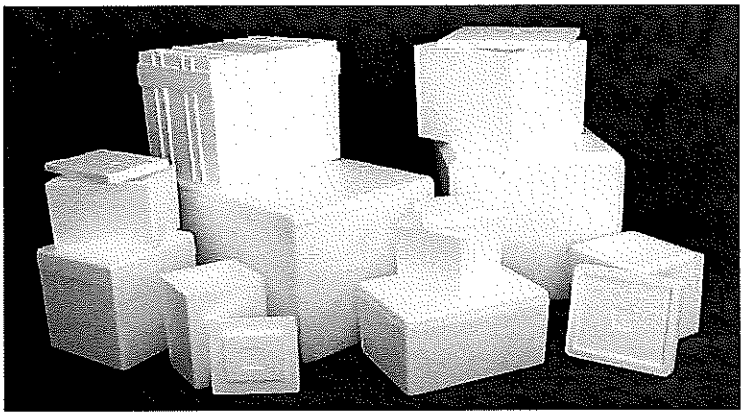
Expanded polystyrene (EPS) is one of the most common materials in use (at time of publication). While it is generally used for its insulation properties, the material is also good at protecting products from physical shocks. Many single use applications specify this material.

Production of EPS is a mature technology; advantages of the material include low density/weight, low cost, and flexibility (can be molded and fabricated). The insulation is relatively low with an R value of approximately 4.

EPS may be reprocessed, but the ability to reprocess EPS is dependent on the geographical region.

Examples of molded EPS insulated shippers are shown in Figure 7.1.

Figure 7.1: Examples of Molded EPS Insulated Shippers



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7.3.2 *Polyurethane*

Polyurethane (PUR) is also a commonly used insulation material (at time of publication). PUR is usually molded, and considered to be more robust (not as brittle) than EPS. It has better insulation properties than EPS. PUR is usually selected where higher performance (R values of 7 to 8) and reusability are required. The material is heavier than EPS.

Expanded polyurethane is also used frequently with the advantages of improved insulation, lighter weight, and can be less resistant to damage unless combined with a support material such as corrugate or hard shell plastics.

7.3.3 *Vacuum Insulated Panels*

Vacuum Insulated Panels (VIPs) are a comparatively new technology (at time of publication) for this application. Pre-formed panels offer significantly higher thermal performance with R values of around 40. Although the panels are re-usable, they have a cost premium. (Note: if the panels are to be re-used, the integrity of the vacuum should be verified since this is critical to the performance). Panel insulated shippers are typically composed of six matching components (sides, ends, top, and bottom) and are more likely to be subject to increased thermal losses at the corners, especially when subjected to drop and vibration forces. The overall performance of the package is reduced by the corner joints.

The design of these systems means that the containers are collapsible; therefore, they may be returned to the manufacturer and re-used.

7.4 Alternative Designs

Containers that do not require refrigerators or freezers are available. These operate on a system where a chemical and water combination is released by depressing a 'button' on the top of the cooling brick. A temperature of between 2°C and 8°C (36 ° and 46 °F) can be achieved within 5 minutes of initiation and can be maintained for up to 78 hours, depending on pack size, configuration, and external temperatures.

At time of publication, there is ongoing development in the area of passive systems, because the packaging and related processing represent a significant operational cost, and the process and materials used are of environmental concern. These factors encourage organizations to carry out a periodic review of the process to ensure that the technology being used represents the best value.

7.5 Developing a Distribution Process and Qualifying a Shipping Process

There are several options for approaching the development of a distribution process and qualification of a shipping process. Guidance on one such approach is contained in ISTA Procedure 7E (Reference 14, Appendix 5). An alternative approach is described in this section.

Available options should be considered and an approach which is best suited to an organizational structure and systems should be agreed.

The initial requirements for distribution of a product should be clearly defined and may include:

- product storage conditions – (temperature, humidity, or other sensitivities, e.g., UV, exposure to CO_2, radiation, pressure)
- Final destinations:
  - This may include major distribution centers, as well as local distribution centers.

- hazard classification (in accordance with IATA for air, DOT for ground, IMDG for sea)
- potential transportation time ranges and modes of transport
- external temperature profile to which the material will be subjected (potential seasonal variations should be noted)
- likely variation in quantity and schedule requirements for deliveries, e.g., 4 lbs (1.8 kg) every day
- capabilities required/available at the destination, e.g., acceptable pallet sizes/weights

A distribution process map may then be developed, defining the:[2]

- shipment size range per shipment stage
- selection of the optimum shipping method
- selection of shipping routes
- selection of the shipping material (packaging)
- selection of the temperature monitoring system
- preparation of the shipping unit
- reception of the shipping unit (touch points)
- release of the shipping unit
- qualification of the shipping unit/method/route

Packaging and any re-packaging requirements can be defined using this information for each shipment stage, for investigation, and selection of the chosen solution.

Aspects to consider at this stage include:

- ground transport (trailers) – non urgent domestic commonly used for regional (cross-border) transport, e.g., throughout Europe
- ocean (containers) – not time restrictive, temperature sensitive (usually only worth considering for full container loads; offers a more tamperproof (sealed), generally, more temperature stable and more environmentally friendly mode of transport compared to air freight)
- integrated carrier – domestic or international deferred service
- express (next day)
- specialty (time, temperature, sensitive, shipment value, additional costs)
- shipping lanes – what are the needs of the shipment?

[2] Note that, although out of the scope of this guide, gathering this information also will allow the shipping documentation/inspection requirements to be defined.

- customs (customs regulations, import, and export licenses are outside the scope of this Guide, but should be understood by the organization.)
- brokerage arrangements
- temperature control during clearance
- transport schedules
- depot locations
- contingency planning, e.g., test shipments
- splitting shipments for contingency reasons
- handoffs, e.g., truck to plane
- receiving limitations in regard to utilities available and connection types, size, and storage
- requirements for breaking down bulk shipments and repackaging products for local shipment or distribution
- local suppliers of materials and services
- monitoring requirements, e.g., temperature

Figure 7.2: Transportation Options

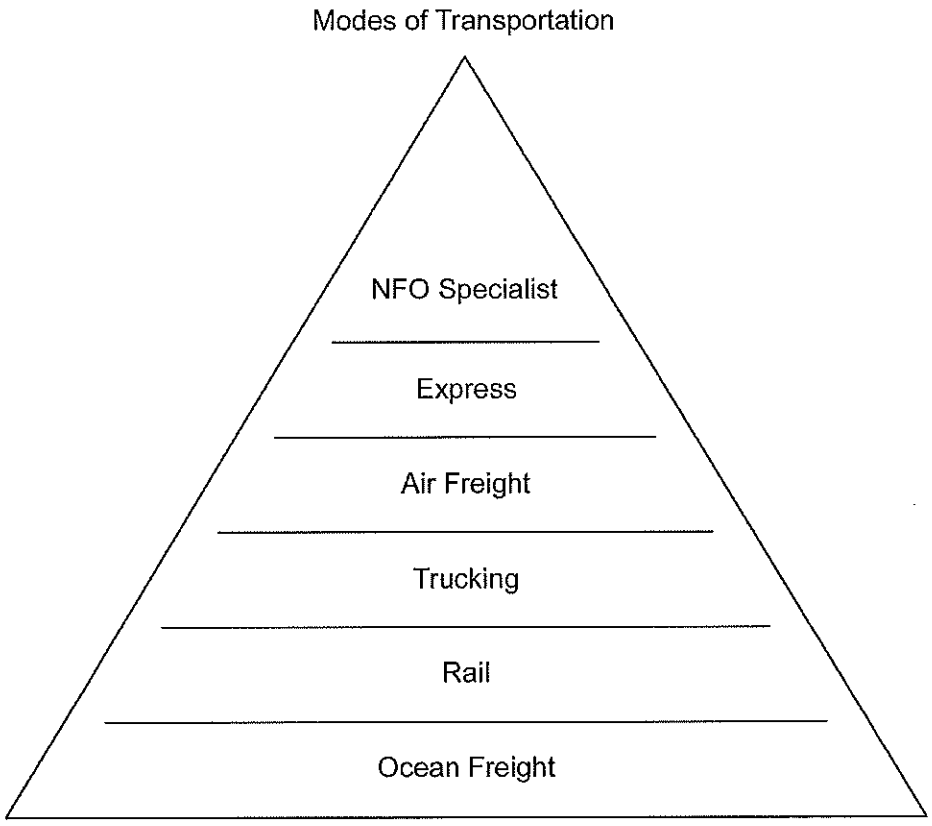


Figure 7.2 outlines various transportation options available; the largest volumes being shipped by ocean freight, moving up to the smallest volume by a Next Flight Out (NFO) specialist. The express portion of the pyramid refers to the large express organizations. The smallest niche in this arena falls to the Specialty Couriers on an NFO basis. As time, temperature, and shipment value has become of increasing concern, the need for the specialty courier has grown to fill in the service gaps of express organizations.

Original distributing site packaging may be broken down and local couriers used for redistribution. (Note: this is not shown on Figure 7.2).

Where applicable, prototype packages of placebo product incorporating condition monitoring instrumentation could be constructed and performance tested before shipping trials are arranged with product. This should confirm the physical strength of the container and can be used to define risk to product.

A risk assessment for each shipping stage should be used to help to improve the definition in user requirements specifications and in developing packing and shipping solutions and procedures.

The overall process requirements may include:

- provision of local conditioned and monitored hold boxes to prolong the permissible time allowed for a package
- a well defined pack-out process for maximum efficiency ensuring minimal product exposure (pick/pack) considering:
  - Transferring material into preconditioned containers to minimize the time the container is open to warm air. (Storing the containers in a controlled environment: typically, container manufacturers recommend storing the container at ambient conditions for a specific period of time prior to utilizing the container. This minimizes the risk of driving the inner temperature of the container below intended ranges. It may be necessary to pre-cool some containers). The impact and likelihood of condensation should be considered.
  - Time required for a shipping package to reach thermal equilibrium after closing. This typically takes 30 to 90 minutes depending upon the size of the container and the temperature of the air outside the container. (The location used should be in an area with a low risk of frequent temperature swings, such as near outside doorways, beneath air supply vents, etc.)
  - systems and equipment to pre-condition all components used in the packaging of the shipment.
  - use of a conditioned environment to pack the shipment such as walk-in storage – significantly reducing the time required to pre-condition the product load area
- Additional coordination of the cooling medium may be required, such as the use of an insulated storage cart or similar device, to ensure the thermal heat of the gel packs is preserved and that the gel packs are not exposed for an excessive period to the external environment during the packing process
- pre-conditioning of gel packs is usually required to prevent thermal shock to the product, particularly for small packs
- post packaging handling of shipping containers
- temperature monitoring of shipments/containers (Note: data are owned by the party which owns the monitoring device. Data may be kept on file by multiple parties.)
- review of this data as a pre-requisite to releasing the shipment for distribution
- cleaning, sanitizing, and hold time limits for the shipping/storage containers

- pre-use inspection requirements for the shipping/storage containers
- documentation checks/reporting
- First-In-First-Out (FIFO) may be used to identify the order for handling both product and stored packing materials.

When evaluating potential solutions the following should be considered:

- life cycle cost
- customized solutions versus off the shelf solutions
- pre-qualified systems
- recyclable systems
- storage time required at specified conditions
- environmental considerations (recycle) – carbon footprint, organic, inorganic, foam, etc.
- storage space requirements, any assembly/disassembly/test requirements
- excursion assessment process
- ambient exposure
- availability of the systems (in terms of quantities and geographic location)
- seasonal demand (e.g., allergy treatment)
- complexity of the shipping system
- potential failure modes/operating limitations
- potential shipping unit return costs
- impact of a lost shipment

7.5.1 Qualification/Verification of a Shipping Method

A shipping method may be considered qualified/verified if the capability of the shipping system to maintain the required product storage conditions when exposed to a predetermined sequence of external conditions is documented after adequate testing to confirm the repeatability of the results.

The qualification/verification process also should confirm the location of temperature and other monitoring devices that show the worst conditions the shipped product could experience during routine shipping.

Product requirements should be known from the outset and the transportation sequence outlined accordingly. Items to note include:

- Temperature and humidity profiles may be determined by the season, location, and the interactions with the shipping method – if multiple choices are available, the "design space" or potential range of conditions needs to be defined, along with the packing suitable for that range.

- Ground transportation may be achieved by a truck subject to the influence of the external conditions (temperatures) or by a temperature-controlled truck.
- Air transport temperatures depend on the size/type of the aircraft and which cargo bay is used.
- Sea transportation also may be used – transit and dock conditions should be considered.

The organization conducting the qualification/verification is normally considered responsible for accurately mapping the transportation sequence and determining the acceptable range of conditions (design space) or acceptance criteria.

During primary container integrity testing, air freight pressurization differentials should be considered to cover transport eventualities.

The design space may be determined by actual measurement, use of supplier data, or by reference to published standards, e.g.:

- International Safe Transit Association (ISTA) Procedure 7E (Reference 14, Appendix 5) or supplier data.
- Archival recorded temperatures from the National Oceanic and Atmospheric Administration's (NOAA) National Weather Service (Reference 30, Appendix 5).
- Other nationally or internationally recognized weather databases.

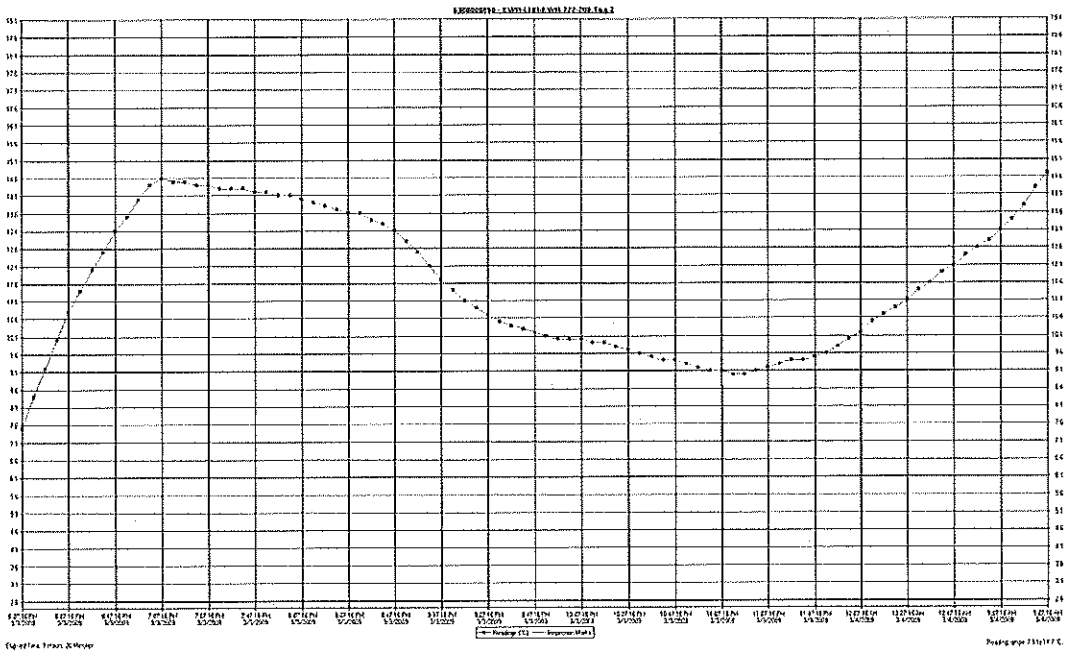
This published data can be supported by making actual or trial (lower risk) shipments through the transportation sequence to verify assumptions. This can be accomplished by the use of temperature recorders and humidity recorders, where appropriate, in product shipping boxes. Initial shipments, with either placebo or actual product, can be used as test shipments. These can be used to compare assumptions and measured readings for vibration and shock loads. Where actual product is used, product quality can be checked to verify it has not been affected by, e.g., vibration and shock loads.

The temperature profile for the designated transport sequence should be planned and mapped based upon an examination of actual data recorded by either the organization or through an accumulation of data from published reports. This data should be examined for ambient temperature extremes as well as average extremes and applied with specific reasoning as part of the design qualification process used to qualify the container.

Note that there can be significant differences between these profiles on the same route. Figure 7.3 and Figure 7.4 show two example temperature profiles to illustrate this point. These profiles provide details of the flight no., date, and location of logger.

Note: as the figures are intended only as examples to illustrate significant differences on the same route, information on the instrument type, range, accuracy, and confirmation of current calibration/calibrated range is not provided.

Figure 7.3: Sample Temperature Mapping of a Flight (1)

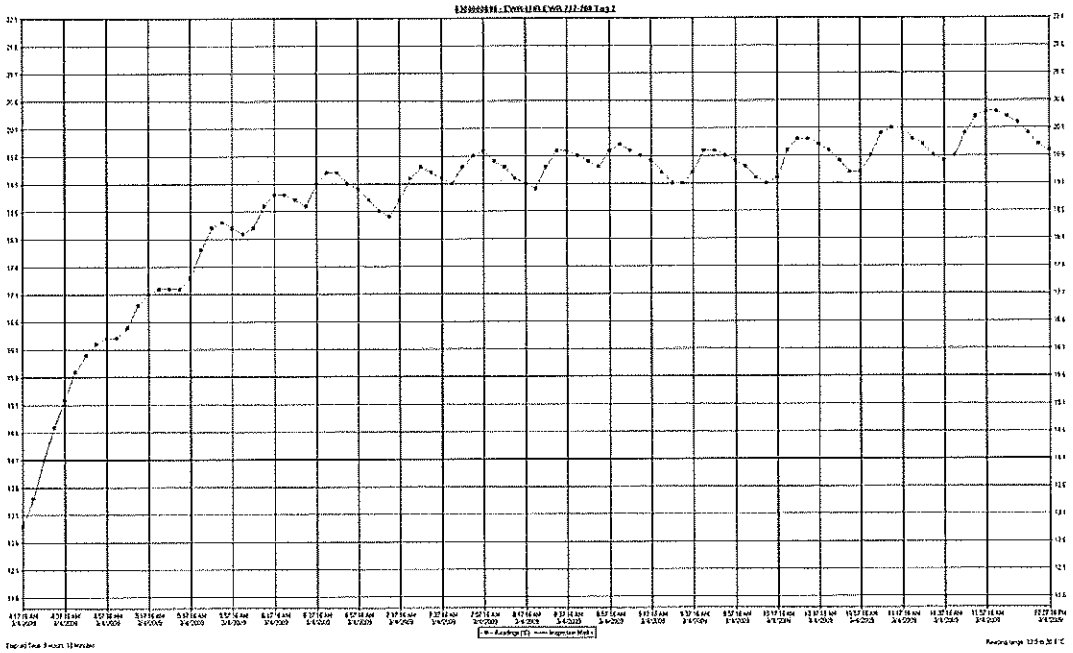


EWR>LHR-Flight 28 Departed 18:07 CST Arrived 01:18 CST-Aircraft Type 777-200-Ship 003

Sensor located on AKE33285CO-Position 25R

Temperature checkpoints are in Celsius.

Figure 7.4: Sample Temperature Mapping of a Flight (2)



LHR>EWR-Flight 29 Departed 04:28 CST Arrived 12:24 CST-Aircraft Type 777-200-Ship 004

Sensor located on AKE36865CO-Position 33L

Temperature checkpoints are in Celsius.

The acceptable degree of risk may vary between clinical and commercial product.

Clinical Supply Chain

The focus of the cold chain management approach for the clinical supply chain is typically based on maintaining temperature, unless there is adequate data that would identify other critical parameters, e.g., light levels.

Temperatures (and other defined characteristics) should be maintained within the defined stable range of the material with excursions allowable only as supported by data. Temperature should be monitored as necessary within the assurance limits provided by the qualification/verification of the transport and storage units. As such, platform technologies are generally employed for the storage of clinical stage biopharmaceuticals while stability data is generated for the product.

Clinical trial shipments tend to be lower in number, span a shorter timeframe, and may be to different destinations than the commercial product, so different approaches may be taken that have a higher degree of risk. For example, the packaging configuration can be developed based on an organization's experience and qualified using reference data obtained from a test chamber or selected based on the systems performance history. The actual shipments should be individually monitored with release dependent upon satisfactory review of the recorded product-space temperature data.

Note this arrangement requires:

- local infrastructure to be in place
- appropriately trained personnel and associated procedures to interpret the data/release the product
- product shipping condition limits to be known for the critical factors
- the capability to download and store the relevant data

Commercial Supply Chain

The focus of the cold chain management approach for the commercial supply chain is on the entire cold chain process and compliance with regulatory expectations and product filings. At the commercial stage there should be an established understanding of product attributes and verification of planned commercial transport supports. The product temperature stability profile should be well established, including storage temperature, allowable excursions, and the effects of freeze/thaw. There also should be available data on other physical restrictions such as limitations for CO_2 exposure, acidity/alkalinity, and vibration effects.

Commercial product tends to be from manufacturer to distribution center to pharmacies, hospitals, and clinics. These shipments are in qualified/verified shipping configurations, usually with internal temperature/condition monitoring to ensure that the shipment remains within the predefined acceptance criteria.

The degree of control offered by "standard" commercial applications may not be adequate. It should be noted that most temperature controlled trucks, trailers, and containers are not intended to meet GMP requirements.

The requirements for maintaining compliance with cGMPs include training, using written procedures for operation, maintenance, change control, and deviation handling. These may not be maintained by commercial carriers. From a quality perspective, the temperature of the transportation environment should not be relied upon.

Other aspects to consider:

- Shock – approved packaging (standard test methods, e.g., ASTM D4169-08 Standard Practice for Performance Testing of Shipping Containers and Systems (Reference 19, Appendix 5) or ISTA Procedure 7D (Reference 14, Appendix 5) may be useful).
- Vibration – the mode of transport/transfer points should be considered.
- The impact of any product/coolant leakage should be considered (particularly important for dosage forms utilizing dry ice, a nitrogen blanket, or a gaseous active).
- track and trace – requirements (see Section 11 of this Guide)
- proof of delivery
- data transmission of temperature/location

A risk assessment should be performed on the proposed shipping process with the product Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) defined (as determined through stability testing). The results of this assessment may be used to review and confirm the defined qualification/verification requirements.

Laboratory Testing

System performance may be qualified/verified in a test laboratory, simulating the worst case shipment conditions. ASTM D4169-08 (Reference 19, Appendix 5) or the International Safe Transit Association's specifications (ISTA Resource Book 2009) (Reference 14, Appendix 5) may be used to provide guidance for the development of the test protocols.

Tests may be customized according to available historical data from live shipments. The validity of the laboratory testing should be confirmed through monitoring of the initial shipments as performance qualification shipments.

Qualifying/Verifying the Process

The approach used to qualify/verify the process depends on an organization's practices. These may follow the commissioning and qualification process described in ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5) or a risk-based approach as described in ICH Q9 or ASTM E2500 (References 4 and 19, Appendix 5).

The traditional stages include:

- Design Qualification/Verification:

  The proposed equipment systems to be used for the shipment are qualified/verified by an experienced multi functional group to ensure that the proposed solution is robust and fit for purpose, considering the organization skills and experience. Parameters that may be measured during Design Qualification include:

  - product stability data – temperature acceptance criteria for the packout
  - drug product package information
  - number of shipments expected per day/week/month/year
  - mass/volume calculation – how much to qualify in the packout, minimum and maximum loads

- product image – primary, secondary, tertiary packaging, components
- risk assessment – value of goods, level of protection desired
- regulatory positioning – local requirements, product regulatory filing
- security considerations
- floor operations aspects – ease of use, floor logistics
- ship-to locations
- transit lane characterization
- critical component qualification – insulated shipper, temperature monitors, refrigerants, re-use/recycle applicability
- seasonality considerations – summer, winter, all-year

- Installation Qualification/Verification:

  As equipment/systems used for cold chain shipments may be rented and/or disposable, IQ/V testing as a minimum will consist of documenting the identification of the equipment/system and calibration status (where applicable). For equipment/systems which are rented and/or disposable, careful attention should be paid to the Quality Systems, Validation, and Maintenance Programs of the supplier. An audit of these programs can be used to reduce the level of routine qualification/verification by the user, with a quality agreement in place so that users are kept aware of any proposed changes.

The equipment specifications and the procedures used pack, handle load, and unload form a definition of the system. These should be reviewed to ensure that they are adequate as part of the approval process – these form an IQ/IV package in this context.

Operational Qualification/Verification

Operational Qualification/Verification testing usually consists of tests performed in a laboratory. These tests should demonstrate that the defined packaging or shipping solutions are capable of maintaining the defined internal conditions when tested using either product or a placebo (with similar thermal characteristics), when subject to worst case external conditions and durations.

Tests should include the requirement to identify cold spots and hot spots, and locations indicating the worse case stress to the product for other tests (e.g., shock and vibration tests). Testing may include turning the shipper upside down to simulate worst case conditions during transport within the specified packaging solution. Variable load sizes and the worst case load configurations, e.g., one sample with the minimum load and one sample with the maximum load should be considered. Typically, minimum load sizes are used based on the low thermal inertia/mass. Considerations for Operational Qualification/Verification testing include:

- design qualification should be complete
- an OQ test protocol should be in place
- temperature profiles should account for summer and winter variations
- time profile – logistical mapping

- minimum and maximum mass/volume of product (or placebo)
- repeatable testing – three times for each test, minimum maximum mass, seasonal packing
- thermocouples/temperature monitoring placement
- adequate data on supplier-qualified containers should be available
- deviations should be documented, investigated, and reviewed

Testing should be timed for a longer duration than the anticipated shipment time to allow for unforeseen delays during actual shipments. Worst case conditions can be simulated via a controlled temperature chamber set at the extreme high and low temperatures (as applicable) simulating other physical tests as required near the limits of, or outside of, the ranges expected to be experienced on the projected transportation route. Where appropriate (e.g.., qualification of a controlled temperature truck), static external summer/winter conditions can be used as worst case conditions with the choice of conditions, and impact of variations from those conditions defined and understood.

Where active systems are used, the function of the alarms and the set points to be used should be qualified/verified.

If a shipping company is renting equipment, testing will be required on a rented sample to qualify/verify that the solution is appropriate.

The location and quantity of calibrated temperature monitoring devices to be used should be included in relevant protocols and should be justified in a supporting rationale .See Section x of this Guide.

Where a new product has similar characteristics to an existing product, the data already available should be used to help minimize repeating testing where adequate data is already available.

Performance Qualification

Performance Qualification (PQ) testing may be included as part of the OQ/V. PQ testing should be performed under actual transport conditions, demonstrating that the packaging/transportation solutions, refrigerant types, loading procedures, and loading patterns maintain the defined temperature conditions under actual environmental extremes. Where applicable, PQ testing should be conducted during winter and summer months to ensure that worst case actual conditions are qualified. As defined in the OQ, worst case load sizes (as applicable) should be included during PQ (if applicable). Considerations for PQ testing include:

- OQ testing should be complete.
- A PQ test protocol should be in place.
- Three consecutive shipments should be tested on different days.
- Testing personnel should be trained.
- SOP should be in place.
- Shipping/distribution should be from or to the actual commercial shipping location(s).
- Routes, modes, seasons, and times should representative of commercial shipping conditions.
- Representative product loads should be utilized.
- One temperature monitor and one backup monitor should be included in each container/shipper/pallet with one additional monitor on the exterior.

- A PQ report summarizing results should be produced. Results should meet pre-determined criteria.

- Deviations should be documented, investigated, and reviewed.

Note: shipments which occur during the PQ timeframe, but do not meet the required environmental extremes required by the PQ, should be tested, documented, and verified in a rigor similar to that of the PQ.

PQ testing should be repeated a sufficient number of times to document replicate field transportation tests to demonstrate that the entire system/process is effective and reproducible. The number may change depending on the repeatability of the process; a minimum of three runs is common practice. Statistics may be used to determine an appropriate number. PQ testing may be performed prospectively using the actual shipping medium (i.e., drug product), an approved representative material, or concurrently using product.

Performance Monitoring

The location and quantity of calibrated monitoring devices should be included in the protocol and include the spots identified during OQ testing or equivalent. Devices should be placed directly in contact with the product containers or representative material where possible, to record the parameter as seen by the container; therefore, simulating the stability test conditions.

The approach that will be used to confirm that the packaging/shipping process is fit for purpose should be discussed and agreed with the Quality Department.

7.6 Ongoing Monitoring

Following a traditional model, after the successful completion of PQ, shipments should continue to be monitored for temperature at locations identified to be "worst case" in the PQ. The ongoing monitoring of a shipping program following PQ is critical for several reasons:

- The control variables (i.e., environmental conditions, time for each phase of transportation, condition of the containers, etc.) may change over time and exceed the limits tested within the qualification protocols during summer or winter conditions.

- The periodic use of monitors to check external conditions may be considered to confirm the actual conditions to those used for system testing/qualification/verification and provide accurate data for future use.

- Personnel and organizations outside of the shipment owner's Quality System are likely to be responsible for a portion of the transit.

- Shipping containers which are disposable or leased are outside of the shipment owner's Quality System.

- Potential mechanical issues of the shipping controls such as an RTD or a battery failure.

It should be noted that the PQ and an audit of the supplier's Quality Systems can help mitigate a large portion of the risks associated with the points above with a robust quality agreement. The quality agreement should be used as a supplier management process to maintain a formal change control and ensure that all changes to the process, shipping equipment, shipping lanes, supplier Quality Systems are understood and evaluated before implementation to understand any potential impact to the shipping qualification/verification. Integration into the supplier's process for the management of changes, their preventative maintenance, and calibration management program for any supplied equipment/shipping containers, and deviation/complaint handling process are critical to managing risk to the shipments.

The monitoring should be maintained based upon a risk evaluation and regulatory evaluation at pre-determined intervals, considering seasonal variation. A periodic evaluation of the monitoring data should be conducted to facilitate extension of worst case criteria and identification of problematic shipping routes/lanes helping assess the cumulative impact of multiple changes to the systems, degradation in equipment performance, and notice any unusual trends that may indicate a process or practice change, etc.

7.7 Governing Documentation

For shipping of pharmaceutical goods, the supplier maintains responsibility for delivering the product to the purchase organization and the product quality to that point. Responsibility for product quality transfers to the purchase organization on delivery. Records should be maintained, as the supplier should be able to recall that product in the event of a quality issue.

The transfer may be in a single stage or via an organization owned distribution center.

To manage and control these processes a series of documented procedures should be developed and maintained, these include:

7.7.1 Packaging System Specifications

The packaging specification should define the following:

- a brief explanation of how the packaging works
- the temperature range to which the material should be maintained in transit
- a specification of all of the materials used
- a list of the tests the unit has been subject to and passed

7.7.2 Standard Operating Procedure

Local Standard Operating Procedures (SOPs) should describe how the operator uses the packaging – to ensure that the method used for the qualification tests is copied. The scope may encompass the entire process or be subdivided to suit activities within the department, e.g.:

- receiving incoming packaging components
- receiving packed product from the packaging operation
- order receipt and dispatch (including packaging)

The packaging SOP may include the following:

- storage and pre-conditioning requirements for the packaging
- storage and pre-conditioning requirements for the gel pack
- temperature/status check of the gel pack before use
- checking the cleanliness of the shipping container, function, and alarm set points

- packaging instructions including package layout and any space requirements between containers with a list of the materials used
- location for temperature/humidity or other sensors

Where the responsibility for the distribution of product is outsourced or contracts are in place for some of the related goods and or services, a technical or quality agreement is usually established. These are written to clearly define the technical aspects, roles, and responsibilities related to the contract.

A technical or quality agreement may be in place between a pharmaceutical manufacturer and the immediate direct main transport company (contract acceptor) , but if a contract acceptor does not have a similar agreement with its subcontractors there may be a high risk that product traceability can be lost.

As part of the agreement, there should be a clear requirement that any subcontractors used are subject to the same terms defined in the agreement with the contractor. Other aspects to consider include:

- handling limitations
- procedures for cleaning (and sanitizing) shipping containers
- alarm set points
- actions required in the event of an alarm
- material classification – hazard level in accordance with IATA
- time limits
- storage location limitations
- receiving organization limitations – volume
- record requirements – maintenance, calibration, material name/batch number/expiry date when and where delivered, who accepted the product
- shipping limitations – type of transport that has been qualified
- action in the event of an emergency – accident/spillage/loss of goods

8 Mapping and Monitoring Equipment

This section provides information on mapping and monitoring equipment. For guidance on determining where the mapping and monitoring sensors should be placed, see Sections 6 and 8 of this Guide.

8.1 Sensors

8.1.1 Temperature

There are three main types of temperature sensor:

1. Thermocouples
2. Resistance Temperature Detectors (RTDs) and Thermisters
3. Chemical

8.1.1.1 Thermocouples

Thermocouples work due to the Seebeck effect – when a conductor is subjected to a temperature gradient, it will generate a voltage. Measuring this voltage involves connecting another conductor to the "hot" end, the joint is usually a weld between the two metals, often protected by a thin wall polytetrafluoroethylene (PTFE) sleeve. This additional conductor will then also experience the temperature gradient and develop a voltage of its own which will oppose the original. The magnitude of the effect depends on the metal in use and the extent of the temperature gradient. Using a dissimilar metal to complete the circuit creates a circuit in which the two legs generate different voltages, leaving a small difference in voltage available for measurement. The difference is typically between 1 and 70 µV per degree Celsius (µV/°C) for standard metal combinations and varies according to the temperature difference.

The cables and joints can be prone to damage. During validation and commissioning, provision may be made in a test protocol to prevent any effect on the validity of a test (1% is a figure commonly used) by the failure of a sensor or a failure in the recalibrating of a sensor. Care should be taken to ensure that, if a sensor fails, and it is located in a region where results may be unpredictable, it may be advisable to repeat a test run.

Thermocouple Accuracy

The accuracy of a thermocouple is affected by its type and the operating temperature. See Table 8.1 for the maximum permitted error (in degree Celsius) for various common thermocouples that comply with the International Electrotechnical Commission (IEC) Publication 584 (Reference 16, Appendix 5).

Table 8.1: Maximum Permitted Errors (in Degree Celsius) for Thermocouples

Temperature °C	J Type	K Type
-200	-	3.0
-100	-	2.5
0	1.5	1.5
200	1.5	1.5
400	1.6	1.6

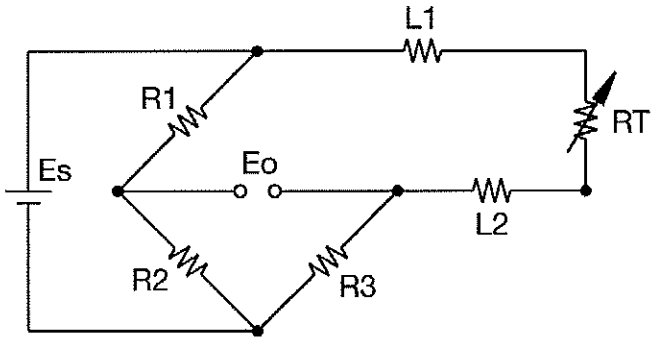
Resistance Temperature Detectors and Thermisters

Resistance Temperature Detectors (RTDs) and Thermisters are available to various grades and manufactured in a variety of housings. The operating principle considers the change in resistance of the sensor as the temperature changes. The change in resistance is measured by passing a small current through the device, measuring the voltage drop using a Wheatstone bridge.

An RTD is constructed from metal with the resistance of the device increasing with the temperature. A thermister is made using a ceramic material with the resistance decreasing as the temperature increases.

High quality sensors are considered reliable and accurate and may last more than eight years in accelerated life tests, while maintaining the specified accuracy. Various wiring configurations are used to minimize the impact of the cable between the instrument and the sensor – three wire or 4 wire configurations for example:

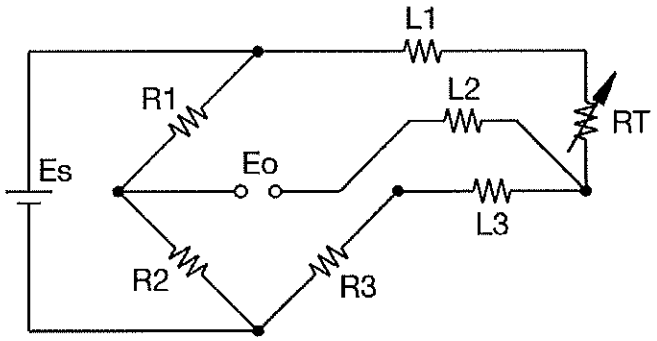
Figure 8.1: Standard 2-Wire Connection



Used with permission from TEMPCO Electric Heater Corporation, www.tempco.com

This is a typical connection for a 2-wire RTD connected to a Wheatstone bridge circuit. Es is the supply voltage; Eo is the output voltage; R1, R2, and R3 are fixed resistors; and RT is the RTD. In this, lead resistance L1 and L2 add directly to RT, hence it has the lowest accuracy.

Figure 8.2: 3-Wire Connection



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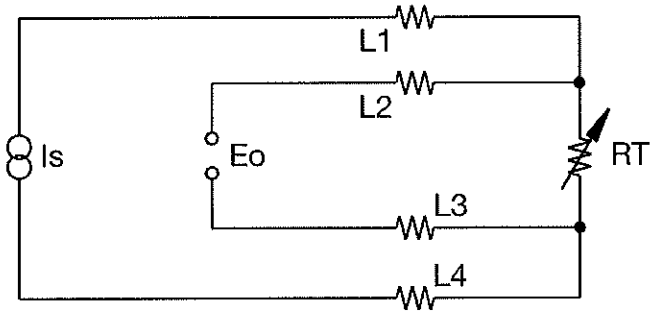
Three leads are used to connect the RTD. L1 and L3 carry the measuring current while L2 acts only as a potential lead. No current flows through it while the bridge is in balance. Since L1 and L3 are in separate arms of the bridge, the cable resistance is canceled. This circuit assumes high impedance at Eo and close matching of resistance between wires L2 and L3. This configuration is used for improved accuracy and longer cable runs of up to 100 ft (35 m).

Figure 8.3: 4-Wire Connection



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The 4-wire RTD circuits not only cancel the effect of the lead wires, but remove the effects of mismatched resistances such as contact points. Is drives a precise measuring current through L1 and L4; L2 and L3 measure the voltage drop across the RTD element. Eo must have high impedance to prevent current flow in the potential leads. 4-wire circuits may be usable over a longer distance than 3-wire, consider using a transmitter in electrically noisy environments.

Accuracies

The accuracy of an RTD is defined by its class according to the International Electrotechnical Commission (IEC) Publication 751 (Reference 16, Appendix 5); it is affected by the operating temperature:

A class A device will be within ±0.15 degrees C at 0°C (±0.27 degrees F at 32°F)

A class B device will be within ±0.3 degrees C at 0°C (±0.54 degrees F at 32°F)

There are no international standards for thermisters, but they typically are similar in accuracy to a class B RTD.

Chemical

There are chemicals that change in color depending on the temperature. These indicators can be used to record the minimum and maximum temperatures. These devices are not considered accurate and normally there is no time record associated with temperature change.

8.1.2 Humidity

There are two common types of humidity measurement sensor in use:

- capacitative units
- resistive units

8.1.2.1 Capacitative Units

These are based on measuring the change in capacitance between two plates as the humidity level between the plates changes.

8.1.2.2 Resistive Units

These devices measure the change in resistance of a polymeric membrane.

Accuracies of ±1% RH are readily available in commercial equipment; accuracies of up to ± 0.5% RH are also available in higher grade equipment.

With both of these instrument types changes in temperature may impact the accuracy. Supplier specifications should be used to confirm any potential impact.

8.1.3 *Uses for the Equipment*

There are four main uses for this type of equipment:

1. measuring the critical parameters during the mapping of a controlled temperature store
2. measuring the critical parameters of the product during the qualification of a shipping container
3. monitoring the critical parameters in a controlled temperature store
4. recording the critical parameters during the shipment of product to ensure that it has remained within the defined conditions

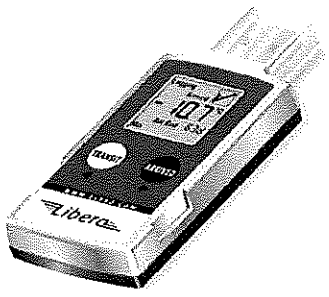
There are a number of basic categories of device:

Recording Devices

These may be single use or reusable individual data loggers, e.g., Elpro, 3M TL30. See Figure 8.4 and Figure 8.5.

There are other devices that may be used to provide the data in a number of formats to facilitate analysis, e.g., Kaye Validator 2000. See Figure 8.6.

Figure 8.4: Example Data Logger 1



Typical datalogger
Up to 100 day operating time
Range of -35°C to 70°C ±0.2°C (-°F to °F 86 ±0.36°F)
16,000 point memory

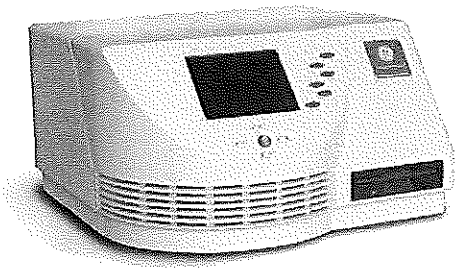
Used with permission from Elpro Services Inc., www.elpro.us

Figure 8.5: Example Data Logger 2

Alternative data logger
Up to 360 day operating time
Range of -40°C to 80°C ±0.5°C (-40°F to 176°F ±0.9°F)
50,000 point memory

Used with permission from 3M, solutions.3M.com

Figure 8.6: Other Device for Recording Input from Sensors

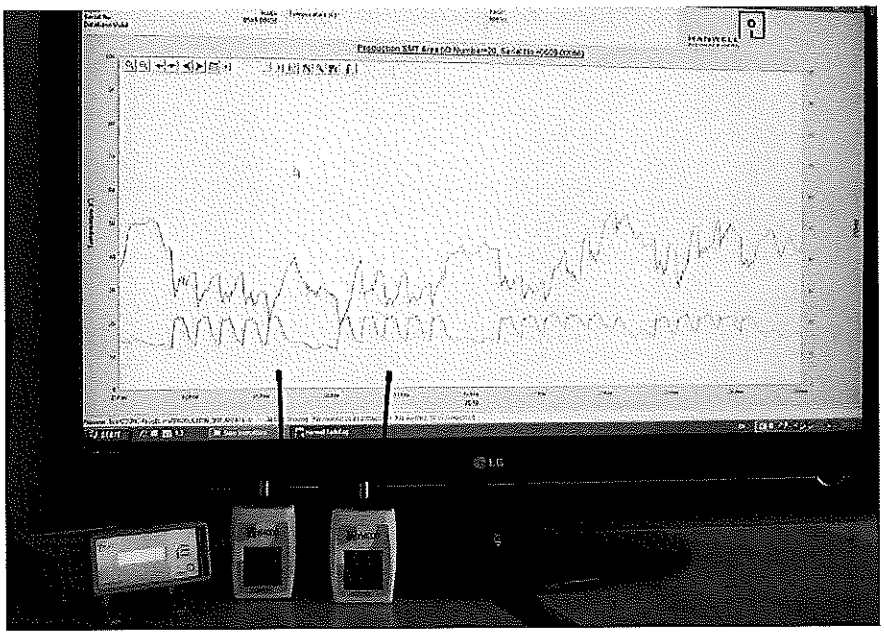


Used with permission from GE Measure & Control Solutions, http://www.ge-mcs.com/en/validation-and-environmental-monitoring.html

Real Time Monitoring and Recording Devices

These are radio transmitters that transmit the data from a local sensor to a base station allowing real time monitoring, recording, and analysis of the data, e.g., datatrace or Hanwell devices. See Figure 8.7. These may allow review of data during recording and allow review and analysis of the data after the test is complete.

Figure 8.7: Radio Data Logger System, Providing Live Information to a Computer



Used with permission from The IMC Group Ltd., www.the-imcgroup.com

The objectives of employing temperature and or humidity monitoring devices should be clearly defined; the user should select equipment with the appropriate capabilities to ensure that the selection meets the user requirements in an efficient manner.

It should be understood that temperature and humidity monitoring, in most cases, do not provide product protection. Monitoring conditions over time documents the maintenance of product quality and does not provide information to improve the quality of the product; product loss may not be avoided through the use of such systems.

Real time temperature monitoring systems may provide an alarm; either due to failure of the conditions or failure of the monitoring system and allow a rapid response to the failure for permanent installations, this may not be feasible for goods in transit.

8.1.4 User Requirements

The following aspects should be considered when establishing monitoring system requirements:

Compliance Requirements

The chosen system should provide proper evidence that the integrity of the information provided is well understood and sufficient. Qualification of the system can provide the proper level of assurance. The regulatory requirements for temperature monitoring for all of the markets being served should be clearly understood. For further information, see Section 4 of this Guide.

Scope within compliance requirements:

- Does the organization have a policy to determine what is monitored and what is not?
- Risk management: does the policy differentiate between high risk and low risk shipments? Does the monitoring plan differentiate between different levels of risk, and provide guidance accordingly (shipment X will get Y number of monitors and Z locations with or without monitor redundancy)
- What products/controlled temperature areas will be monitored (i.e., refrigerated, CRT, biologics, etc.)
- What shipments will be monitored (i.e., wholesaler, intra plant, clinical trials, end user, etc.)

8.2 Monitoring – Key Considerations

8.2.1 Performance

8.2.1.1 Temperature/Humidity Measurement Accuracy

The accuracy and repeatability of a system to measure the specified variable is critical and should be properly matched to the range of interest. Calibration of the system should include points at or outside the anticipated measurement extremes as well as at least one mid range point.

8.2.1.2 Time Accuracy

For systems which provide measurements at specific intervals or which can provide a time stamp for measurements, the accuracy of the internal time measurement component is important. The tolerance of these measurements over the recording time period and recording intervals should be understood.

8.2.1.3 Resolution

The resolution of the output should be properly matched to the application.

8.2.1.4 Response Time

This variable reflects the ability of the system to notice and record a temperature change within a specified amount of time. The size of a device, the location of a sensor within the device, and the characteristics of the sensor itself all will contribute to how quickly a physical change is captured and recorded by the system. The response time of the temperature monitoring system should be understood relative to the response time of the product/s being monitored.

Sensor "Damping"

It is a common practice to use a defined time delay on temperature alarms, or to mount a sensor in vessel containing a thermal fluid to simulate the damping effect of the packaging on the packaged product in response to changes in local air temperature, where this practice is used there should be data to show the system is representative of the packaging system temperature response.

8.2.1.6 Distance to Product

The location of the probe or sensors measuring temperature is typically not located within the product volume. The assumption made is that if the product enters the storage or shipping area within the acceptable temperature range, and the air temperature local to the product remains in that range, so will the product.

Systems may be able to measure temperatures within or very close to the product because of the size of the unit allows this or because the design incorporates a remote wired or wireless probe. The system response time combined with the distance of the unit to the product should be well understood; the temperature recordings may reflect temperature conditions which may or may not be representative of the actual temperature of the product.

8.2.1.6 Sensor Options

In addition to temperature and humidity measurements, other information can be captured, e.g.:

- shock and vibration
- GPS coordinates
- pressure/altitude
- light exposure
- door opening events

8.2.1.7 Pre/Post-use Shelf Life

This relates to the amount of time and storage conditions for which a unit's performance can be assured prior to and after use.

8.2.1.8 Reliability

When a system is specified, actions that could be taken should the system fail should be considered, e.g.:

- spare parts supply
- time before the end user is aware of a system failure
- other sources of data to confirm the system operation/temperate

The conditions in which a system will be used should be specified so that appropriate construction standards are used for the equipment and sensors.

8.2.2 Compliance

Traceability: the ability to trace the calibration or accuracy of components to recognized reference standards should provide confidence in the data output.

Computer system compliance (e.g., with EU GMP Annex 11 (Reference 9, Appendix 5)) and fitness for intended use should be achieved and maintained. If the system maintains electronically records required by US GxP regulations, then 21 CFR Part 11 (Reference 7, Appendix 5) may apply and should be considered.

For further guidance on computerized system compliance, see GAMP 5 (Reference 28, Appendix 5) and the GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures (Reference 29, Appendix 5).

8.2.3 Input

8.2.3.1 Data Input Options

This relates to the ability to differentiate the unit itself, by physical appearance, as well as the ability to program the unit with parameters which may affect the functioning of the device to match customized application requirements (start-up delays, recording intervals, etc.) or which may provide information about the shipment itself.

8.2.3.2 Alarm Selection

This relates to the ability to select specific events which will yield an alarm output. Different alarm types may be available, such as exceeding specific high or low temperatures or exposure to certain temperatures for specified periods of time.

8.2.4 Output

8.2.4.1 Data Output Types

Data output types relate to the system's ability to provide a full picture of the events, such as when a temperature occurred and for how long it occurred, rather than a histogram of events. Compatibility for use with database applications for trending and data analysis and cumulative exposure tracking for specific product batches also should be considered.

8.2.4.2 Data Output Retention

This relates to the ability of the system to maintain the output integrity, as well as allow retrieval after specified periods of time compatible with internal record retention policies.

8.2.4.3 Alarms Output

This relates to the ability of the device to inform a user that a specific alarm event has been triggered. This may include simple visual indicators or more advanced actions, such as automated email, phone, or text message notifications.

8.2.4.4 Data Output and Alarm Interpretation

In some cases, the data or alarm provided by the device may be subject to interpretation by the recipient of the device.

8.2.4.5 Communication Options

The system design may allow programming or transmission of the information captured by the device to occur from within the transport system. Depending on the transport system used, this may be critical to proper temperature maintenance. Systems may be available with GSM technology so that data can be accessed during use.

8.2.4.6 Computer Dependence

The type of information which can be extracted from a device may be influenced by whether a computer is connected to the device. Since the connection standards and hardware/software availability may vary from site to site, care should be taken to assure the necessary information can be obtained upon receipt. Alternatively, processes can be implemented to stop and ship units to another site with full data extraction capabilities.

8.2.5 General Use

8.2.5.1 Reusability

Some systems can only be used once, while others can be used multiple times. While re-usable systems can be attractive due to the amortization of their initial cost and possible lower overall cost, care should be taken to avoid issues relating to calibration, shelf life, traceability, data archival, and other related factors.

8.2.5.2 Activation and Deactivation

How is the system started and how is it stopped? It is important to have assurance that the information provided by the system reflects events which take place during transit and excludes or differentiates events which take place prior to and after shipment.

8.2.5.3 Mounting Options

This relates to the options available for properly securing the temperature monitoring device easily in a specific location.

8.2.5.4 Reversibility

Systems which only show the current temperature, but cannot provide a historical record of transit events, have very limited usability, such as providing the real time conditions for systems to provide logistics partners a means of evaluating a shipment status while in transit. Reversible chemical systems may not be suitable for transport of critical products since they are typically not accessible from outside of the transport system.

8.2.5.5 Support for Multiple Languages and Time-Zones

If the devices will be shipped to multiple countries, and across multiple time zones, the capabilities of the system in regard to these aspects should be well understood.

8.3 Recording Intervals

The reading interval should be sufficiently frequent to demonstrate changes in conditions, considering the length of time that the monitoring will be operating, e.g., the frequency for condition monitoring of a warehouse or a temperature controlled shipment may be acceptable at one reading every 15 minutes.

For open door testing of a cold room, intervals of 15 minutes would provide insufficient data to determine the impact of the short term event and allow analysis. A 1 second or a 5 second interval between readings may be more appropriate.

8.4 Qualification of Temperature Monitoring Systems

Qualification/verification of temperature monitoring and control devices and the systems used to download data should be based on guidance provided in GAMP 5 (Reference 28, Appendix 5). The GAMP Good Practice Guide on A Risk-Based Approach to Compliant Electronic Records and Signatures (Reference 29, Appendix 5) also provides useful information.

The degree of specification and verification should be commensurate with the GxP risk and the complexity and novelty of the system. A risk-based approach should be adopted and applied by appropriate SMEs.

Temperature monitoring and control devices should be checked for correct operation through a range of transportation conditions (e.g., temperature, humidity, vibration). Electronic temperature records should have a timestamp and an audit trail that should be preserved during downloading of data to the designated information management system. Power supplies for these devices should be considered as they may need to be operational for considerable periods and data should not be lost. Records should be secured from unauthorized modification or deletion.

8.5 Handling Excursions – Data Analysis and Interpretation

Organizations should identify and implement a proactive program for the resolution of temperature controlled shipping excursions.

An excursion is defined as a period of time at a condition that exceeds the specified shipping conditions.

An investigation has two objectives:

1. to determine if the product is still useable
2. to determine the root cause of the problem to prevent re-occurrence

If risk assessments have been performed in this area previously, they should be utilized during an investigation and revised as necessary to incorporate findings from the investigation.

8.5.1 Timeline

In cases where an excursion is recognized, a detailed timeline should be compiled. This should establish where the product was at time of excursion and enable cause to be diagnosed.

8.5.2 Temperature Out-Of-Specification at Origin

Possible causes of temperature out of specification at origin include:

- incorrect pack used
- time taken to complete packaging of product excessive
- product not packaged in appropriate environment
- product not preconditioned to required temperature
- temperature monitor started too early
- temperature monitor start delay too short, not giving the packaging system time to stabilize

- temperature monitor not started
- gel packs not properly conditioned
- excessive or incorrect dunnage
- temperature monitor too close to the refrigerant
- gel packs or PCMS
- active unit not preconditioned
- truck not preconditioned
- truck door open too long to upload pallets

8.5.3 Temperature Out-Of-Specification during Transit or at Destination

Possible causes of temperature out of specification during transit or at destination include:

- During ground transit:
  - failure of temp controlled vehicle
  - not using temp controlled vehicle
- While in warehousing:
  - not in required heated or cooled environment
- During air transit:
  - temperature outside of qualified range for packaging
  - inappropriate temp control on aircraft
  - incorrect placement of cargo
  - lack of adequate labeling/or understanding informing ground crew of temperature controlled product
- On tarmac:
  - excessive heat/cold exposure – pallet left out for too long
- During customs inspection/hold times:
  - package opened/and or not closed properly
  - no temperature controlled facilities available/used
  - failure of active unit
  - gel packs not properly conditioned

- incorrect gel packs
- gel packs incorrectly replenished
- incorrect placement of gel packs
- insulated packout not configured for ambient temperature exposure
- transit time exceeds temperature monitor settings
- faulty/expired temperature monitor
- monitor used not appropriate to temperature range
- temperature monitor incorrectly placed
- packout not sealed correctly
- packaging damage

- Temperature out of specification at destination:
  - shipment duration exceeded acceptable time limit
  - shipment exposed to unexpected conditions
  - temperature monitor not deactivated immediately upon receipt
  - material not promptly stored upon receipt
  - material not correctly stored upon receipt
  - probe moved from the specified location
  - two probes do not show similar readings
  - faulty monitor

Information that should be recorded includes:

- origination site
- destination site
- shipping method – carrier details
- estimated transit time
- actual transit time
- number of monitors
- type and accuracy of monitors

- number of shipments YTD
- number of deviations YTD
- product shipped
- shipped temperature range (CRT, 2°C to 8°C, -20°C (36°F to 46°F, -4°F))
- root cause (if available)
- preventative actions (consider findings from previous investigations)

Once the data of time and temperature is available, the data may be analyzed considering the stability data for the product and an assessment made by the quality department as to the sale ability of the shipment.

8.6 Economics

Within a complex regulatory environment, cold chain and temperature monitoring may be essential business strategies in research, clinical trials, and drug storage and distribution. The need for these management systems is linked to product integrity and ultimately patient safety. Consequently, organizations are challenged to develop a strategy to incorporate compliance and quality in a cost-centric environment. Choosing low-cost devices may satisfy immediate budgetary demands, but indirect costs may have a lasting impact on long-term monetary requirements. Hidden costs associated with temperature monitoring devices should be considered as variables of strategic business planning which should result in long-term cost savings, while preserving product integrity.

Data loggers are considered as the industry standard for temperature monitoring in cold chain monitoring. Choosing a data logger based on initial cost and compliance standards may meet short-term project objectives, but hidden costs associated with end user support, multiple product inventories, exception handling, and approval processes could affect long-term expense.

Analysis of Indirect Cost

One consideration is whether there is a software requirement for the end user. The logistics associated with training end users in multiple locations can involve several aspects depending on organization policy and operations. Resources required to develop new procedures, coordinate training schedules across multiple time zones, and to instruct training classes can all affect costs. Choosing a data logger that is easy to use with seamless integration can reduce or eliminate additional infrastructure expenditure. A corporate time-saving feature can include manufacturer and support of the product software integration into a QA/QC system. Data logger qualification (IQ/OQ) or other verification documents should be available and manufacturer should support on-site audits.

Inventory requirements can contribute to indirect costs. Organizations with multiple projects may be required to stock data loggers unique to their QA/QC requirements. A customizable, multi-use data logger can be programmed with several unique profiles to meet individual product specifications, and could reduce the need for a stock of specific data loggers. Customizable products also may simplify the data acquisition and reporting process. The ability to display project-specific instructions or information on a report can save time for end users and streamline the report archiving process.

Immediate data download capability is another time-saving feature that can expedite corporate acceptance of questionable temperature excursions.

- For example, a single alarm data logger is programmed for a temperature range of 2°C to 8°C (36°F to 46°F), and the product arrives at the destination with an indication of alarm. An alarm may require a significant time investment with respect to investigation, review, and release following a temperature alarm. During this process, the product could be put at risk. Data loggers that have instant download capability can have temperature/time details emailed to the supplier/shipper for verification of whether the product is usable.

The ability to program multiple temperature alarms may affect costs. Depending on QA/QC allowances, product stability could have multiple excursion parameters outside one high/low alarm. Regulatory agencies and pharmaceutical manufacturers may recommend five zone alarm limit monitoring (see PDA Report 39) (Reference 32, Appendix 5) which highlights temperature/time excursion beyond the standard high/low alarm parameters. This five alarm zone also provides temperature stability data during a shipment.

In the event of a non-critical temperature excursion, the ability to program multiple alarm parameters can result in a significant process improvement and reduce the potential for human error. With an electronic file containing multiple, easy-to-decipher alarm parameters that are universally recognized, end users can make instant decisions or electronically send a PDF report to project management for a final analysis. This can result in quicker and more efficient project team decisions. A comprehensive picture of the temperature throughout the shipment is a significant time and cost saving that can potentially avoid product replacement and maintain product integrity.

Reliability may be fundamental in choosing a device. If the data loggers fail, temperature-sensitive products can be rendered useless. The probability of device failure can be reduced by choosing a data logger type with a low failure rate.

9 Location of Temperature Monitoring Devices

This section discusses temperature monitoring devices and their operating principles. The operating principles discussed apply to all sizes of insulated, non-insulated, active, and passive shipping containers used to protect product for the duration of transit.

Temperature monitoring or data logging devices accurately document temperature variation during transit within product shipping containers. A temperature monitor or data logger placed within a shipping container that is used to transport product should be located in a position that is representative of the temperature of the product during transit. This allows the in-transit temperature data obtained to be compared to product temperature specifications and stability data. This information can be used for the evaluation of any impact to the safety, potency, and efficacy of the product that may have occurred during a journey. Optimal placement of these devices should help to maintain the temperature control continuum for heat labile pharmaceutical and biological products during transit.

While the temperature of the product itself is the critical variable, it may not be easy to determine the temperature within a packout during transport.

A validated measurement of temperature would require a complex system of thermocouples located within the primary containers; since this method would destroy the package integrity, a non-destructive alternative method is required. A generally accepted alternative is to place the temperature monitoring/data logging device in proximity to the product, measuring the air temperature surrounding the primary container while avoiding direct product contact.

Types of temperature monitoring devices include:

- chemically activated
- battery powered mechanical recording devices
- minimum and maximum reading thermometers
- freeze indicators
- heat indicators
- battery powered electronic devices that incorporate an assortment of operating features including:
  - pass/fail readouts
  - computer connectivity
  - time delayed activation
  - radio frequency capabilities
  - data storage
  - local programmability

One approach to determining the optimal location of a temperature monitor is to perform a "worst case" analysis. This approach requires thermal mapping data of the transit container derived from Operational Qualification (OQ) activities which, upon interpretation, define the range and heterogeneity of temperatures expected during transit. The temperature monitoring/data logging device would be placed within the packout at a location that demonstrates the widest temperature variation. While active and passive insulated packouts are designed to limit such variation, temperature swings of 2°C (3.6°F) are typically seen and are dependent upon the characteristics of the container. Although the air temperature may not be entirely representative of the product temperature, this approach can be beneficial because the device will record the widest ranges of air temperatures within the packout.

The optimal placement of temperature monitors or data loggers in a given packout may depend upon:

- the number of primary and secondary packages within the payload, which is derived from the minimum and maximum volume and mass studies performed during design testing
- the amount of drug substance contained in the packout, also derived from the minimum and maximum volume and mass studies performed during design testing
- the actual volume and mass of the payload
- air convection or circulation within the shipping container
- worst case design characteristics of the packout
- the position of temperature control materials (gels) within the packout

In completing a satisfactory OQ and Performance Qualification (PQ) for a packout that clearly defines the mass, volume, time, and temperature parameters of the container, the need for constant temperature monitoring of ongoing shipments, (although not strictly a requirement), is dependent upon:

- risk profile of the product being shipped
- complexity of the supply chain
- internal organization quality policy
- local regulatory requirements

Periodic monitoring should be an integral part of a qualification maintenance program.

The purpose of monitoring the temperature of product while in transit is to determine a level of temperature compliance and to determine if there is a chance of any degradation or loss of potency, which may occur if the product is exposed to external ambient temperatures beyond the transit temperature specifications. The temperature monitor or data logger should provide the documentation that the product temperature is satisfactorily maintained in accordance with the product stability profile described in regional regulatory filings that supports the safety and efficacy of the product. The temperatures seen during transit should be aligned to those experienced during the OQ of the packaging and shipping materials.

The design qualification parameters for a shipping container should specify the correct shipping and distribution temperature range for the product as defined in stability reports. The OQ testing should align to the design qualification requirements, i.e., the temperatures should be supported by product testing data.

During OQ testing, thermocouples measure the product temperature directly, either by placement within the primary container in direct contact with the product or contiguously attached to the primary container. Consequently, the OQ testing data should describe accurately the product temperature inside the insulated package.

An "air" probe thermocouple may be used in the OQ phase of testing to measure the air surrounding the product in the payload. This should approximate the readings that a traditional temperature monitor or data logger would record during shipment.

During OQ testing, there is usually a small difference in temperature between the air surrounding the secondary package and the product within the primary container. This is due to the insulating characteristics of air itself, as air has little density.

Within the packout, heat transfer occurs due to the:

- interior air movement or convection flow
- insulating properties of the secondary packaging
- conduction of heat across the surfaces of the primary container
- insulation property of the air itself

The requirement for temperature monitoring or data logging is based upon the known product stability data, its regulatory filing, the label storage condition, and the ambient temperatures to which the product could be exposed during transit.

Considerations for the use and placement of temperature monitors and data loggers include:

- Initial time delay of the data logger: the time delay programmed into the validated data logger allows for the time required to achieve an equilibration of temperature within the packout. The OQ may require the packout to be assembled with the shipping container, coolant gels, product, dunnage (filler material used to pack in the shipment and stop it moving within the package), and other packing materials such that ambient (room) temperature air is initially enclosed within the packout.

Depending upon product and component volume and pre-conditioning, plus the length of time required to complete the packout, several hours or longer may be required for the air inside the shipper to equilibrate to the expected internal shipping temperature once a container is sealed. During this package equilibration period, the actual product temperature may drift toward ambient conditions depending on the package configuration. This can be seen by evaluating the temperature data in the associated OQ tests.

The air being measured immediately next to the product may read outside of the product shipping temperature specification until all the contents within the shipping container fully equilibrate. A time delay programmed into the data logger helps to eliminate or limit "false positives" that can occur during this equilibration time. The data logger also may be pre-conditioned at cooler temperatures to limit equilibration time.

The packout and shipping fulfillment process should be evaluated and understood prior to implementation of a time delay in order to retain proper temperature control of the product. The packout equilibration time and product temperature impact should be in conformance with the stability profile of the drug.

Guidance for acceptable locations to position the temperature monitoring or data logging device:

- The temperature monitor should be placed as close to the product as practical. It is generally considered more important that the temperature monitor is located in a position that is representative of the product's temperature, rather than having it located in a worst case position.
- The top center position in a packout is frequently utilized as a worst case. Hotter air in the container rises due to internal convection and gathers more readily toward the center of a packout. Applying heat transfer principles, a worst case cold position in a packout may be seen at the bottom where there is settling of colder air. This concept is most applicable with passive shipping containers.

- Secondary packages should not be disassembled or destroyed in order to place the temperature monitor closer to the product.

- Temperature monitors or data loggers should not be 'buried' in the payload such that they are thermally protected by other product packages and do not represent the worst case position within the payload. For example, the temperature monitor should not be placed at the base of a case or carton of product near a cooling source (gel) which would insulate that location from temperature variations within the packout.

- Temperature monitors should not be placed immediately next to a coolant gel, which is not representative of the product's true temperature. The exception to this situation is when the packout design calls for gel wraps to encase secondary finished packages directly. While the temperature monitor is in contact with both the gel and the product, it will capture the worst case situation within the packout as the gels warm from the outside-in. The product will be the final point in the packout to succumb to warming or cooling from exterior ambient temperatures.

- Where a corrugated payload box defines the maximum volume of a payload, the temperature monitor should be placed inside the corrugated box. In addition, product should not be displaced in order to fit the temperature monitor into a complete corrugated product shipper. In this case, the temperature monitor should be attached to the exterior of the full corrugated box to approximate the product's temperature.

- If a protective plastic bag is used to isolate the product from contact with other products or gels, the temperature monitor should be placed inside of the bag to better represent actual product temperature. Alternatively, placement of the temperature monitor outside of the plastic bag would represent the air within the packout.

- For active containers with full or partial pallets of product, the method of conveyance is based upon the PQ testing of the truck, ocean container, or air cargo container. Temperature monitors or data loggers should be placed in either a worst case position as determined by OQ thermal mapping and reflective of the entire container where multiple pallets are involved or placed in proximity to the product to capture temperature more directly.

- For Active Pharmaceutical Ingredient (API) and Bulk Drug Substance (BDS) containers, consideration should be given to the shape and size of the primary container such that proximity to product, protective secondary container, interior air convection, proximity to cooling elements, and interferences (i.e., valves, closures, inlet and outlet lines, gauges, or sterile enclosures) are accounted for in capturing accurate worst case temperature results for the shipment.

- If the packout container is designed to have divided internal compartments to separate the refrigerants (such as frozen phase change bricks) from the product, the temperature monitoring device should be positioned in the compartment where the product is located, not in the compartment with the refrigerants.

- The temperature monitoring device should not be placed in direct contact or in proximity with any frozen refrigerants, such as phase change bricks, since this may result in a 'false negative' temperature reading. The temperature monitoring device should be separated from these refrigerants with an insulating material delineated in the OQ.

- The temperature monitoring device should not be placed in direct contact or proximity with refrigerants, such as gel packs used for controlled room temperature thermal mass, since this material may insulate the temperature monitoring device and result in false high temperature readings that are not reflective of the temperature of the packout and the product.

The placement of the temperature monitoring device should include 'ease of use' considerations. As packout timing is important in keeping product within the proper temperature range, the placement of the monitor by the shipping site as well as retrieval by the receiving site should be considered so that the product itself is not exposed to room ambient temperatures for an extended period of time. The sending site should be able to efficiently activate and place the monitor into the packout quickly. The position should be such that the receiving site can locate and de-activate the monitor quickly upon receipt. Reducing the complexity of the packout helps to drive consistency in training and enhance compliance.

The thermal mapping process is performed during OQ and provides the core data from which to best evaluate temperature monitor or data logger placement.

Many temperature monitor or data logger operational errors happen through mishandling of the units themselves. For example, devices may be left activated outside of a cold vault after a shipment is completed and the product itself securely placed in proper cold storage. During the excursion investigation process, this possibility should be taken into consideration.

For active containers (e.g., trucks and ocean containers), it remains critical that there be sufficient airflow throughout the container. Overloading or "wall-loading" will restrict air flow. Therefore, blocking and bracing methodologies should take into account the need for container wall clearance. The vehicle loading plan Standard Operating Procedure (SOP) is a viable communicative method for addressing air circulation in active container.

9.1 Product Payload

The minimum and maximum payload sizes should be defined in the OQ report. Since the quantity of product may vary between the mass and volume, the exact position of the temperature monitor may vary slightly depending on the number of product packages contained in the packout. It is considered impractical to perform laboratory chamber testing for every conceivable variant of product package numbers and positions contained in the payload; therefore, the principles of temperature monitor or data logger placement should be followed.

9.2 Number of Temperature Monitors

The minimum number of temperature monitoring devices is commonly defined in an organization's specific conformance standard for shipping and distribution or in a validation master plan. Factors for this decision include the:

- mode of transportation being used
- volume of product being shipped
- number of individual pallets or containers in the shipment
- corresponding value of the product

The guidance for the number of temperature monitors placed into a PQ shipment should be defined in the PQ protocol. The number of temperature monitoring or data logging devices placed in an insulated shipping container should be described in operational documents such as SOPs. That number of devices utilized in regular shipments should be based upon the Design Qualification, OQ, and PQ results.

10 Maintenance and Cleaning

10.1 Maintenance

The supplier of the refrigeration equipment should provide general recommendations for the maintenance of the equipment. These recommendations may not recognize the high value of the stored goods in this application. The potential impact on the maintenance program should be assessed.

This section discusses factors which should be considered in a maintenance program.

10.1.1 Cleaning of the Coils

The coils (unit cooler and air cooled condenser) should be regularly cleaned and checked for any damage to ensure that the performance levels are maintained. Damaged or distorted fins should be straightened with a suitable comb. This inspection also should ensure that there is no corrosion of the fins.

10.1.2 Check the Condense System

The condensate pipework should be checked to ensure that it is not damaged and that it has the correct fall and flows freely. Trace heating or insulation also should be checked.

10.1.3 Functional Testing of the Unit Coolers/Defrost Elements

There is usually no feedback from the solenoid valve on the unit coolers, so the only way of checking their correct operation is to check the performance of each unit cooler.

10.1.4 Leak Testing

It is considered a good practice to periodically check the pipe runs, as well as the equipment for leaks using one of the electronic test devices now available. This may be a mandatory requirement, depending on region.

- The system refrigerant fluid level and pressure against the system specification should be periodically checked and documented. Early detection may help avoid system failure.
- It may be necessary to keep a record of the refrigerant used for the system.
- Equipment rooms may be fitted with leakage detectors/alarms; these should be calibrated and checked regularly.
- End users should be aware of the local regulatory requirements.

10.1.5 Thermal Scanning

The panels, doors/door seals/sealing of utility penetrations can degrade over time (foamed panels may be better in this respect than panels filled with mineral wool). A thermal scan of the installation will allow any degradation to be seen and appropriate action taken. As a minimum, the penetrations should be inspected to ensure that they are sound with no leakage/ingress of condensation. For conduit penetrations, the internal sealing also should be checked to ensure that condensation is not leaking inside the conduit.

10.1.6 System Alarms

The entire alarm system should be periodically tested by direct or simulated temperature change against the specified alarm setpoints and proper functionality of audible and visual alarms at local and/or remote alarm stations should be observed. Test results should be documented.

Regardless of the root cause, product losses from cold storage-related failures can be prevented with the proper design and operation of the alarm system, and proper user response to an alarm event. Periodic testing of the alarm system should help to ensure that it will work when needed.

10.2 Cleaning

Where freezers are located in environments with high humidity, the accumulation of ice that builds up on the cold room frame/walls/ceiling due to the system defrost or ingress of moist air should be removed.

Where excessive ice buildup interferes with operation, e.g., door closure, a full defrost may be required, removing the stored product and allowing the room to warm to ambient temperatures using standard cleaning regimes. If this is the case, the design should be reviewed to determine the cause of the problem and if it would be cost effective to improve the design.

Cold rooms and freezers present unique challenges, due to the risks associated with condensation. Therefore, routine wet cleaning of a cold room facility is not recommended, as any moisture will take a long time to dry out.

For small units, a cloth moistened with IPA may be used to clean the inside with approval of the environmental health and safety department.

A common practice for cold rooms used to store finished product is to only wet clean internally if the facility looks visually dirty (a white cloth test can be used if a formal test method used for inspection is required).

If wet cleaning is used, consideration should be given to the grade of water to be used and the addition of a microbial growth inhibitor, e.g., hypochlorite.

As an alternative a "soft" non corrosive disinfectant can be used; this may be done routinely for storage areas used in other applications where desired.

10.3 Calibration

During the system design, a calibration strategy should be defined, considering the features of the specific design, the reliability, function, and likely failure modes of the sensors.

Advice should be obtained from the equipment suppliers on calibration and/or checking of the refrigeration sensors. For further information, see the GAMP Good Practice Guide: A Risk-Based Approach to Calibration Management (Reference 29, Appendix 5).

Development of a strategy, integrated with the extent of the routine maintenance can provide a more cost effective approach than one where all the sensors are routinely calibrated over multiple points.

An example of such a strategy developed based on a simple risk assessment is included as Section 12 (Appendix 1) of this Guide.

11 Product Traceability

11.1 Supply Chain Visibility

Product traceability in the supply chain includes traceability of documentation and materials and the location used for temperature measuring equipment during testing. This section provides background information on this topic and related requirements and technologies. This technology may be beneficial in the case of a recall.

The aim is to have end-to-end drug product visibility within an existing pharmaceutical supply chain, including two key considerations:

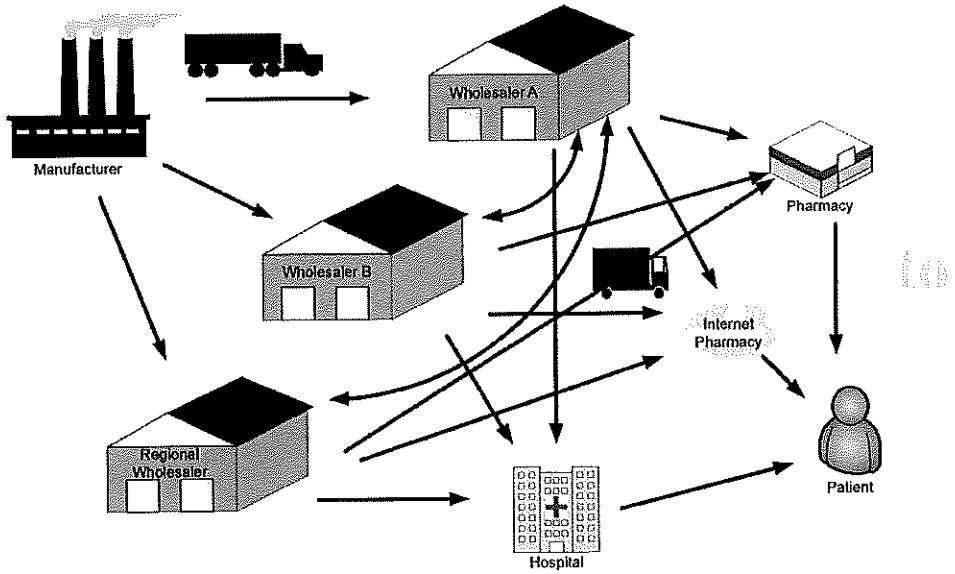
1. extent of traceability (e.g., internal, external end-to-end, or only at point of sale)

2. hierarchy of traceability (e.g., lot, pallet, case, or unit level)

At time of publication, the level of product visibility can be limited to lot level for drug products that are shipped from a manufacture to a downstream trading partner. Once the drug product is received and sold or transferred to subsequent trading partners, the visibility of the product at the lot level diminishes significantly, as the requirement for tracking product by lot is mandated by local regulations.[3] Visibility at the unit level generally does not exist although it may be provided for some specialist products.

The pharmaceutical supply chain can be complex, as products can change hands many times from when the product leaves a manufacturer's facility and ultimately dispensed to a patient as illustrated in Figure 11.1. Products may be traded between wholesalers in different countries to provide more favorable pricing. (In the European Union, this may be known as "parallel trade."[4]) Products can be subjected to multiple, sometimes inconsistent, regulations as they cross geographic borders.

Figure 11.1: Pharmaceutical Supply Chain



[3] There currently are several exceptions to this in the United States where state law (e.g., Florida) requires tracking a product from the Authorized Distributor of Record (ADR) to the pharmacy through the use of a "pedigree." A pedigree is used to document transactions as the product moves through the legitimate supply chain. Other US states, such as California, the FDA, and the EMA also have regulations that are current, pending, or in consideration (at time of publication).

[4] Parallel trade refers to the trade of branded goods legally within and across all member countries of the EU. Parallel trade currently is not authorized with in the US.

11.2 Traceability

A global organization (GS1)[5] has developed an approach where **end to end** product traceability can be attained, which allows a greater degree of product visibility within the supply chain. There are two aspects of traceability:

1. tracking backward the path a product has made through the supply chain and identifying the change of physical possession and or ownership[6] of the product as it moved through that supply chain (i.e., chain of custody/chain of ownership)

2. tracing forward where the product currently is within the supply chain and if in transit, current disposition of the product

Traceability is the term used to define track and trace, as tracking and tracing may not be differentiated.

The implementation of a traceability solution should be designed based on specific use cases. These use cases can be taken from current business processes, along with any required new business processes. Existing standards,[7] e.g., barcode symbology, RFID, database repositories, and IT infrastructure should be understood in order to properly define new business use cases. A gap analysis can then be performed to complete the planning phase of a project.

Figure 11.2 shows how traceability can take place by means of one trading partner up and one trading partner down the supply chain. For complete visibility (e.g., end to end) a request would be made by a trading or traceability[8] partner through the supply chain. Each participant[9] within the supply chain would then provide the electronic information back to the requesting entity.

Figure 11.3 illustrates a vision of the future of traceability, as technology progresses. When a request is made about a product that has moved through the supply chain, a discovery service[10] would provide information regarding which trading or traceability partner had physical contact or ownership of the product. The requester will then be able to directly contact each partner without going through the supply chain in a sequential manner.

[5] GS1 is a global organization dedicated to the design and implementation of global standards and solutions to improve the efficiency and visibility of the global supply chain. Further information can be found at www.gs1.org.

[6] A recipient of a product does not necessarily need to take physical possession of a product, but retains ownership of the product such as in the instance of a dock to dock transfer.

[7] Examples of existing standards are:
- www.epcglobalinc.org/standards
- www.hibcc.org/index.htm
- www.gs1.org/barcodes/technical/genspecs/
- www.gs1.org/sectors/healthcare/

[8] A traceability partner is any partner for which trading information is shared. A partner does not necessarily imply that a direct relationship exists as the "partners" may be several degrees of separation within the supply chain.

[9] A participant can be an entity who has or had taken physical possession and or ownership of a product.

[10] Discovery Service is an EPC Global standard that is currently (at time of publication) under development. The concept of the Discovery Service is analogous to a search engine used in the internet.

Figure 11.2: Traceability (Current – One Up/One Down)

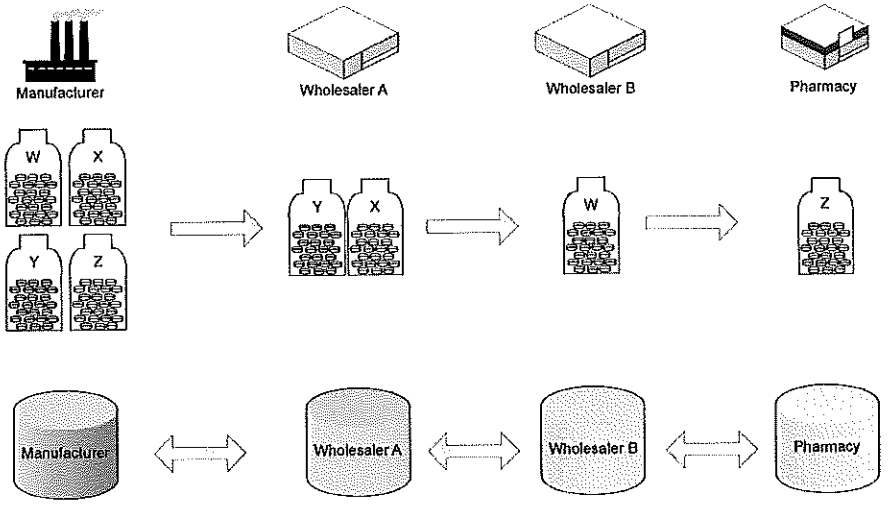
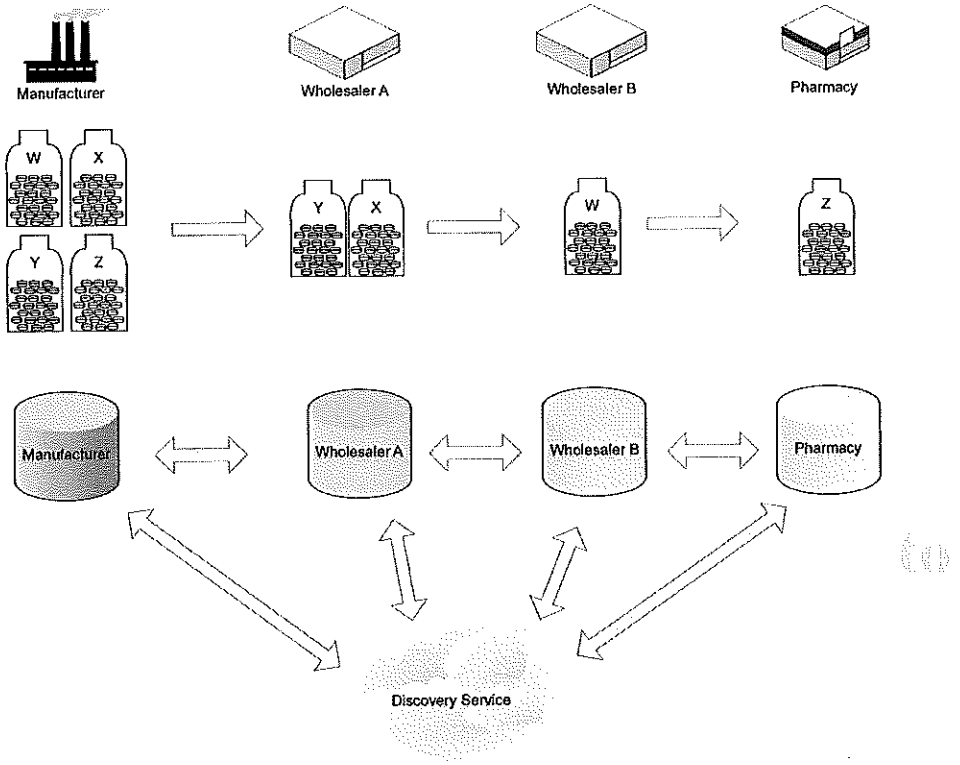


Figure 11.3: Traceability (Future)



11.2.1 Enablers

Traceability data should include information regarding:

- Who? (business partner)
- Where? (location)

- When? (date/time)
- What? (traceable item)
- What happened? (event)

There are three key enablers for traceability:

1. data carrier
2. database
3. IT infrastructure

Each enabler has a purpose and inherent complexity, but should be able to be an integral part of a cohesive and interoperable system which delivers required functionality.

Several enablers need to be available in order to implement traceability. The scope of implementation should cover both internal tracking (within an organization) and external tracking (across trading partners) for complete end-to-end visibility throughout a supply chain.

Enablers allow supply chain visibility. GS1 has published a range of standards which cover the design and implementation aspects of enablers. If enablers are not compliant with industry standards, interoperability may be hindered and full traceability also may be hindered or prevented. Organizations may implement traceability in different ways and have different objectives for the implementation, based on:

- role in supply chain (e.g., manufacturer, distributor, or dispenser)
- business case (cost and benefits)
- diversity of products and regulatory environment

When determining how to implement each enabler for an organization, business processes, customer requirements, and regulatory requirements (where applicable) should be used to determine the level of technology to be implemented to attain supply chain improvement and product visibility.

The GS1 Global Traceability Standard in Healthcare (GTSH) (Reference 34, Appendix 5) provides a framework for how traceability can be achieved.

11.2.2 *Data Carriers*

Data carriers are methods of representing information about a product in a machine readable form. Data carriers can take the form of a linear barcode, 2-dimensional barcode (2D), and RFID tag. For products moving through the supply chain, the data encoded into the carrier should have an identification number that uniquely identifies the object class.[11] The method for encoding the information into a data carrier will depend upon which symbology standard an organization uses. There are several standards available, such as GS1 or HIBC for barcodes and EPC Global for RFID tags.

[11] An object class is used to describe a distinct product that moves through the supply chain.

A manufacturer may choose to encode additional data by concatenating two or more pieces of information into a barcode,[12] e.g., when serializing a unit, case, and or pallet. The more information encoded the larger and thus more space needed to print the barcode on the product packaging or logistical unit.

11.2.2.1 Serialization

What a data carrier contains can range from the object class[13] to identifying a lot, pallet, case, or unit within an object class. Serialization enables traceability by incorporating a unique serial number into a data carrier, along with the object class identifier, at a specified packaging level. The packaging level serialization used is usually determined by a business process.

Serialization can begin with the lot level, by using existing regulatory identifications of a lot number by batch. However, this may not offer the required level of traceability within the supply chain. Serialization should be implemented at that desired packaging level. The level of serialization will indicate the level of visibility a product has through the supply chain, e.g., if the level of traceability of a product is to be at the unit level, the packaging component that crosses the point of sale would need to be serialized with a unique serial number. When this number is connected to the object class, he product can be uniquely identified through this identifier (serial number + object class).

Aggregation is a method of serialization where a hierarchy is established, recorded, and maintained until the time a parent child relationship needs to be broken. For example, if the requirement is to have traceability of a specific unit within an order of thousands of units without physically opening each and every case or pallet, an established parent child hierarchy should tie individual unit serial numbers to a specific case serial number which in turn would be tied to a specific pallet serial number.

If the outcome is to determine that the product (in a manufactured sealed and un-tampered package) received at the end of the supply chain is genuine, aggregation is not necessary.

Point of dispense authentication is a method of serialization where a unit that passes across the point of sale register is serialized.

Authentication of an identifier may take place at each point in the supply chain where product physically changes hands and or ownership, not just at the end of the supply chain (where the product is dispensed).

Authentication may require physical verification of **all** identifiers so the choice of data carrier is important.

Authentication of several unique identifiers in a case or pallet can be completed by physically verifying the parent and through inference; it would be inferred that the children also have been verified.

Both approaches to authentication (each physical unit or using inference) have inherent issues.

11.2.3 Database

Databases are usually the preferred method of storage for large multi-user applications, where coordination between many users is needed. The data which is generated during the serialization process has to be organized, stored, and shared by the applications internally within an organization and externally with business partners. Well designed database architecture will help prevent application errors when using the system, rendering it difficult to understand and control the flow of data within such applications. It is a recommended practice for an organization to separate the databases for its internal use and external use.

[12] Additional information may be encoded into a RFID tag; however, due to the memory capacity limitations of a tag, the amount of data encoded is limited.

[13] Using object class as an enabler would not require serialization.

11.2.3.1 Internal Database Applications

Database applications which manage the internal business processes for serialization and handle the serialized product throughout its life cycle until it is dispatched to the business partner typically include:

- ERP
- MES
- WMS
- SCADA

Data generated during unit serialization process will be homogenous and it is important to ensure that it is not duplicated unnecessarily within different applications, adding to the overheads for maintaining multiple databases.

In order to add the business context to the serialization data, a variety of events (e.g., commissioning, de-commissioning, dispatched) should be captured by operators using scanners or vision systems. As product moves forward within the supply chain, database applications should allow re-processing of product, modification of aggregation relationships, and correction of operator mistakes.

11.2.3.2 External Database Applications

A global repository to host the serialization data, event data, and master data for the purpose of information sharing with external business partners should be built as per the industry standard (e.g., GDSN, EPCIS) to ensure the smooth flow of information across the trading partners. Trading partner communication, security and integrity of the data, and interoperability are the key areas of focus while deploying such database applications.

11.2.4 IT Infrastructure

IT infrastructure is a general term used to represent collectively the IT assets and resources which take manage networking, computing, storage, security, and management of database applications.

IT Infrastructure management should assist in:

- reducing duplication of effort
- ensuring adherence to standards
- enhancing the flow of information throughout the information systems
- promoting adaptability necessary for a changeable environment
- ensuring interoperability among organizational and external entities

Efficient, secure, and interoperable IT Infrastructure is a key enabler to obtain supply chain visibility.

Appendix 1

Science-Based Quality Risk Management

12 Appendix 1 – Science-Based Quality Risk Management

Risk management is a systematic application of management policies, procedures, and practices to the task of identifying, assessing, controlling, and monitoring risks. It is typically an iterative process.

Risk management should be based on good science and product and process understanding - for example, an understanding of Critical Quality Attributes (CQAs) – which is based upon and ultimately traceable back to the relevant regulatory submission.

Qualitative or quantitative techniques may be used. The focus should be on the risk posed to patient safety and product quality.

Risk management should reduce risks to an acceptable level. Complete elimination of risk is neither practical nor necessary.

For a given organization, a framework for making risk management decisions should be defined to ensure consistency of application across functions. Such a framework is most effectively implemented when it is incorporated into the overall Quality Management System.

12.1 Quality Risk Management for the Qualification of Equipment

Some organizations are moving away from the traditional qualification model (IQ, OQ, PQ) to a risk- and science-based approach with the objective of identifying the areas of risk to product quality (and hence patient safety), improving the focus on these aspects of the equipment design and operation. ASTM E2500-07 (Reference 19, Appendix 5) provides a standard guide to this approach and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline ICH Q9 (Reference 4, Appendix 5) describes a systematic approach to quality risk management.

Two examples showing utilization of a risk-based approach are described here.

Example One

ICH Q9 defines two primary principles of quality risk management:

1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
2. The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q9 is intended for general application within the pharmaceutical industry.

The example described here considers the qualification of a cold room showing the process for quality risk management consisting of the following elements:

- Risk Assessment
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation

- Risk Control
  - Risk Reduction
  - Risk Acceptance
- Risk Communication
- Risk Review

There are a number of ways a risk-based approach may be used – this attachment describes one example, ISPE Guide: A Risk and Science-Based Approach for Delivery of Facilities, Systems, and Equipment (under development at time of publication, Reference 27, Appendix 5) will provide more information on the adoption of a risk-based approach.

Stage One:

The following is one example of this approach used for the qualification of a cold room. In this example, the Good Engineering Practices (GEPs) are used to provide documented evidence that the cold room is installed and operates according to the design specification through the following documents:

12.1.1 Installation Verification

The commissioning would include an inspection of the installation to ensure that it is in accordance with the specifications with a walk down of the drawings, but not necessarily a check of the data. An increase in the scope with a defined format for documenting the checks is adequate to meet the requirements for an "IQ" as defined above. The work is conducted in the GEP environment.

Similarly the putting to work and engineering testing would meet the requirements of an "OQ" as defined above

12.1.2 The Risk Assessment

The risk assessment process is used to:

- identify
- analyze
- evaluate risks

There are many ways of doing this, one example is described here.

The form shown is populated as follows:

- Identify the potential risk to patient safety/product quality in the appropriate column.
- Define the potential sources of the defined risk in the third column – only consider "real" risks – it is not likely for example that a meteorite hitting the cold room would be a risk worth evaluating.
- For each potential risk, define the controls for this risk from:
  - Equipment Design (forth column)
  - Quality Systems (fifth column)

In this application, procedural controls are included as well as the testing during commissioning is included as a quality system – i.e., verification that a design control operates as specified and procedures include specific controls that the assessment has identified.

- In column eight, record how the risk would be detected if the risk control failed.

In this example, the scoring (columns three, six, and nine) are completed as follows:

- The risk assessment can be scored using standard scoring systems with the risk categorized.

If the assessment is carried out at an early stage, it may be used to revise the design or define aspects to be considered in the operation/maintenance procedures.

Alternatively, it can be used to develop a list of aspects that require verification, before releasing the system for use operationally, essentially "qualifying" the system.

Table 12.1: Risk Rating Criteria Definitions
(Example of scoring tables as used for the assessment example above)

Rating	SEVERITY of the effect of failure (System/Equipment)	Likelihood of OCCURRENCE	Ability to DETECT the failure
9	Severe – serious impact to QA of the output of the system/ equipment. Impact to final product quality attribute.	Frequent – failure is almost inevitable. Consistent failures observed (e.g., once a week).	Absolutely uncertain existing controls cannot detect the failure. No controls are in place.
7	Major – significant impact to QA of the output of the system/ equipment. Possible impact to final product quality attribute.	Likely – failure is likely and will occur in most circumstances. Repeated failures observed (e.g., once a month).	Remote – remote chance that controls will detect the failure. A control may be in place but is untested or unreliable.
5	Moderate – possible impact to QA of the output of the system/ equipment. No impact to final product quality attribute.	Occasional – failure is probable at some time and has been observed (e.g., once a year).	Moderate – a moderate chance that the control will detect the failure.
3	Minor – minor impact to QA of the output of the system/equipment. No impact to final product quality attribute.	Unlikely – failure could occur at some time. Only isolated incidents observed (e.g., once every 5 years).	High – very likely that the control will detect the failure.
1	Insignificant – no impact to QA of the output of the system/ equipment. No impact to final product quality attribute.	Remote – failure is extremely unlikely. No history of failure.	Almost certain – the control will detect the failure in almost every instance.

Table 12.2: Risk Thresholds for Severity and Likelihood of Occurrence

		Severity of Risk				
Likelihood of **Occurrence**		**1** Insignificant	**3** Minor	**5** Moderate	**7** Major	**9** Severe
	9 – Frequent	Medium	Medium	High	High	High
	7 – Likely	Low	Medium	High	High	High
	5 – Occasional	Low	Medium	Medium	High	High
	3 – Unlikely	Low	Low	Medium	Medium	High
	1 – Remote	Low	Low	Low	Low	Medium

Table 12.3: Risk Thresholds for Risk Assessments with Three Ratings

		Detection				
Risk Classification	Risk Level from Table 12.2	**1** Almost Certain	**3** High	**5** Moderate	**7** Remote	**9** Absolutely Uncertain
	High	Low	Medium	High	High	High
	Medium	Low	Low	Medium	High	High
	Low	Low	Low	Low	Medium	Medium

Stage Two:

If the risk values are considered acceptable, the risk assessment and results can be communicated to the team and management.

If they are not, the design and the quality systems can be reviewed and revised, until the design and controls are considered to provide an acceptable risk profile.

Stage Three:

Risk Review:

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output and results of the risk management process should be periodically reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall).

Use the data gathered by the quality system to find opportunities to further minimize the GMP risks.

Table 12.4: Risk Score Thresholds

Cold Room Risk Assessment – Room Used to Store Finished Product

Critical Aspects — Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding.

Critical Quality Attributes — A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. — Product Temperature

Critical Process Parameters — A process parameter whose variability has an impact on the critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. — Room Temperature

Reference	Potential Risk to Patient Safety or to Product Quality	Source of the Risk (How can the risk happen?)	Severity	How does the design mitigate this source of risk? (Instrumentation, Alarms, and Interlocks)	How do site quality systems mitigate this source of risk (SOPs)?	Occurrence	Interim Risk Classification for Severity and Likelihood of Occurrence (Appendix B of BP) Low; Medium; High	What mechanisms would detect the result if risk occurred?	Detection	Final Risk Level – Interim Classification (Column H) and Detection Rating (Appendix B of BP) Low; Medium; High	Comments
1	Product degrades as not kept as temperature.	Variable temperature in the room		System is specified to maintain the necessary temperature.	Will be verified through temperature mapping of the product storage locations during commissioning.			Alarm from the monitoring system			
				Racking located in areas not subject to significant temperature variations in use.	Mapping will be used to determine the locations of the temperature sensors.						
					PM is used to calibrate the monitoring system temperature sensors.						
		Failure of the refrigeration system		Alarm signals from the duty refrigeration system will disable the duty system and automatically start the standby system.	SAT will include a functional test of the alarms.			Alarm from the control system			
					Operational SOP will include action in the event of an alarm.						

Table 12.4: Risk Score Thresholds (continued)

Reference	Potential Risk to Patient Safety or to Product Quality	Source of the Risk (How can the risk happen?)	How does the design mitigate this source of risk? (Instrumentation, Alarms, and Interlocks)	How do site quality systems mitigate this source of risk (SOPs)?	Interim Risk Classification for Severity and Likelihood of Occurrence (Appendix B of BP) Low; Medium; High	What mechanisms would detect the result if risk occurred?	Final Risk Level – Interim Classification (Column H) and Detection Rating (Appendix B of BP) Low; Medium; High	Comments
		Failure of the unit cooler control temperature sensor	The temperature sensors are specified as RTD's, open or closed circuit failure of the sensor/associated wiring will give an alarm from the control system. RTD's are very robust when used in this low stress environment and not prone to drift.	SAT will include a functional test of the duty standby interlocks and alarms.		Alarm from the control system		
				Operational SOP will include action in the event of an alarm.				
2		Failure of a unit cooler fan	Current monitoring on the unit cooler fans with alarm on fan failure.	SAT will include a functional test of the alarms.		Alarm from the control systrem		
3				Operational SOP will include action in the event of an alarm.				
4		Failure of a unit cooler control valve	Discharge temperature monitoring	The PM will include checking the unit cooler performance.		The monitoring system		Depending where they are…
		Door remains open outside normal operating ranges specified	Alarm on door open time	SAT will include a functional test of the alarms.		Alarm from the door control system		
				Operational SOP will include action in the event of an alarm.				

Stage Four:

In order to qualify the equipment and show that the risk profile is the actual in operation profile, the correct operation of the risk controls should be verified.

This can be accomplished using a "verification summary report" to cross reference where the control was tested, together with confirmation that the other requirements required to release the system for use are in place e.g.:

- The system is in the maintenance management system.
- The instruments are in the calibration management system.
- The procedures are in place for:
  - operating
  - monitoring
  - cleaning
  - action in the event of an alarm
  - maintenance

Example Two

A second option that could be used, based on the component assessment process described in the ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5), is to use the component assessment results to define the system scope for commissioning, and that for qualification, as a hybrid between the two approaches described above.

- Define the system boundaries:
- The cooled chamber, including the box, doors, racking, and cooling units.
- Conduct the component risk assessment following the principles described in ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5).

Components should be classified as critical components of a GMP critical system if the answer to one or more of the following questions (Q1 to Q7) is 'Yes' 1:

- Is the component used to demonstrate compliance with the registered process?
- Does the normal operation or control of the component have a direct effect on product quality (without independent monitoring of the critical parameters by another GMP critical component? E.g., monitor or control a critical or key operational or performance parameter).
- Will failure or alarm of the component have a direct effect on product quality or efficacy (where the failure or alarm is not detected by another component in the same system or separate system?)
- Is information from this component recorded as part of the batch record lot release data or other GMP documentation?

- Does the component come into contact with the product or other components (including excipients, ingredients, solvents, or processing materials or with utilities which contact the product)?
- Does the component control the critical process elements that may affect product quality without independent verification of the control system performance?
- Is the component used to create or preserve the critical status of the system without independent monitoring of the critical parameters by another GMP critical component?

Note that the text in italics has been added to the text from the ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5) as clarification.

Components should be classified as non-critical components of a GMP critical system if the answer to all of the above questions (Q1 to Q7) is 'No' 1.

Table 12.5

Component Tag No.	Description	P&ID No.	Assessment Questions Yes/No (Y/N)							CIA[2]	Comments (if applicable)
			1	2	3	4	5	6	7		
TBA	Facility – provides a segregated insulated area.	N/A	No	No	No	No	No	No	No	NC	Any failure of this system would be immediately seen.
TBA	Door	N/A	No	No	No	No	No	No	No	NC	Any failure of this system would be immediately seen by the operators.
TBA	Racking – provided pre-defined storage locations, maximizing area storage capacity.	N/A	No	No	No	No	No	No	No	NC	Any failure of this system would be immediately seen by the operators.
TBA	Lighting – allows operators to see labeling/location tags.	N/A	No	No	No	No	No	No	No	NC	Any failure of this system would be immediately seen.
TBA	Condenser/ compressor system and pipework – provides a cooling medium.	N/A	No	No	No	No	No	No	Yes	NC	These items would be considered in the same way as a chilled water system for HVAC plant, i.e. as indirect impact.

Table 12.5 (continued)

Component Tag No.	Description	P&ID No.	Assessment Questions Yes/No (Y/N)							CIA[2]	Comments (if applicable)
			1	2	3	4	5	6	7		
TBA	Evaporator and fan – distribute and cool the cooling medium within the space.	N/A	No	Yes	Yes	No	No	No	Yes	C	These items are critical to the unit temperature mapping – any change could invalidate the original temperature mapping – hence they need to be qualified and maintained under GMP change control.
TBA	Control panels – provides sequencing of the duty standby refrigeration units, system engineering alarms.	N/A	No	No	No	No	No	No	No	NC	Note: the environmental monitoring system is the GMP alarm system.
TBA	Environmental Monitoring System	N/A	Yes	No	No	Yes	No	No	No	C	See above.
TBA	Control Sensors	N/A	No	No	No	No	No	No	No	NC	Any change could invalidate the temperature mapping due to refrigeration system impact.
Note 1: Questions are used as guidance but experience or subject matter expert judgment may ultimately be used to determine final classification. This must be documented in the comments section of the form. Note 2: Component Impact Assessment (CIA); GMP Critical (C); GMP Non-Critical (NC).											

Appendix 2
Current Regulations by Country and Regulatory Guidance

13 Appendix 2 – Current Regulations by Country and Regulatory Guidance

While every attempt has been made to make sure this list is complete at the time of publication, it is provided as a guide to assist readers confirm the current applicable regulations

Table 13.1: Current Regulations by Country and Regulatory Guidance

Country	Regulations/Regulatory Body/Guidance
Argentina	Government Executive Branch, Decreto 248/2009, Boletin Oficial de la Republica Argentina, No 31.624, 30 March 2009, http://www.anmat.gov.ar/Legislacion/Medicamentos/Decreto_248-2009.pdf Ley de Regulacion de la Cadena de Frio de los Medicamentos, No 26.492, 11 March 2009, http://www.puntofocal.gov.ar/doc/arg2009/248.pdf
Australia	Therapeutic Goods Agency (TGA) GMP Guide "Australian Code of Good Manufacturing Practice for Medicinal Products" "Australian Code of Good Wholesaling Practice for Therapeutic Goods for Human Use" "Australian Code of Good Wholesaling Practice for Medicines, Schedules 2, 3, 4 and 8"
Austria	Austrian Consortium of Wholesalers (Arge Pharmazeutika) "Code of Conduct for the Transportation of Medicinal Products in Austria"
Brazil[14]	The Brazilian National Sanitary Surveillance Agency
Canada	GUIDE-0001 Good Manufacturing Practices (GMP) Guidelines – 2009 Edition GUIDE-0069 Guidelines for Temperature Control of Drug Products during Storage and Transportation
China	Related regulations: <drugs distribution monitoring regulation>2007 edition <vaccine storage and shipment regulation>2006 edition <vaccine distribution and vaccination regulation>2005 edition
EU	Directive: EC/2001/83 (lists the applicable regulations), EC/1394/2007, EC/1902/2006, EC/2001/20 Guidance: 94/C 63/02 Guidelines on Good Distribution Practice of Medicinal Products for Human Use, Volume 9 (Pharmacovigilance) and Volume 10 (Clinical Trials) Non-member countries also may have specific guidance. e.g., UK: *Notes for Applicants and Holders of a Wholesale Dealer's Licence – Appendix 1 (Control and Monitoring of Storage and Transportation Temperatures)*
India	Organization of Pharmaceutical Producers of India (OPPI) Guidelines on Cold Chain Pharmaceutical Products

[14] The GMP regulations for the most countries in Latin America are based in WHO technical reports, depending on the grade of development, includes:
- WHO Technical Thirty-second Report. Annex 1. Good Manufacturing Practices for Pharmaceutical Products: 1.2 h, 2.1 c (vi), 2.1 h, 11.11 to 11.16.
- WHO Technical Thirty-seventh Report. Annex 4. Good Manufacturing Practices for Pharmaceutical Products: Main Principles: 2.1 h, 8.2 d, 9.8 h, 11.7, 12.8, 12.15 to 12.19.

Table 13.1: Current Regulations by Country and Regulatory Guidance (continued)

Country	Regulations/Regulatory Body/Guidance
Singapore	There are no agencies that govern cold chain specifically. The following agencies regulate importation generally. Health Sciences Authority Health Products Regulation Group (HPRG) • Medicinal and clinical trial pharmaceuticals Customs Narcotic Bureau • This agency is focusing on the more serious drugs that can be misused by the public "controlled drugs" (heroin, cocaine, etc.) If the pharmaceutical contains any kind of pathogenic virus or bacteria, the Ministry of Health (MOH) would be another controlling agency to factor in.
South Africa	Department of Health, Republic of South Africa; The Good Wholesaling practice for Wholesalers, Distributors and Bonded Warehouses, Medicines Control Council
Southern Ireland	Irish Medicines Board Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances, Current Edition IND-003 Version 01
United States (US)	CFR Title 21 Parts 203, 205, 210, 211, and 600
Venezuela	Ministry of Popular Authority for the Health
Other Guidance Documents	
American Society for Testing of Materials (ASTM)	ASTM E2500-07, Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment D3103-07e1 Standard Test Method for Thermal Insulation Performance of Distribution Packages E2637-08 Standard Guide for Utilizing the Environmental Cost Element Structure Presented by Classification E 2150
Parenteral Drug Association	Technical Report 39, Guidance for Temperature Controlled Medicinal Products
ISPE	• ISPE Baseline® Guide, Volume 5 – Commissioning and Qualification (Reference 24, Appendix 5) • ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment (Reference 27, Appendix 5) • ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification (Reference 25, Appendix 5) • ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Operations (Reference 26, Appendix 5)
International Safe Transit Association (ISTA)	ISTA 79 (new procedure due out in 2009)

Table 13.1: Current Regulations by Country and Regulatory Guidance (continued)

Other Guidance Documents	
Healthcare Distribution Management Association (HDMA)	Guidelines for Managing Cold Chain and Temperature Sensitive Products, December 2008
International Air Transport Association (IATA)	Chapter 17
International Conference on Harmonization (ICH)	Q1a, Q7, Q9, Q10
US Pharmacopeia	Information from the US Pharmacopeia used for this Guide came from USP 34–NF 29 (this is official on 1 May 2011)
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)	PIC/S document PE009-09 part 1– GMP guidance used by member countries
World Health Organization (WHO)	WHO Expert Committee on Specifications for Pharmaceutical Preparations – Fortieth Report 2006 • Proposal for Revision of WHO Good Distribution Practices for Pharmaceutical Products – 2008 • Manual on the Management, Maintenance and Use of Blood Cold Chain Equipment – 2005 • Guidelines on the International Packaging and Shipping of Vaccines – 2002

13.1 Example Review Document

A facility for example may be serving the following markets:

- USA
- EU
- Africa

The regulations governing storage and distribution could include those suggested below:

- USP General Chapter: <1079> Good Storage and Shipping Practices (Reference 8, Appendix 5)
- HPFBI Guide-0069: Guidelines for Temperature Control of Drug Products during Storage and Transportation (Reference 22, Appendix 5)
- EECEU 94/C 63/03: Guidelines on Good Distribution Practice of Medicinal Products for Human Use (Reference 9, Appendix 5)

- IMB Draft: Guidance Note on Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products (Reference 23, Appendix 5).
- ICH Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Reference 2, Appendix 5).
- World Health Organisation: WHO Expert Committee on Specifications for Pharmaceutical Preparations – Fortieth Report 2006 (Reference 6, Appendix 5)
  - E1: Equipment Performance Specifications for Cold Rooms and Freezer Rooms
  - E3: Equipment Performance Specifications for Refrigerators and Freezers
  - E4 and E11: Equipment Performance Specifications for Insulated Containers
  - E5: Equipment Performance Specifications for Ice Packs
  - E6: Equipment Performance Specifications for Temperature-Monitoring Devices
  - E7: Equipment Performance Specifications for Cold Chain Accessories
- TGA: Australian Code of Good Wholesaling Practice for Therapeutic Goods for Human Use (Reference 10, Appendix 5)

13.2 Review Organization Practices Compared to the Requirements

One approach that may be used to do this is a table – an example is shown below:

The relevant regulations are defined across the top row of the table.

The requirements are categorized in the left hand column and the specific regulation entered into the table.

The regulations generally cover each requirement area so this is not as onerous as it sounds. The organization practice that meets the regulatory requirement can then be defined – this can be done in the same cell as the regulation or in a separate cell below the requirement.

This process makes it easy to confirm compliance or identify gaps.

The information also could be used to develop a process map; the map then being reviewed to ensure it is the most effective.

Appendix 3

Example Instrument Impact Assessment

14 Appendix 3 – Example Instrument Impact Assessment

The example provided in this appendix shows a simplified approach that could be used for determining the criticality of the instrumentation of a cold storage system, and the definition of a calibration strategy. This approach may be used in conjunction with more detailed processes.

More information on a method that provides a complete and detailed process in setting strategy, as well as for risk, impact, and criticality assessment are provided in the GAMP Good Practice Guide: A Risk-Based Approach to Calibration Management (Reference 29, Appendix 5).

Instruments shall be classified as GMP critical components if the answer to one or more of the following questions (Q1 to Q7) is 'Yes.' (Questions are used as guidance, but experience or subject matter expert judgment may ultimately be used to determine final classification. This must be documented in the comments section of the form).

1. Is the component used to demonstrate compliance with the registered process?
2. Does the normal operation or control of the component have a direct effect on product quality (without independent monitoring of the critical parameters by another product/process critical component?)
3. Will failure or alarm of the component have a direct effect on product quality or efficacy (where the failure or alarm is not detected by another component in the same system or separate system?)
4. Is information from this component recorded as part of the batch record lot release data or other GMP documentation?
5. Does the component come into contact with the product or other components (including excipients, ingredients, solvents, or processing materials or with utilities which contact the product?)
6. Does the component control critical process elements that may affect product quality without independent verification of the control system performance?
7. Is the component used to create or preserve the critical status of the system (without independent monitoring of the critical parameters by another product or process critical component?)?

Note that the text in italics has been added to the text from the ISPE Baseline® Guide on Commissioning and Qualification (Reference 24, Appendix 5) as clarification.

Instruments shall be classified as non-GMP critical if the answer to all of the above questions (Q1 to Q7) is 'No.'

Table 14.1

Component Tag No.	Description	P&ID No.	Assessment Questions Yes/No (Y/N)							IIA[1]	Comments (if applicable)
			1	2	3	4	5	6	7		
TE-1	Temperature Control Sensors		N	N	N	N	N	N	N	NC	The environmental monitoring system provides independent monitoring of the room environmental conditions.
TE-2	Temperature Monitoring Sensor		Y	N	N	N	N	N	N	C	The sensor is the Environmental Monitoring System (EMS)
TE4-9	Unit Cooler Discharge Temperature Monitoring Sensor		N	N	N	N	N	N	N	NC	The sensor provides data for use in commissioning and maintenance.
TE-10, TE-11, TE-12	Refrigerant Compressor Temperature Sensors		N	N	N	N	N	N	N	NC	These sensors provide data that is used by the compressor control system to shut it down if readings are outside the normal operating range – i.e., equipment damage protection.
PE-1, PE-2	Refrigerant Compressor Pressure Sensors		N	N	N	N	N	N	N	NC	These sensors provide data that is used by the compressor control system to shut it down if readings are outside the normal operating range – i.e., equipment damage protection.

Table 14.1 (continued)

Component Tag No.	Description	P&ID No.	Assessment Questions Yes/No (Y/N)							IIA[1]	Comments (if applicable)
			1	2	3	4	5	6	7		
PE-3	Refrigerant Compressor Suction Pressure Sensor		N	N	N	N	N	N	N	NC	This sensor is used to provide the control setting for the unit; however, the performance of the whole room and refrigeration is monitored independently by the environmental monitoring system.
LS-1	Oil Separator Level Switch		N	N	N	N	N	N	N	NC	This sensor provides data that is used by the compressor control system to shut it down if readings are outside the normal operating range – i.e., equipment damage protection.
Note 1: Product or Process Critical (C); Non-GMP Critical (NC).											

14.1 Sample Instrument Calibration Strategy

For a system, a calibration strategy can be produced, covering the GMP safety and environmental requirements. This calibration strategy may be produced by engineering, as an SME it should be approved by Quality.

14.2 Environmental Monitoring System

The EMS system is used to monitor the conditions in the cold room.

The sensor locations are determined based on the system mapping to represent worse case conditions as found during normal operation, i.e., the hottest and coolest locations.

The EMS system is the Quality "system of record" for the quality critical conditions within the cold room (temperature in this example).

Therefore, the EMS temperature measuring instruments are considered process critical and will be calibrated on installation, testing a minimum of three points that cover the operating range of the equipment, and will then be routinely calibrated with the process managed through the calibration management system.

14.3 Cold Room Control Systems

There are two sets of controls for this sample system:

14.3.1 Refrigeration Control Panel (RCP)

The RCP is used to manage which of the available compressors skids is operating, providing time based auto-changeover, and enabling the standby unit in the event of a failure of the duty system or an unusual high temperature. The control panel also provides the control for the inlet solenoid valves for the individual cooling units.

The panel has two sets of temperature sensors.

14.3.1.1 Control Temperature Sensors

These are used to provide the temperature control with an indication of the conditions inside the chamber and are used to control the solenoid valve controlling refrigerant flow to the cooling unit.

These are calibrated at three points on the initial installation.

14.3.1.2 Discharge Temperature Monitoring Sensors

These are used during commissioning or maintenance to provide an indication of the discharge temperature from the coolers.

These are calibrated at three points on the initial installation.

14.3.2 Compressor Control Panel

The refrigeration compressor has its own proprietary control system, which monitors pressure and temperature at various points, and acts to provide control and system monitoring to protect the unit.

The system can be set up to operate in different modes, depending on the application. In this installation, the system is set to maintain a constant suction pressure.

The control system will give an alarm if any of the sensor inputs fail open or closed circuit, and provision is provided for internal calibration verification at a single point.

All of the temperature sensors are resistance devices that are unlikely to fail in a non linear mode.

The experience of the specialist supplier would indicate the same characteristics for the pressure sensors; hence, the recommendation that a periodic single point check is adequate.

It also should be noted that the majority of these sensors are used to provide equipment protection functions. The control sensors are used to control the system to the set point.

14.3.3 Conclusions

The EMS sensors are considered process critical and will be routinely calibrated.

The refrigeration units with the associated instrumentation will be checked and maintained following the manufacturers recommendations.

The unit cooler discharge temperature sensors will be checked on an as required basis – these sensors are used for engineering monitoring of the system performance.

The control sensors will be checked on an "as required" basis, managed as follows:

A maintenance procedure will be written to ensure periodic comparison of the system operating performance, as seen on the EMS data to be reviewed against a reference set of data taken from the EMS system during commissioning of the system.

This data will be kept as an attachment to the associated calibration work instruction.

The data will be reviewed by an experienced engineer who will assess the overall system performance and determine if the performance is consistent with expectations or if there are any signs of performance degradation.

If there are signs of degradation the work instruction will require the system to be subject to an engineering review. (**Note:** all quality actions derive independently from the EMS system).

The engineering review will cover the operation, maintenance, and calibration of aspects of the system as required.

Appendix 4

Example Commissioning Strategy

15 Appendix 4 – Example Commissioning Strategy

Rationale for Positioning of the Thermal Mapping Sensors and load testing of the 2 to 8°C Cold Rooms in XYZ.

Document No. _____ Revision A _____ Date _____

Approvals

Prepared by: _____

Approved by: _____

System Owner _____ Date _____

Engineering _____ Date _____

Validation/Quality _____ Date _____

Revision History

Revision	Date	By	Description
A			Issue for Review
XXX	XXX	XXX	XXX

Table of Contents

1.0 Introduction

This document has been written to provide a record of the rationale used to select the sensor locations for the temperature mapping of cold rooms xyz.

If any changes are found necessary during test execution, a drawing showing the final arrangement with a supporting rationale will be appended to this document.

The number of sensors may be reduced during qualification based on the results in order to simplify data analysis.[15]

[15] Note that it is expected that the initial mapping will confirm that the symmetrical nature of the design will show similar performance trends in equivalent zones.

The Mapping will be used to determine the locations and number of permanent temperature monitoring sensors, based on the product storage locations that experience maximum and minimum temperature conditions during simulated normal use.

It should be noted that the product stored within the cold rooms has no humidity requirements; hence, humidity will not be monitored or mapped.

2.0 Approach

The following points were considered:

3.0 External Heat Gains and Losses

The major heat gains and losses to the cold room are due to the influences of the external environment with the most significant being through the doors/door seals, walls, and ceiling.

These will be consistent as the structure is uniform and enclosed in a controlled room temperature area with the following exceptions;

The influence will vary during loading/unloading depending if the doors are open due to the infiltration of warm air past the door curtains especially as they are moved during entrance and exit. This is a significant factor in the system operation.

4.0 Internal Heat Gains and Losses

Lighting – the lighting is from low energy fluorescent lamps that are left on during the working day.

Product – the product stored in the cold room is supplied at the storage temperature so will not put a significant cooling load onto the cold room.

Equipment – the equipment used in the cold room comprises a stacking fork truck – a relatively small intermittent load.

People – there are approximately two people working in the area – the heat gains are therefore considered small and transient.

Refrigeration – the cold room is cooled by one of two refrigeration systems, one duty one standby.

For xyz cold rooms, each refrigeration system supplies 9 dual coil evaporator units with common continuously[16] running fans, one set of coils supplied from refrigeration system A, one from system B, see Figures 15.1 and 15.2.

5.0 Mapping Sensor Placement

The areas considered for mapping are only the areas where product will be stored.

The sensor locations proposed have been generated considering the following:

[16] There is an option to operate the fans based on the cooling requirement, but it is anticipated that they will run continuously unless the initial mapping demonstrates that this is not advantageous.

The chamber may be considered as a number of zones with each zone supplied by a cooling unit. The end zones are different to the center zones in that they have the end walls/door influences, but the symmetrical nature of the design of the central zones has allowed the number of mapping sensors proposed to be reduced.

The sensor locations proposed are shown on the attached drawings, see Figure 15.2.

As a minimum, a temperature sensor will be placed in the location of the lowest and highest storage point that product could be stored at each corner of the room on the racking nearest the perimeter.

One temperature sensor will be located in the center of these locations at mid level as shown.

Additional sensors are proposed as shown to monitor the local effect of the cooling units.

Note that the commissioning report will provide the dimensions for the sensor locations.

A sensor will be located adjacent to the unit cooler control sensor.

6.0 Monitoring System Sensor Placement

The mapping will be used to define the sensor locations which typically indicate the positions where the minimum and maximum temperatures are found; these positions will be used for mounting the monitoring probes a report will be prepared proposing the locations for review and approval by the system owner and Quality

7.0 Load Testing

The unit will be mapped using two "load" scenarios – in both cases, there will be a minimum amount of thermal mass so that the worst case scenario is tested:

7.1 Empty Chamber

The chamber will be mapped empty, i.e., with the lowest average airflow velocity in the room.

Note that the cooling units have a constant flow rate, and with the room empty, there are no constraints on the airflow direction; hence, the airspeed will be low. When the room is full of boxes, the airflow will be at a higher speed as the same volume of air will need to travel through a smaller area.

7.2 "Full" Sections

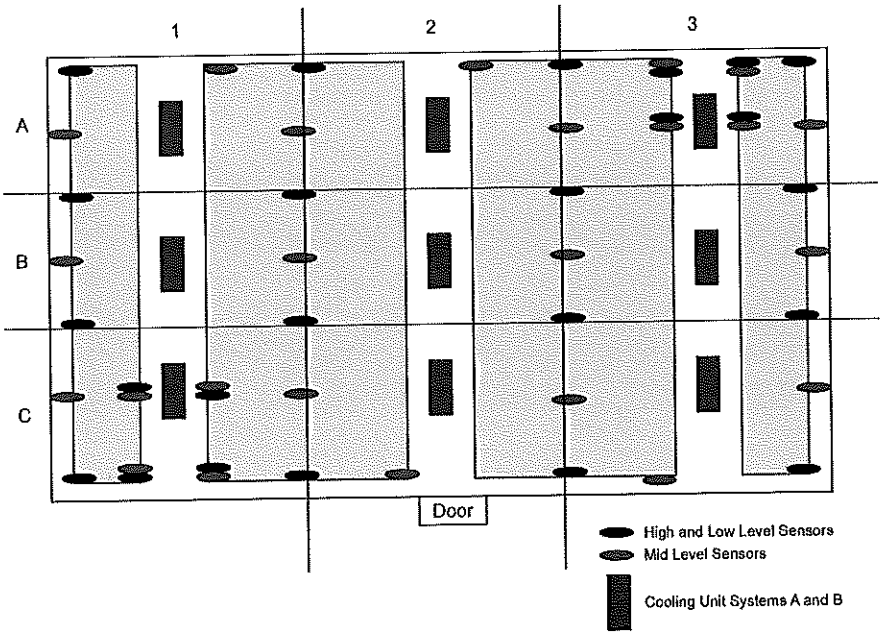
The area that is shaded will be filled with empty boxes simulating the largest stored full pallet (40" by 48" by 46" tall). This scenario will give minimum thermal mass, but maximum interruption of airflow, allowing the effect of a full chamber to be seen in the filled zones. Note that the area selected was based on the fact that the room is symmetrical, and the area with the most sensitivity is likely to be near the access door, due to infiltration when the door is open. (Note the User Requirements confirm that product to be stored in the unit will be supplied at the storage temperature).

8.0 Summer/Winter Conditions

Typically, for a controlled temperature environment (warehouse), it is necessary to carry out summer and winter temperature mapping to monitor the impact of external conditions and the change in airflow due to the duty reversing from heating to cooling.

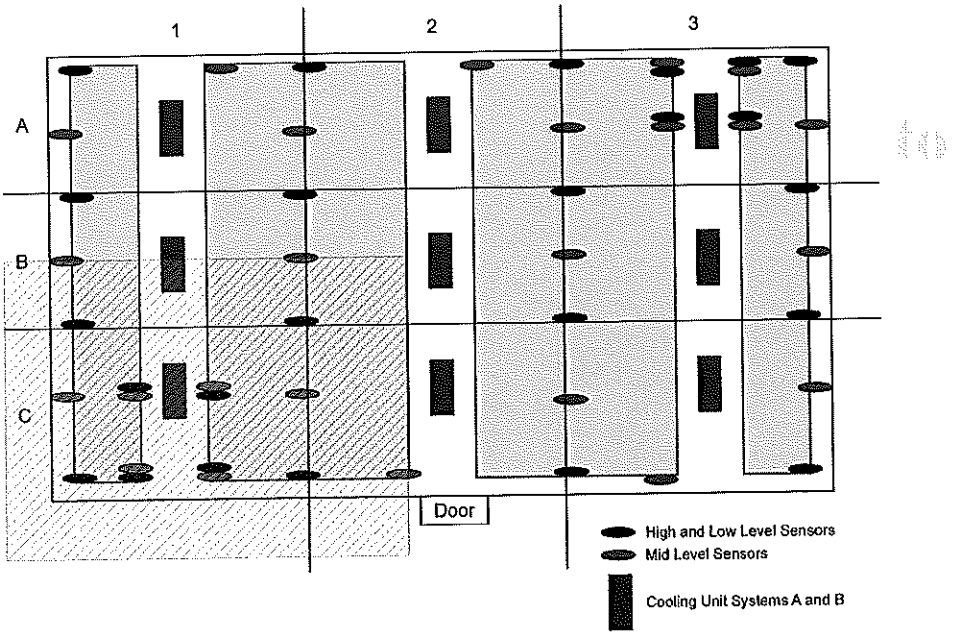
The cold rooms and freezers in this instance are located in a conditioned space with an air gap of approximately four feet to any external wall; hence, the affect of the external conditions is very limited – the monitoring system sensors will give an accurate indication of the internal conditions regardless of the external conditions; hence, it is not intended to map during summer/winter conditions.

Figure 15.1: Plan View Showing the "Zoning" Concept and the Sensor Locations Proposed for the Cold Rooms



Note that the sensor locations are shown on the outside of the zones with the high/low positions representing the highest and lowest product storage locations. During initial mapping, the locations will be reviewed to determine if the worst case situation is being mapped – see Introduction.

Figure 15.2: Proposed Location of the "Load" for the Cold Rooms



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    - Temperature Control Training for Active Systems
    - Guidance for the TSA Cargo Screening
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Appendix 6
Glossary

17 Appendix 6 – Glossary

17.1 Abbreviations

ASTM	American Society for Testing of Materials
DOT	Department of Transportation (USA)
EU	European Union
FDA	Food and Drug Administration (USA)
HDMA	Healthcare Distribution Management Association (USA)
HPRG	Health Products Regulation Group (Singapore)
IATA	International Air Transport Association
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
MOH	Ministry of Health (Singapore)
NFPA	National Fire Protection Association (USA)
NOAA	National Oceanic and Atmospheric Administration (USA)
OPPI	Organization of Pharmaceutical Producers of India
PDA	Parenteral Drug Association (USA)
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
TGA	Therapeutic Goods Administration (Australia)
WHO	World Health Organization

17.2 Acronyms

ADR	Authorized Distributor of Record
AHU	Air Handling Unit
API	Active Pharmaceutical Ingredient
BAS	Building Automation System
BDS	Bulk Drug Substance

BMS	Building Management System
CCT	Controlled Cold Temperature
CFC	Chlorofluorocarbon
CIA	Component Impact Assessment
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRT	Controlled Room Temperature
CTC	Controlled Temperature Chamber
EMS	Environmental Monitoring System
EPC	Electronic Product Code
EPCIS	Electronic Product Code Information Services
EPS	Expanded Polystyrene
ERP	Enterprise Resource Planning
FAT	Factory Acceptance Test
FEFO	First-Expired-First-Out
FG	Finished Goods
FIFO	First-In-First-Out
GDSN	Global Data Synchronisation Network
GPS	Global Positioning System
GSM	Global System for Mobile Communications
GTSH	Global Traceability Standard in Healthcare
GWP	Global Warming Potential
GxP	Comprises:
	GCP Good Clinical Practice
	GDP Good Distribution Practice
	GEP Good Engineering Practice
	GLP Good Laboratory Practice

GMP	Good Manufacturing Practice
GQP	Good Quality Practice
HAZOP	Hazard and Operability (Study)
HC	Hydrocarbon
HCFC	Hydrochlorofluorocarbon
HFC	Hydrofluorocarbon
HIBC	Health Industry Bar Code
HID	High Intensity Discharge
HVAC	Heating, Ventilation, and Air Conditioning
IMDG	International Maritime Dangerous Goods
IPA	Iso Propyl Alcohol
IQ	Installation Qualification
IT	Information Technology
IV	Installation Verification
L&I	Licenses and Inspections
LIFO	Last-In-First Out
MES	Manufacturing Execution Systems
MFL	Maximum Foreseeable Loss
MHE	Materials Handling Equipment
MKT	Mean Kinetic Temperature
NFO	Next Flight Out
ODP	Ozone Depletion Potential
OQ	Operational Qualification
P&ID	Piping and Instrumentation Diagram
PDF	Portable Document Format
PPE	Personal Protective Equipment
PQ	Performance Qualification

PTFE	Polytetrafluoroethylene
PUR	Polyurethane
QA	Quality Assurance
QC	Quality Control
RCP	Refrigeration Control Panel
RF	Radio Frequency
RFID	Radio Frequency Identification
RT	Resistance Temperature
RTD	Resistance Temperature Detector
SAT	Site Acceptance Test
SCADA	Supervisory Control and Data Acquisition
SME	Subject Matter Expert
SOP	Standard Operating Procedures
TA	Technical Agreement
TEWT	Total Equivalent Warming Impact
TLV	Threshold Limit Value
TWA	Time Weighted Average
UL	Underwriters Laboratories
UPS	Uninterrupted Power Supply
VIP	Vacuum Insulated Panel
WIP	Work-In-Process
WMS	Warehouse Management System
YTD	Year to Date

17.3 Definitions

Cold

Any temperature not exceeding 8°C (46°F) is cold. A refrigerator is a cold place in which the temperature is maintained thermostatically between 2° and 8°C (36° and 46°F).

Cool

Any temperature between 8° and 15°C (46° and 59°F) is cool. An article for which storage in a cool place is directed may, alternatively, be stored and distributed in a refrigerator, unless otherwise specified by the individual monograph.

Controlled Cold Temperature (CCT)

Controlled cold temperature is defined as temperature maintained thermostatically between 2° and 8°C (36° and 46°F), that allows for excursions in temperature between 0° and 15°C (32° and 59°F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8°C (46°F).

Controlled Room Temperature (CRT)

Controlled room temperature indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Cryogenics

The study of phenomena and processes at low temperatures, defined arbitrarily as below 150K (-190°F). Phenomena that occur at cryogenic temperatures include liquefaction and solidification of ambient gases.

Dry Place

The term dry place denotes a place that does not exceed 40% average relative humidity at Controlled Room Temperature or the equivalent water vapor pressure at other temperatures.

Excessive Heat

Excessive heat means any temperature above 40°C (104°F).

Freezer

Freezer indicates a place in which the temperature is maintained thermostatically between -25° and -10°C (-13° and 14°F).

Note: the freezing point is defined as the temperature at which a liquid substance turns to a solid. The term frozen is applied to the solid product.

Mean Kinetic Temperature

Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures.

Pack-out

The pack-out process is used to describe how the packaging is assembled with the product and cooling medium.

Protection from Freezing

Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Room Temperature

Room temperature indicates the temperature prevailing in a working area.

Warm

Any temperature between 30° and 40°C (86° and 104°F) is warm.