



Good Practice Guide

Cold Chain Management

Facility Requirements

Storage Requirements

Controlled Temperature Storage

Packaging/Unpacking

Transportation

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Good Practice Guide

Cold Chain Management

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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 (EMA) 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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Table of Contents

1	Introduction	7
1.1	Background	7
1.2	Purpose	7
1.3	Scope	8
1.4	Benefits	8
2	Regulatory Requirements	9
2.1	Defining the Relevant Regulations	9
3	Quality Plan	11
4	Production Considerations	15
4.1	Introduction	15
4.2	Related Definitions	16
5	Facility Design Considerations	19
5.1	Work Flow Considerations	19
5.2	Surface Finishes	22
5.3	Layout	22
5.4	Facility Systems	23
5.5	Security (Layered Design)	25
5.6	Specialized Equipment	27
5.7	Sustainability	27
5.8	Controlled Substances	27
6	Fixed Equipment	29
6.1	Procurement Processes	29
6.2	General Considerations	30
6.3	Pre-requisites to Commissioning	40
6.4	Commissioning	42
6.5	Mapping Sensor Locations – Number of Sensors Required	43
6.6	Qualification/Verification	48
7	Portable Packaging or Shipping Systems	51
7.1	Active Systems	51
7.2	Passive Systems	52
7.3	Insulation Materials	52
7.4	Alternative Designs	54
7.5	Developing a Distribution Process and Qualifying a Shipping Process	54
7.6	Ongoing Monitoring	65
7.7	Governing Documentation	66
8	Mapping and Monitoring Equipment	69
8.1	Sensors	69
8.2	Monitoring – Key Considerations	74
8.3	Recording Intervals	77
8.4	Qualification of Temperature Monitoring Systems	78
8.5	Handling Excursions – Data Analysis and Interpretation	78
8.6	Economics	81

9	Location of Temperature Monitoring Devices	83
9.1	Product Payload.....	87
9.2	Number of Temperature Monitors	87
10	Maintenance and Cleaning.....	89
10.1	Maintenance	89
10.2	Cleaning.....	90
10.3	Calibration.....	90
11	Product Traceability	91
11.1	Supply Chain Visibility.....	91
11.2	Traceability.....	92
12	Appendix 1 –Science-Based Quality Risk Management	97
12.1	Quality Risk Management for the Qualification of Equipment.....	98
13	Appendix 2 – Current Regulations by Country and Regulatory Guidance	107
13.1	Example Review Document.....	110
13.2	Review Organization Practices Compared to the Requirements.....	111
14	Appendix 3 – Example Instrument Impact Assessment	113
14.1	Sample Instrument Calibration Strategy	116
14.2	Environmental Monitoring System	116
14.3	Cold Room Control Systems.....	117
15	Appendix 4 – Example Commissioning Strategy	119
16	Appendix 5 – References	125
17	Appendix 6 – Glossary	129
17.1	Abbreviations	130
17.2	Acronyms	130
17.3	Definitions	133

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):

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

in which T_k 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; T_1 is the value for the temperature recorded during the first time period, e.g., the first week; T_2 is the value for the temperature recorded during the second time period, e.g., second week; and T_n 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 = $\{[(^{\circ}\text{F} - 32) \times 5/9] + 273.1\}$

Celsius to Kelvin = $273.1 + ^{\circ}\text{C}$

Fahrenheit to Celsius = $[(^{\circ}\text{F} - 32) \times 5/9]$

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 receive 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" (Reference 18, 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 led 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 CO₂.

Currently, refrigerants are selected according to:

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

Once these criteria have been considered, the fluids will be evaluated according to 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 and 134a 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 (CO₂) 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