BRIEFING

Good Storage and Shipping Practices, USP 34 page 595. The chapter revision proposed in PF 36(1) [Jan.–Feb. 2010] was canceled; a new revised chapter is now being proposed. This general information chapter provides guidance on the proper storage and transportation of drug products from manufacturer to end user. From 1997 to 2000, five shipping studies were undertaken that examined the effect of temperature and humidity fluctuations on drug products shipped around the world. The results of these initial studies led to the development of this chapter, first published in Pharmacopeial Forum in 2003. The chapter recognizes that the pathway from manufacturer to end user is usually complex and that numerous parties are involved in a series of handoffs. During this process, different modes of transportation may be used between holding facilities, and every storage area may have different controls and procedures. The proposed revision of the entire chapter is intended to reflect the globalization of activities surrounding the storage and transportation of drug products. As we have moved from a regional to a global supply chain, it has become more important to adhere to labeled temperature requirements. In addition, the importance of cold chain storage has increased with the increase in biotechnology-derived drugs requiring refrigerated storage.

(PSD: D. Hunt.)

Comment deadline: September 30, 2011

Change to read:

GOOD STORAGE AND SHIPPI NG PRACTICES

This general information chapter is intended to provide general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures to maintain proper storage environments for individual articles and to ensure a preparation’s integrity, including its appearance, until it reaches the user. There is no change to any applicable requirements under Current Good Manufacturing Practices, approved labeling, state laws governing pharmacies, the USP General Notices and Requirements, or monographs. The section Preservation, Packaging, Storage, and Labeling under General Notices and Requirements provides definitions for storage conditions. All equipment used for recording, monitoring, and maintaining temperatures and humidity conditions should be calibrated on a regular basis. This calibration should be based on NIST or international standards (see Monitoring Devices—Time, Temperature, and Humidity (1118)). A Pharmacopeial preparation may follow several potential routes from the original manufacturer to the patient. Figure 1 documents present-day routes and the associated risks. These risks include...
exposure to temperature excursions, humidity, light, and oxygen. For a discussion of climates, stability, and mean kinetic temperature, see *Pharmaceutical Stability* (1150). Temperature- or humidity-sensitive articles are to be handled in accordance with General Notices.

**PACKAGING AND STORAGE STATEMENT IN MONOGRAPHS**

Most articles have storage conditions identified by their labeling. Otherwise, it is expected that the conditions for storing the article are specified in the monograph according to definitions provided by the General Notices and Requirements in the section Storage Temperature, and Humidity under Preservation, Packaging, Storage, and Labeling. In cases where additional information on packaging and storage is desired, a specific statement can be provided in the Packaging and storage or the Labeling section of the individual monograph.

**STORAGE IN WAREHOUSES, PHARMACIES, TRUCKS, SHIPPING DOCKS, AND OTHER LOCATIONS**

Pharmacopeial articles are to be stored in locations that adhere to conditions established by the manufacturer. Where the desired conditions are not established, use storage conditions described in the General Notices and Requirements or in the applicable monograph.

**Warehouses**

Observation of the temperature variations in a warehouse should be made over a period of time to establish a meaningful temperature profile, including the temperature variations and conditions in the different parts of the warehouse. Such observations provide data and information as to where various products should and should not be stored.

**ESTABLISHING TEMPERATURE PROFILES**

Temperature profiles can be compiled by using a suitable number of thermometers or other temperature recording instruments. They should be placed throughout the warehouse in divided sections and should record the maximum and minimum temperatures during a 24-hour period for a total of three consecutive 24-hour periods. The following factors, some of which may give rise to extreme temperatures, should be considered during the process of temperature profiling: the size of the space, location of space heaters, sun-facing walls, low ceilings or roofs, and geographic location of the warehouse. Temperature profiling for warehouses already in use should be done at known times of external temperature extremes, e.g., for a period of not less than 3 hours when air...
temperatures are higher than 25°C or less than 15°C. Profiling should be conducted in both summer and winter. A mean kinetic temperature (MKT) should be obtained for any separate areas within the warehouse (see Pharmaceutical Calculations in Prescription Compounding 4160 for samples of MKT calculations). The temperature profile report should provide recommendations for the use of each area and identification of any areas that are found unsuitable for storage of Pharmacopeial articles.

**CONTROLLED ROOM TEMPERATURE**

The General Notices provide a definition for Controlled Room Temperature. A temperature profiling study should demonstrate suitability for storing Pharmacopeial articles in areas determined to be at room or controlled room temperature. A suitable number of temperature and humidity recording instruments should be installed to record temperatures and to provide temperature and humidity profiles. Temperature recording should be conducted to meet the recommendations for establishing mean kinetic temperature and to comply with the warehouse's written procedures. These written procedures should have a reporting mechanism in place whereby a management tree is informed in the event that predefined high or low temperatures or humidity limits have been exceeded. Records can be reviewed as determined by the management system in accordance with established guidelines. Suitable training should be provided to persons who record temperatures, and proper quality accountability and tracking systems should be maintained.

**STORAGE AT “COOL,” “COLD,” “REFRIGERATOR,” AND “FREEZING” CONDITIONS**

The General Notices provide definitions for cool, cold, refrigerator, and freezer temperatures. A temperature profiling study can be used to establish suitable areas for storing Pharmacopeial articles designated to be stored under these conditions. Equipment used for storing Pharmacopeial articles at these low temperatures should be qualified according to written procedures provided by the management system. Recording devices can be installed within the equipment and used to enable both air and product temperatures to be recorded at regular intervals. The number and location of monitoring devices should be determined based on the result of the temperature profile. Temperature records should be examined at least once every 24 hours or as provided in the equipment protocol. Cool or cold conditions are moisture-condensing conditions. Humidity monitoring devices should be used in cases where the repackaged Pharmacopeial article is humidity-sensitive or labeled to avoid moisture. Additionally, there can be installed temperature-monitoring, and where necessary, humidity-monitoring alarm devices that have the capability of alerting personnel in the event that control is compromised. There should be protocols in place to address procedures for responding to failed temperature and humidity ranges both for normal working hours and outside normal working hours. Temperature and humidity should be reviewed at
the times designated by the established protocol. The calibration and functioning of all temperature and humidity monitoring devices, including alarms and other associated equipment, should be checked on an annual or semiannual basis. Regular maintenance protocols should be in place for refrigeration equipment. There should be written agreements in place for all maintenance and evaluation procedures, and this may include an emergency situation protocol.

PERSONNEL TRAINING

Suitable training should be provided for personnel who handle Pharmacopeial articles with special storage temperature requirements. Personnel should know how to monitor temperatures and how to react to situations where adverse temperatures are identified. There should be written procedures in place such that the adverse temperatures are recorded and a report provided to the parties designated in the protocol.

QUALIFICATION OF "COLD" EQUIPMENT OR STORES

Only climate control equipment for which a contractor has provided documentation to assure its suitability for temperature and humidity requirements should be considered for use in cold storage. Qualification procedures on a regular basis should be independently conducted on equipment in cold stores to guarantee suitability and proper functioning. The procedure should demonstrate the temperature profile for both air and product temperatures when empty as well as when loaded. The procedure should also demonstrate the time taken for temperatures to exceed the maximum temperature in the event of a power failure. Qualification should consider thermal fluctuations that occur during stock replenishment and order removal. The results of the qualification should demonstrate the ability of the equipment to maintain the required temperature range in all areas, defining any zones which should not be used for storage such as those areas in close proximity to cooling coils, cold air streams from equipment ventilation, or doors. The variability of the system can be characterized by using the relative standard deviation. Thermal monitoring should establish that the system is rugged in that its temperature profile is consistent and reliable.

DISTRIBUTION AND SHIPMENT OF PHARMACOPEIAL ARTICLES

As indicated in Figure 1, a drug can take a variety of paths from the manufacturer to the patient. In the simplest form of the distribution system, the manufacturer ships directly to the customer, such as a doctor's office, clinic, or hospital. However, more often, the article leaves the manufacturer's chain of control and enters a complex system of handoffs that involve the distribution chain to the patient.
Figure 1. Drug product distribution.

Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer. For particular cases, such as shipment of vaccines or other special care products, manufacturers may require special shipping and storage conditions generally referred to as "cold-chain management". For example, manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution (see Monitoring Devices—Time, Temperature, and Humidity). Validated, available temperature- and/or humidity-monitoring technologies can be used to monitor the overall environmental effect on compendial articles during shipment and distribution. In these cases, the shipping conditions of the package are recorded. In general, extreme temperature conditions (i.e., excessive heat, freezing) should be avoided. Distribution systems chosen to deliver pharmaceutical products from the manufacturer to the consumer should take into account basic operational parameters, including timeliness and accountability. The manufacturer’s FDA-approved storage conditions, printed in the labeling of the product, should be observed carefully at each destination of the distribution chain (see Figure 1), unless specifically instructed otherwise in the immediate label of a shipping container. This may be the case for certain pallet-sized shipping containers where the amount of refrigerant contained (e.g., dry ice, gel packs) is based on an anticipated exterior condition approximating controlled room temperature. In such cases, placing the shipping container in a refrigerator could lead to the product inside freezing, potentially affecting its quality. Items requiring special handling conditions will have these conditions clearly indicated in the labeling for the product. The Prescription Drug Marketing Act of 1987 and the ensuing regulations in 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors, provide the necessary regulations and guidance for several legs of the distribution chain for the prescription drug. The manufacturers and distributors should work together to establish proper distribution and product handling requirements for the purpose of ensuring appropriate product maintenance in transit. Pharmacists and physicians should educate patients regarding proper storage of products to ensure product integrity at the patient level. Information that may be considered in determining the ability of pharmaceutical articles to
maintain their Pharmacopeial requirements of identity, strength, quality, and purity through the
distribution channel may include, but is not limited to the following: ICH stability studies, temperature
cycling studies, stability shipping studies, ongoing regulatory stability commitment studies, market
experience portfolio (i.e., product complaint files, historical product performance data, product
development data), and product labeling commitments.

Qualification Protocol

Operational and performance testing should be parts of a formal qualification protocol that may use
controlled environments or actual field testing based on the projected transportation channel. These
should reflect actual load configurations, conditions, and expected environmental extremes.
Temperature and humidity monitors should be placed into the product or a representative thereof.
Testing consists of consecutive replicate field transportation tests using typical loads, according to
an established protocol.

Physical Challenges

Most products are sufficiently robust to withstand distribution with minimal protection from routine,
well-understood physical and environmental hazards. Several standard test methods are available
for evaluating package performance factors under well-documented shock, vibration, and other
Performance Testing of Shipping Containers and Systems” (ASTM D4169-98), and the International
Safe Transit Association’s (ISTA) specifications have similar methods for evaluation of shipping
performance for various types of transit modes such as less than truckload (LTL), small package,
rail car, air freight, etc. From the manufacturer’s perspective, these tests are very useful in
evaluating the product and package durability and fragility. The tests are usually performed on
shipping carton quantities of a specific stock keeping unit (SKU) as an unbroken whole. Fragility
problems can be corrected with package modifications, which could include placing cotton or rayen
coilers in bottles or placing top and bottom pads in the shipping case to reduce package breakage.
Not all protective packaging elements follow the SKU through the system.
Basic packaging principles are observed when separating the contents of the manufacturer’s
shipping container or pallet load into smaller quantities or when shipping mixed product loads. For
example, glass containers are wrapped in a bubble wrap or other shock absorbent material, and the
void spaces are filled with dunnage (e.g., foam “peanuts,” shredded or tightly crumpled paper,
bubble wrap) to protect the contents from shifting and drop impact. Large volume liquid containers
may be bagged in plastic and kept isolated to prevent leakage to, or damage of, adjacent packages.
“Skin packaging,” a term describing a heat shrink film that anchors the load to fiberboard and
prevents load shift, can be an excellent method of protecting some products, but it may be
Temperature Challenges

Shipping of temperature-sensitive articles requiring thermally controlled packaging presents a special challenge. Unlike shock, vibration, and other physical hazards, thermal hazards tend to be unique to a given system. Except for temperature-controlled trucks, the distribution environment is widely variable and depends upon a range of factors, including points of origin and destination, article and container sensitivities to cold, accidental freezing or heat, transit mode (e.g., air, truck, combination), time, weather or season, and carrier type (e.g., small package carrier or integrator, freight forwarder, U.S. Postal Service). The shippers should know and understand the systems they use and should design the protective package accordingly. Storage temperature ranges may not be indicative of the allowable tolerances during shipping. Articles labeled for special storage conditions (between 2° and 8°) vary widely in their tolerance of short-term exposure to heat and cold. Some, such as soft gelatin capsules and suppositories, carry specific upper limits on both shipping containers and SKUs. A temperature cycling study intended to identify those articles affected by multiple, short-term excursions beyond the storage temperature limits should be performed. These data provide wholesalers and distributors with clearer identification of those drug products that may require special handling during particular climate conditions.

Materials

Two commonly used types of refrigerant are dry ice (frozen carbon dioxide gas) and wet ice (frozen water), which appears as crushed ice or in various refrigerant packs containing water mixtures with specific freezing points. Phase change materials are also available for specialized needs. Refrigerant packs should have the correct freezing point and be cooled to the proper surface temperature prior to use. Articles harmed by accidental freezing may require a barrier between the refrigerant and the product or some other special packaging. Insulating materials commonly available include foil laminates, bubble pack, corrugated, fabricated, and molded expanded polystyrene (EPS) cartons, and fabricated or molded urethane foam cartons, with or without additional interior components. Recognized standard test methods for evaluating insulated containers are currently limited to ASTM D3103-92, Standard Test Method for Thermal Insulation Quality of Packages and a method under development by ISTA. Neither one fully addresses all of the issues involved, but both include useful information on testing procedures. The tests should be modified based on the specific system adopted by the shipper. The manufacturer may be able to supply helpful data on specific articles and their requirements.
SPECIAL HANDLING

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as dangerous goods under the Department of Transportation (DOT), state, local, or carrier rules; or products classified as controlled substances by the Drug Enforcement Administration (DEA) or by individual states.

Receipt of Pharmacopeial Articles

Upon arrival of Pharmacopeial articles at warehouse loading docks, premises, and other arrival areas, the Pharmacopeial articles are to be transferred to their manufacturer-designated storage environment within 2 hours of receipt. Limitation of the time spent in the uncontrolled environments of the loading dock is important to ensure that the integrity of the preparation is maintained. This is particularly important for temperature-sensitive items. The delivery document should be reviewed at receiving sites to ensure that the Pharmacopeial articles have not been subjected to any delays during shipment that could result in exposure of the article to extremes of temperature, or to any other extreme or undesirable conditions. In addition, to the extent possible, the receiving personnel should ensure that the ruggedness requirements in shipment have been met. For Pharmacopeial articles requiring extreme caution, special handling, or refrigerator temperature storage conditions, those who supply the articles (e.g., wholesalers and manufacturers) and delivery contractors should provide documented evidence to show that the required temperature range has been maintained during transportation. In the event that a deviation from the required temperature range has been observed during shipment of an article requiring such a shipping condition, the supplier or delivery contractors should document the temperature and the length of time the compendial article was not within the designated storage temperature. The pharmaceutical manufacturer may be contacted to determine the significance of unusual variances.

Distribution or Shipping Vehicles

Vehicles used for shipping or distribution of Pharmacopeial articles designated for storage at controlled room temperature should be suitably equipped to ensure that the temperature excursions encountered are within those allowed under the definition of controlled room temperature. Steps should be taken so that extremes of temperature, whether above or below the specified temperatures, should not be encountered during delivery procedures.

Vehicle Qualification
Where practical, suitable monitoring devices, as determined by the manufacturer and vehicle supplier, should be placed in different areas of the truck to establish a temperature profile of the truck over a 24-hour period during a hot summer day, average high, and a cold winter day, average low, and during a normal or typical day. The derived temperature of the different parts of the truck may be used to determine the location on the truck where Pharmacopeial articles can be stored appropriately during shipping (see Monitoring Devices—Time, Temperature, and Humidity). Pharnaceutical Delivery Staff

As part of the contractual agreement between the delivery contractors and the manufacturers, the delivery staff should receive appropriate training to ensure that they are aware of the correct procedures to follow in maintaining products at the correct temperature. There may be written procedures that should be documented. In addition, the transportation personnel should have proper knowledge of the temperature profile of the vehicle to ensure proper placement of the Pharmacopeial articles in the vehicle. Pharmacopeial articles requiring special handling (e.g., refrigeration) or environmentally sensitive preparations should be transported in a suitably equipped vehicle to ensure that the articles are maintained at the correct temperature during distribution, shipping, and delivery and up to the point of receipt. Special arrangements should be made to inform receiving personnel, pharmacists, or other appropriate customers that the package includes articles with special storage and handling specifications and are to be transferred immediately to the appropriate storage location. The manufacturer, shipper, or delivery agency should provide appropriate evidence to show that the required temperature has been maintained throughout shipment and distribution.

SHIPMENT FROM MANUFACTURER TO WHOLESALER

Wholesaler

The wholesaler receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The wholesaler should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution that could result in products being exposed to extreme temperatures (see also the previous section, Pharmaceutical Delivery Staff, for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the wholesaler, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct

http://www.usppf.com/pf/pub/data/v374/CHA_IPR_374_c1079.xml
temperature during shipping and distribution and up to the point of receipt. The receiving wholesaler staff should be informed that the articles are transferred to appropriate storage locations without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage at room or controlled room temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Warehouse staff may receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see Pharmaceutical Delivery Staff). Where necessary, a monitoring device for temperature and/or humidity should be used during shipping and distribution.

Compromised Temperature Conditions

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.

SHIPMENT FROM MANUFACTURER OR WHOLESALER TO PHARMACY

Pharmacy

The pharmacy receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The pharmacy personnel should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution, which could result in the products being exposed to extreme temperatures (see also the section, Pharmaceutical Delivery Staff, for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the pharmacy, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. Receiving pharmacy staff should be informed that the articles are to be transferred to appropriate storage without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage at room or controlled room temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Pharmacy staff may
receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see Pharmaceutical Delivery Staff). Where necessary, a monitoring device for temperature and/or humidity may be used during shipping and distribution.

**Compromised Temperature Conditions**

The pharmacy should maintain appropriate procedures to define action that should be taken in the event of deviation from the required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action taken (including whether the product is issued to the patient or customer). Advice on the suitability of the product for use as an acceptable drug article should be sought from the manufacturer or supplier of the product.

**SHIPMENT FROM PHARMACY TO PATIENT OR CUSTOMER**

The pharmacy should provide an appropriate label on the package sent through air or surface routes so that the deliverer does not place the package in a mailbox exposed to extremes in temperature. In the event that no one is available to receive the package, the deliverer should return the package to the post office or service office, and store it in a cool or air-conditioned area until the patient can receive the medication. In the event that the package has not been delivered for more than 2 days, the package may be returned to the pharmacy. For temperature-sensitive articles, it is important that proper arrangements be made to protect the drug from exposure to high temperatures, or in some cases, from freezing conditions. Such arrangements may include the following: insulating the packaging, or packaging with coolant included; overnight shipping; and pre-arranged pick-up. In such cases, the pharmacy should provide on the external package a statement of an acceptable period of delay for delivery. The patient or customer should examine the delivery documentation to ensure that the package has not been subjected to any unacceptable delays during shipping and distribution. The patient or customer receiving the pharmaceutical articles, either by mail, delivery vehicle from the pharmacy, or directly from the physician or pharmacy, should be advised that upon receipt the articles are to be transferred to appropriate storage conditions without delay, as directed by the pharmacy, ideally within 2 hours of receipt. The vehicle used for air or surface shipping and distribution of pharmaceutical packages to the patient or customer, especially those requiring low temperatures, should contain the article suitably packaged in containers that maintain the desired storage conditions until the article reaches the patient or customer. The vehicles used for shipping and distribution of pharmaceutical articles to patient or customer, especially those requiring storage at room or controlled room temperatures, should be suitably equipped during extreme temperature conditions such that the packages are not exposed to extremes of temperature either in winter or summer months. In the event that the vehicle is not
adequately equipped with air conditioning or heating to protect the product, the time that the article is exposed to ambient conditions should be strictly limited, ideally not more than 2 hours. Where appropriate, a monitoring device may be used to ensure that required temperatures are maintained until the package reaches the patient or customer. If stability studies for the Pharmacopeial preparation indicate that it is particularly sensitive to environmental insults or if appropriate shipping safeguards described in this section are not feasible, then the preparation should be shipped by a different method whereby environmental control can be maintained.

**Compromised Temperature Conditions**

There should be appropriate procedures in the pharmacy that ships the article to the patient or customer defining the action that should be taken in the event that a patient reports that there has been a deviation from required storage conditions for an article, including any environmentally sensitive preparations, prior to the point of receipt. Advice on the suitability of the product for use should be provided to the patient or customer after the manufacturer or supplier’s advice has been sought by the pharmacy. If the patient is advised to use the article, such advice should be documented and noted appropriately by the pharmacy. Otherwise, appropriate arrangements should be made to promptly replace the suspect article. For mail order items, replacement from local pharmacies may be an option to ensure an uninterrupted supply of medication.

**RETURNS OF PHARMACEUTICAL ARTICLES FROM PATIENTS OR CUSTOMERS**

The wholesaler, manufacturer, and pharmacy personnel should evaluate the validity of the request for return, and maintain an auditable account of the return receipt. For products in unopened manufacturer’s containers that have been at variance during shipment, arrangement may be made to return the products to the manufacturer, wholesaler, or pharmacy preferably within 3 working days of receipt. The supplier may request records or written confirmation by the patient to show that the product was stored properly while in possession of the customer.

**STORAGE OF PHYSICIAN SAMPLES HANDLED BY SALES REPRESENTATIVES IN AUTOMOBILES**

Storage of physician samples by sales representatives is regulated under 21CFR 203.34(b)(4); each manufacturer or distributor is to have appropriate policies in place to ensure that proper storage is maintained. The following suggestions may be considered in response to this need and are of interest to practitioners who may observe actual practices. Automobile trunks or passenger-
cabins used for the storage and distribution of physician samples should be monitored to determine
the temperature profile of the trunk or passenger cabin. Suitable monitoring devices as determined
by the sales representative may be placed in different areas of the trunk or passenger cabin on a
hot summer and a cold winter day. Measurements should also be made during typical 24-hour
periods, and the derived temperature should be used for calculation of the mean kinetic temperature
at which the sample is stored (see Pharmaceutical Calculations in Prescription Compounding
\(^{1160}\) for examples of MKT calculations). If the Pharmacopeial article designated for storage
requires storage at controlled room temperature, then suitable measures should be taken to
maintain the sample within the allowable limits of the storage parameters. Environmentally sensitive
preparations should not be stored in automobile trunks or passenger cabins. Medications stored in
automobile trunks or passenger cabins should be removed at the end of 3 days. Sales
representatives should consider parking automobiles in shaded areas to avoid extreme heat during
the summer and in garages to avoid freezing temperatures during the winter. The use of vouchers
from the manufacturer that patients could use to obtain medication samples from participating
pharmacies is an alternative way of providing drug samples.

**STABILITY, STORAGE, AND LABELING**

The design of stability studies of Pharmacopeial articles is based on knowledge of the behavior,
properties, and stability of the drug substance and experience gained from clinical formulation
studies.\(^{1}\) The length of the studies and the storage conditions for a Pharmacopeial article should be
sufficient to cover storage, shipment, distribution, and subsequent use of a Pharmacopeial article.
The data gathered from ICH accelerated testing or from testing at an ICH 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. See Pharmaceutical Stability\(^{1160}\).

**STATEMENTS/LABELING OF THE IMMEDIATE CONTAINERS OR PACKAGE INSERT**

Storage statements should be based on the stability evaluations of the Pharmacopeial drug
substances and in accordance with national and international requirements.

**Room Temperature Storage Statements**—For products with a storage statement reading, “Store
at controlled room temperature,” the labeling should read as follows on the package insert: “Store at
20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86
°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic
temperature does not exceed 25°C (77°F); however, such exposure should be minimized.”
On the immediate container label, the following may read for controlled room temperature (CRT): “Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).”

Cool Storage Statement: The storage statement for labeling may be as follows: “Store in a cool place, 8°C to 15°C (46°F to 59°F).”

Refrigerator Storage Statement: The storage statement for labeling may be as follows: “Store in a refrigerator, 2°C to 8°C (36°F to 46°F).”

Freezer Storage Statement: The storage statement for labeling may be as follows: “Store in a freezer, –25°C to –10°C (–13°F to –14°F).”

See the General Notices for all other applicable storage conditions, such as Storage Under Nonspecific Conditions and store in a Dry Place. Additional cautionary statements to protect the Pharmacopeial drug product from extreme temperature and humidity conditions may be included on the container label and package insert, as the manufacturer desires.

INTRODUCTION

This general information chapter describes good storage and distribution practices to ensure that drug products (medicines) reach the end user (practitioners and patient/consumers) with quality intact.

In the context of this chapter, the following definitions are used.

Definitions

Continuous improvement: recurring activity to increase the ability to fulfill requirements (see Quality Management Systems—Fundamentals and Vocabulary. ISO Standard 9000:2005).

Distribution: refers to shipping and distribution activities involved in the movement of drug products in various forms of vehicles.

Distribution Management System: a program that covers the movement, including storage and transportation, of drug products.

Documentation: recorded information.

Drug products: medicines, including marketed human and veterinary prescription finished dosage medications, in-process materials, drug product samples, clinical trial materials (investigational medicines/IND), over-the-counter products (OTC).

End user: the patient as well as the practitioner administering the drug product to the patient.

Environmental Management System: a program that covers temperature, humidity, light and/or
other environmental controls that require consideration in the storage and distribution of product throughout the lifecycle.

**Hazardous materials and/or dangerous goods:** any item or chemical which, when being transported or moved, is a risk to public safety or the environment, and is regulated as such under any of the following: Hazardous Materials Regulations (49 CFR 100–180); International Maritime Dangerous Goods Code; Dangerous Goods Regulations of the International Air Transport Association; Technical Instructions of the International Civil Aviation Organization; or the U.S. Air Force Joint Manual, Preparing Hazardous Materials for Military Air Shipments.

**International Conference on Harmonization (ICH) Guidance for Industry, Q10**

**Pharmaceutical Quality System:** an internationally harmonized document intended to assist the pharmaceutical industry by describing a model for an effective quality management system, referred to as the pharmaceutical quality system, the ICH Q10 model.

**Knowledge management:** a systematic approach to acquiring, storing, and disseminating information related, in the context of this chapter, to the storage and distribution processes and components.

**Mean Kinetic Temperature (MKT):** 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.

**Preventive measures:** the actions to eliminate the cause of a potential nonconformity or other undesirable potential situation.

**Quality:** the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain in order to be deemed suitable for therapeutic or diagnostic use. In this chapter, the term is also understood to convey the properties of safety, identity, strength, quality, and purity.

**Quality Management System (QMS):** in the context of this chapter, minimally a set of policies, processes, and procedures that enable the identification, measurement, control, and improvement of the distribution and storage of drug product. It is the management system used to direct and control a company with regard to quality (see ICH Q10 model and Pharmaceutical Quality System—Fundamentals and Vocabulary, ISO Standard 9000:2005).

**Risk Management System:** a systematic process used to assess, control, communicate, and review risks to the quality of a drug product across the product lifecycle. Integral to an effective pharmaceutical quality system, it is a systematic and proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality as described in ICH Q10. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 Quality Risk Management provides principles and examples of tools that can be applied to different aspects of pharmaceutical quality.

**Service Level Agreement or Contract (commonly referred to as a Quality Agreement):** a
negotiated, documented agreement between the customer and service provider that defines the common understanding about materials or service, quality specifications, responsibilities, guarantees, and communication mechanisms. It can be either legally binding or an information agreement. A Service Level Agreement may also specify the target and minimum level of performance, operation, or other service attributes.

**Storage Management System**: a program that covers the control of the storage of drug products.

**Supply chain**: the continuum of entities spanning the storage and distribution lifecycle of a product to the end user.

**Transport vehicles**: vehicles for the supply chain such as semitrailer trucks, vans, emergency medical service vehicles, industry representatives’ automobiles, trains, airplanes, sea vessels, and mail delivery vehicles.

**SCOPE**

Good storage and distribution practices apply to all organizations and individuals involved in any aspect of the storage and distribution of drug products, including but not limited to the following:

- Manufacturers of drug products for human and veterinary use where manufacturing may involve operations at the application holder’s facilities (i.e., facilities that belong to the holder of an approved New Drug Application or Abbreviated New Drug Application) or at those of a contractor for the applicant holder
- Manufacturers of combination products
- Packaging operations by the manufacturer or a designated contractor for the applicant holder
- Repackaging operations in which the drug product may be owned by an organization other than the primary manufacturer
- Laboratory operations at the manufacturer’s or at the contractor’s site
- Clinical trial drug products
- Physician offices
- Pharmacies including retail, mail order, hospital, and nursing home pharmacies
- Brokers, importers, and exporters
- Wholesale distributors; distribution companies involved in automobile, rail, sea, and air services
- Third-party logistics providers, freight forwarders, and consolidators
- Mail distributors including the U.S. Postal Service (USPS) and other shipping services including expedited shipping services
- Health care professional dispensing or administering the drug product to the end user
The information is intended to apply to all drug products regardless of environmental storage or distribution requirements.

It is recognized that conceivably there are special cases and many alternative means of fulfilling the intent of this chapter and that these means should be scientifically justified. Although this chapter is not intended to address the storage and distribution of active pharmaceutical ingredients (APIs), excipients, radioactive products, reagents, solvents, medical devices, medical gases, or clinical trial materials for which storage requirements may not yet be defined (e.g., Phase I clinical trial drug products), the general principles outlined here may be useful if applied selectively or comprehensively.

This general information chapter does not supersede or supplant any applicable national (e.g., European Medicines Agency’s Good Distribution Practices), federal (e.g., FDA’s cGMP, approved drug product labeling), state (e.g., Boards of Pharmacy) storage and distribution requirements, or USP monographs. The *Preservation, Packaging, Storage, and Labeling* section of *General Notices and Requirements* provides definitions and requirements for storage conditions. This chapter is not intended to cover counterfeiting, falsified medicines, drug pedigrees or other supply chain security, or chain of custody issues.

**BACKGROUND INFORMATION**

Storage and distribution processes involve a complex movement of product around the world, differences in documentation and handling requirements, and communication amongst various entities in the supply chain. The translation of best practices into good storage and distribution meets these challenges and sets forth a state of control.

The good storage and distribution practices described in this chapter should facilitate the movement of drug products throughout a supply chain that is controlled, measured, and analyzed for continuous improvements and should maintain the integrity of the drug product in its packaging during storage and distribution.

**RESPONSIBILITIES**

The holder of the drug product application, the drug product manufacturer (in the case of many OTC’s where there is no application) and the repackager bear primary responsibility and accountability including but not limited to the following:

- The decision for regulatory submissions, where applicable, relative to the contents of this chapter for the storage and distribution of drug products. If breaches occur in any of the QMS
systems and cannot be justified or documented with scientific evidence, the appropriate entity should consider action with the product to ensure the public safety.

- Determining proper storage and handling practices.
- Communicating storage and distribution practices through the supply chain.
- Stability profile or the associated stability information from the holder, inclusive of distribution conditions and excursions that may be allowable should they occur. These stability profiles include the approved storage conditions for the shelf life of the drug product and, where appropriate, supporting data for the distribution conditions, if these differ from the storage conditions.
- Appropriate firms, such as an applicant holder, are to convey relevant environmental requirements (e.g., when appropriate, product-specific life-cycle stability data), when needed to support deviations or temperature excursions. If stability data cannot be reviewed or is not shared, an assessment may be needed to consider regulatory review or other appropriate actions (e.g., destruction of product or additional stability testing).
- Recalling the drug product if it is found to be adulterated in any part of the supply chain.

However, all organizations along the supply chain bear responsibility for ensuring that they handle drug products within adequate storage and distribution parameters that will not affect the drug product identity, strength, quality, purity, or safety.

**LABELING CONSIDERATIONS FOR DRUG PRODUCTS**

The environmental requirements for drug product storage conditions should be indicated on the drug product primary container–closure system. If space on the immediate container is too small (e.g., an ampule) or is impractical for the container–closure system (e.g., blister package), this information can be placed on the most immediate container of appropriate size (e.g., carton). Environmental storage conditions and/or environmental warning statements should be evident, securely fixed, and indelible on the outermost container (generally the shipping container).

Products classified as hazardous materials and/or dangerous goods by the U.S. Department of Transportation or other relevant authorities or bodies should be labeled, stored, and handled in accordance with applicable federal/state/local regulations. Drug products classified as controlled substances by the U.S. Drug Enforcement Administration or by individual state requirements should be labeled and handled in accordance with applicable regulations.

Good practices and controls for labeling should direct the receiver about how to handle the drug product upon receipt (e.g., avoid dropping, maintain specified environmental conditions). When a drug product’s storage conditions are not readily available, use the storage conditions described in
General Notices and Requirements or the applicable monograph. Product labels with expanded information beyond the single long-term storage temperature ensure ease of transport and use for shippers, distributors, healthcare professionals, and patients. Product labels should clearly define the storage temperature range, and broader distribution or in-use temperature ranges where allowable. Products labeled “Keep in a cold place” or “Do not freeze” are subject to interpretation and are discouraged if used without accompanying temperature ranges. USP storage definitions and temperature ranges are defined in General Notices and Requirements. During international transport, the proper language(s) should be used to ensure that handlers understand the requirements set forth on drug product labeling. The use of symbols that are recognized by international organizations is advisable. Drug products can be transported at temperatures outside of their labeled storage temperatures if stability data and relevant scientific justification demonstrate that product quality is maintained. The length of the stability studies and the storage conditions for a drug product should be sufficient to cover the shipment, distribution, and subsequent use of the drug product. The data gathered from ICH accelerated testing or from testing at an ICH intermediate condition may be used to evaluate the effect of short-term excursions outside of the label storage conditions that might occur during storage and/or distribution.

QUALITY MANAGEMENT SYSTEM

Good storage and distribution practices require that entities involved in the storage and/or distribution of drug products maintain a Quality Management System (QMS) that is based on standard quality concepts, includes good manufacturing practice (GMP) in compliance with the appropriate regulatory agency(s), and is complementary to the ICH quality guidances, including ICH Q10 Pharmaceutical Quality System and ICH Q9 Quality Risk Management. In the context of this chapter, the QMS includes the following management system programs: (1) Storage Management System, (2) Distribution Management System, (3) Environmental Management System, and (4) Risk Management System.

The storage and distribution QMS should, at minimum, cover the following elements: corrective and preventive actions (CAPA), change management, and the management review process. Written agreements (e.g., Quality Agreement, Technical Agreement, Service Level Agreements) should be in place between applicable organizations involved in the drug product supply chain. The use of Written Agreements ensures clarity and transparency, and delineates the responsibilities of each organization in the supply chain.

Good Documentation Practices
Good documentation practices should be practiced in the QMS. This documentation includes standard operating procedures and corporate policies and standards, as well as protocols and other written documents that delineate the elements of the QMS. The QMS programs should describe events and actions that must be documented as well as the proper verbiage to be used, the copies required, and any other items that will ensure adequate processing of the drug product and prevent delays. The documentation process should use a standard process such as a Quality Manual or other practice to ensure continual improvement.

Written procedures should ensure that drug products are held in accordance with their labeling instructions and associated regulatory requirements. Procedures should provide the written steps needed to complete a process and ensure consistency and standard outcomes. The following elements should be included: (1) how products are handled when equipment malfunctions or when there are delays in distribution due to customs hold or temperature deviations, (2) how and when a product should be moved from one transport container/vehicle into another, and (3) how to communicate with the necessary parties.

The QMS should require monitoring of processes to demonstrate that a state of control has been maintained, where the set of controls consistently provides assurance of continued process performance and product quality (ICH Q10).

If deviations occur, a nonconformance should be documented, and an investigation should be performed as appropriate. The investigative process should determine the root cause(s) of the deviation. For example, the following should be determined: whether the drug product experienced stress, damage, delays, or environmental lapses, or whether there were errors in documentation. The associated supply quality management staff should have final responsibility for approving or rejecting the investigation. The investigation process should be linked to the risk management program to ensure that proper mitigation occurs and preventive measures are put in place. For example, a written investigation should be performed if the receiving and/or transferring processes result in a drug product being subjected to unacceptable temperature conditions or contamination (e.g., pests, microorganisms, or moisture). Any environmental breach should be documented, and the length of time the drug product was not within the designated storage requirements should be determined. This information should be forwarded to the appropriate organization responsible for the drug product. The drug product should be quarantined, and final disposition should be based on good science with appropriate evidence to justify the decision(s).

Manufacturers should develop written procedures for security records that confirm container–closure integrity (e.g., security seals, narcotic controls) and for returned and salvaged goods. These standard operating procedures (SOPs) should address distribution records including, but not limited to, how the drug product was handled environmentally. In addition, training should be part of the QMS and include distribution requirements, documentation, and how to handle breaches. Records should be retained for purchases and sales of drug products and should show the date of
purchase or supply; the name of the drug product and the amount; the name and address of the supplier or consignee; and the associated lot numbers. These records should ensure the traceability from the manufacturer to the end user so that the pedigree of the drug product can be followed throughout its life cycle.

All records and documents should be maintained in accordance with a traceable records-retention program and should be made available upon request to regulatory agencies. These documents should be approved, signed, and dated by the department responsible for the QMS.

**Storage Management System**

**STORAGE LOCATIONS AND PROCESSES**

It is important that each entity define their appropriate storage locations to ensure that adequate controls are in place. These locations include buildings and facilities for drug product storage (e.g., warehouse, storage or hold area, the original manufacturer’s warehouses, contractor warehouses, wholesale distribution warehouses, mail order or retail pharmacy storage area, hospital or nursing home pharmacy storage areas; and border Customs storage areas).

In these locations, two basic processes can occur. First, receiving for storage is the act of bringing a drug product into a facility, while transferring refers to the moving of a drug product internally within a facility or into or out of a vehicle. Second, storing and holding refers to the act of maintaining temporary possession of a drug product in the supply chain process, during which no movement of the product will occur.

**STORAGE IN BUILDINGS AND FACILITIES**

Drug product storage areas are required to maintain the product temperature between the limits as defined on the product label. Buildings and facilities used for the warehousing, storage, and/or holding of drug products should be of adequate size for their intended use. These facilities should be adequate to prevent overcrowding, which can lead to contamination. The building and facility should be designed to control environmental conditions where necessary and should be made of readily or easily cleanable materials. Sanitation and pest control procedures should be written, indicating frequency of cleaning, materials, and methods used. The pest-control program should ensure the prevention of contamination as well as the safe use of pesticides. Records of all cleaning and pest-control activities should be maintained.

Storage should be orderly and should provide for the segregation of approved, quarantined, rejected, returned, or recalled drug product. If computerized systems are used for the control of storage conditions, the software should be appropriately qualified for its intended purposes. Facilities should have controls that mitigate risks such as fire, water, or explosion. Certain drug products may cause these risks and should be stored accordingly. Storage areas, when not
computerized, should be appropriately visually labeled.

RECEIVING AND TRANSFERRING DRUG PRODUCTS

Storage of a drug product includes not only the period during which the drug product is held in the manufacturer’s storage areas but also time spent on shipping dock platforms, in transport vehicles, and in distribution centers or storage areas. When drug products arrive at warehouse loading docks and other arrival areas, they should be transferred as quickly as possible to a designated storage environment to ensure minimal time outside specified storage conditions. Relative to the incoming receipt of drug product, it is recognized that the process of product reaction to ambient conditions begins immediately and may occur quickly (e.g., reach temperature equilibrium within minutes to a few hours depending on details such as the product mass, volume and packaging density taking into account secondary and tertiary packaging)\(^1\).

Receiving docks should protect drug product deliveries from inclement weather during unloading. Any storage area, including loading and unloading docks for receipt and distribution of drug products, should be clean, cleanable, and free from pests. The incoming receiving area should limit access to authorized persons. Smoking, eating, and drinking should not be permitted in any storage/hold areas. Where appropriate, the delivery vehicle should be examined before unloading to ensure that adequate protection from contamination was maintained during transit. The results of this examination should be documented.

Areas should be designated to provide an adequate space in which containers of drug products can be cleaned and opened for sampling. If sampling is performed in the receiving area, it should be done in a manner that prevents contamination and cross-contamination and ensures that environmental requirements for the drug product are not breached.

Adequate precautions should be taken to prevent theft and diversion of drug products. Drug products that have been identified as counterfeit should be quarantined to prevent further distribution. The appropriate regulatory agencies should be contacted according to established procedures.

Appropriate delivery records (e.g., as applicable, transport vehicle movement papers, receiving/delivery records, data logging records, temperature recorders and similar devices, bill of lading, house air waybill, master air waybill, etc.) should be reviewed by each receiving entity in the supply chain to determine if the product has been subjected to any transportation delays or other events that could have exposed the product to undesirable conditions. Each entity should ensure that their respective Service Level Agreement documents and supporting documents such as SOPs cover delivery and receiving responsibilities of the transactional parties.

REFRIGERATORS AND FREEZERS

Refrigerators and freezers used to store drug products are required to maintain the product temperature between the limits as defined on the product label. Typically, a refrigeration unit specification would be set to 5° with an accuracy of ±3° to store products labeled 2°–8°. Freezer temperatures typically range from –25° to –10°. Some frozen drug products, however, require lower temperatures, e.g., dry ice or liquid nitrogen temperatures.

Regular operating procedures and maintenance protocols should be in place along with written contractual agreements for all maintenance and evaluation procedures including the following:

1. Units should store items in a manner allowing sufficient space to permit proper air flow.
2. Units should be positioned in the facility so that they are not subjected to environmental extremes that could affect their performance (i.e., <10° or >32°). If this cannot be prevented, the mapping protocol should include a provision for testing during the anticipated environmental extremes.
3. Large commercial units such as walk-in cold rooms are qualified via a temperature mapping study or other type of qualification process to determine the unit’s suitability for storing drug products. A suitable number of temperature-recording devices should be utilized to record temperatures and to provide temperature area maps. Thereafter, the units should be monitored in one or more locations, as determined by the results of the mapping study. Refer to the Temperature Monitoring section under Environmental Management System.
4. Units should utilize recording systems to log and track temperatures. Alarm systems should be an integral part of the monitoring system for both refrigerators and freezers. While automated systems monitor units continuously, manual checks should be performed as appropriate to the validation program. When automated systems are not available, manual systems may be used.

**Distribution Management System**

Distribution of drug products occurs within a facility or location such as a manufacturer, wholesaler, pharmacy dispensing area, retail site, clinic/hospital/nursing home pharmacy, and the physician’s practice. Distribution of drug products occurs as point-to-point movement within the supply chain between distribution facilities via semitrailer trucks, vans, emergency medical service vehicles, industry representatives’ automobiles, trains, aircraft, sea vessels, and mail delivery vehicles. Communication within the supply chain should be coordinated to determine proper timing for drug products to be transported and received, taking into account holiday schedules, weekends, or other forms of interruption. When international distribution is required, alerts should be made in advance and proper language should be used to ensure understanding of the requirements set forth on drug product labeling.
Pharmaceutical manufacturers should consider primary, secondary, and tertiary packaging that best protects the drug product during storage and distribution. Package performance testing should be documented as part of a manufacturer's robust QMS. Several standard test procedures are available for evaluating package performance for factors such as shock, vibration, pressure, compression, and other transit events. Those tests include the following: the American Society for Testing and Materials (ASTM) Standard Practice for Performance Testing of Shipping Containers and Systems, and the International Safe Transit Association (ISTA) specifications for various types of transit modes such as less-than-truckload, small package, rail car, and air freight.

It is important to be aware that removal or modification of the original packaging may subject the product to unacceptable conditions.

The shipping container used for the distribution of product should be selected to ensure that product quality is maintained and to protect the contents from the rigors of distribution including environmental or physical damage.

All drug products have storage requirements that may contain specific controls. The transport container for drug products should be qualified on the basis of the labeled conditions of the product as well as anticipated environmental conditions (consider seasonal temperature differences, transportation between hemispheres, and the modes of transport). The type, size, location, and amount of refrigerant required to protect the product should be based on documented studies of specific distribution environments including domestic and international lanes, mode(s) of transport, duration, temperature, and other potential environmental exposures or sensitivities that may impact product quality. Transportation container materials such as warm/cold packs and materials used to control temperature conditions should be properly conditioned before use. Barrier protection may be important in helping to determine the position of materials such as gel packs in order to avoid direct contact with the drug product. It should be determined if studies are required to ensure that the dry ice and its vapors do not adversely affect the drug product, including the drug product labeling.

**VALIDATION AND THERMAL PERFORMANCE QUALIFICATION**

If drug products are not continuously monitored by validated monitoring systems (continuous verification), shipping systems should be qualified. "Operational and performance shipping studies should on a generic level be part of a formal qualification protocol that may use controlled environments or actual field testing, depending on the projected transport channel." These studies should reflect actual load configurations, conditions, and expected environmental extremes. Testing should be performed on both active and passive thermal packaging systems.

A transport container/vehicle, or transport packaging system as well as the transport process may be qualified in accordance with current good distribution practices, thereby providing the assurance for environmental control without other temperature monitors. The proper load configuration will help
ensure that the drug product remains stable through the distribution supply chain. The validation or qualification program for a vehicle or storage area should represent a statistically high proportion of the environmental conditions to which a drug product maybe exposed.

Storage facilities themselves, unless thermostatically controlled, cannot be validated because of their unpredictability and the influence of external temperature; however, they can be qualified via a mapping process. The generator back-up power supply should be validated. Tools that may be used for validation assessments are provided in the Parenteral Drug Association Technical Report #39 Revised 2007; *Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment.*

**Environmental Management System**

**TEMPERATURE MONITORING**

Environmental conditions are important parameters to consider in the storage and distribution of drug products and may require monitoring depending on the requirements. When specific storage conditions are required, or in the absence of active or passive containers, environmental recorders or devices should be used to confirm that an acceptable range has been properly maintained during each stage in the supply chain.

Temperature is one of the most important conditions to control, and requirements for each drug product should be based on stability data. Temperatures should be controlled and tracked using a monitoring system, and the monitoring devices used should be included in a preventive maintenance program. Environmental monitoring devices should be calibrated for their range of operation. The monitoring devices used should provide an alert mechanism if the preset ranges are breached. The following practices and controls are examples of appropriate measures that should be put in place to ensure environmental control:

- Temperature-monitoring equipment, a monitoring device, a temperature data logger, or other such device that is suitable for its intended purpose should be used (see *Monitoring Devices—Time, Temperature, and Humidity* (1118)).
- An appropriate number of temperature monitors or some other form of recordation or proof of temperature control. Temperature monitor(s) should be used with every distribution process unless some other process has been put in place to ensure adequate handling (validated containers).
- Electronic temperature monitors should be calibrated to NIST (or other suitable standard) with an accuracy of ±0.5° (or better).
- Predetermined temperature ranges should be set for all applicable areas, as well as a plan of action in the event of an unacceptable excursion.
- Air flow and load patterns should be determined to ensure that all areas are suitable for
product storage.

TEMPERATURE MAPPING

The basis of any temperature mapping in a temperature controlled space (e.g., facility, vehicle, shipping containers, refrigerator, freezer) is the identification and documentation of a sound rationale used for a given mapping procedure. The temperature variability associated with mapped locations and the level of thermal risk to the product should be defined, unless another process has been put in place to ensure environmental control.

A temperature mapping study should be designed to assess temperature uniformity and stability over time and across a three-dimensional space. Completing a three-dimensional temperature profile should be achieved by measuring points at not less than three dimensional planes in each direction/axis—top-to-bottom, left-to-right, front-to-back, where product will be present. Further, points selected in the mapping should represent expected extremes of each of the three axes. Figures 1 and 2 provide an example of how the three-dimensional interior of a trailer/container could be mapped. A similar concept may be applied for mapping a facility or related cold storage equipment.

Facility Temperature Mapping—The following factors, which may contribute to temperature variability, should be considered during the process of temperature mapping storage locations: (1) size of the space; (2) location of HVAC equipment, space heaters, and air conditioners; (3) sun-facing walls; (4) low ceilings or roofs; (5) geographic location of the area being mapped; (6) airflow inside the storage location; (7) temperature variability outside the storage location; (8) workflow variation and movement of equipment (weekday vs. weekend); (9) loading or storage patterns of product; (10) equipment capabilities (e.g. defrost mode, cycle mode); and (11) SOPs. The recording of temperatures during the thermal mapping of a warehouse or cold room should be
sufficient in time frame to capture workflow variation that may impact air flow and the resulting
temperature fluctuation (i.e., a period of two weeks is recommended for data collection enabling the
capture of two week/weekend workflow cycles).
A new facility would require a validation incorporating an Installation Qualification (IQ), Operational
Qualification (OQ), and a Performance Qualification (PQ) as defined in FDA’s CPG Sec 490.100
Process Validation Requirement for Drug Products and Active Pharmaceutical Ingredients Subject
to Pre-Market Approval, 2004.

Equipment (Container/Trailer) Temperature Mapping—To minimize risk of product exposure to
damaging temperatures during transport, every vehicle cargo space should be mapped. If it is
determined that product safety does not require every individual vehicle to be mapped, temperature
mapping for transportation containers/vehicles new or already in use should include expected
temperature conditions and should be representative of the actual transport environment, (i.e., the
time frame and seasonal variation associated with the data collection process should cover the
entire transport period). Such a mapping should take into account specific conditions such as (1)
SOPs, including loading and unloading procedures; (2) route-specific operation of the temperature
control equipment; (3) seasonal effects encountered on expected routes; (4) loading patterns; and
(5) transport durations.
When nondedicated transport containers/vehicles and equipment are used, they should be
designed to minimize the risk of contamination of the product being handled, e.g., transport
containers/vehicles and equipment can be designed to minimize the risk of contamination. If
environmental mapping of such vehicles is not performed, some other means of control should be in
place to ensure that the drug product is adequately protected. Mapping by the shipper may not be
necessary if the shipper uses a transport container that is properly insulated and has been
previously qualified for the duration of the distribution process by the transport container
manufacturer via a mapping study or if drug products are continuously monitored by validated
monitoring systems (continuous verification). When temperature mapping is necessary, it should
begin with an inspection of equipment and/or vehicle and should be re-evaluated as appropriate.
Environmental mapping also should be performed after any significant modification to the
distribution system that could affect drug product temperature.
The vehicle in which drug products are transported should be mapped to determine the appropriate
placement of temperature-recording devices and to confirm that the load configuration is not
restricting air flow. The following are recommended practices and controls for vehicles that receive
and transfer drug products:

1. Transport containers/vehicles and equipment used to store and transport drug products
   should be suitable for their intended function.
2. Procedures should be established that describe how to operate, clean, and maintain
transport containers/vehicles and equipment used in the storage and distribution of drug products.

3. Transport containers/vehicles should be designed to prevent damage to the drug product, and pharmaceutical manufacturers should collaborate with their transporter to determine contingency response plans for how drug products are handled when equipment malfunction.

4. When drug product must be moved from one transport container/vehicle into another the proper load configuration should be followed.

5. It should be understood how communication is made to the necessary entities when such transfer occurs.

6. Subcontracted vehicles should be considered in contractual agreements and audits, and documentation should be maintained for their use.

When completed as part of an Operational Qualification (OQ), a temperature mapping should account for maximum and minimum loads to capture temperature variability resulting from variations in temperature mass of the payload. An OQ should also include performance of equipment under extreme scenarios including door open, door closed, and simulated equipment failure. Thermal mapping of vehicles should be representative of the fleet with the intention of capturing variability across the range of vehicles (type of vehicle including non refrigerated equipment, use, heating and/or cooling system). A periodic requalification program should be documented.

Mapping for both facilities and transportation containers/vehicles should be done in a way that confirms their fitness for operation during periods of expected extreme weather (e.g., summer and winter). Facilities should be mapped under varying operating conditions—ideally during periods of greater variability, accounting for and capturing the result of any seasonal fluctuations of inventory movement, equipment movement, or workflow variation.

The temperature-mapping protocol and associated number of temperature data loggers used to map a three dimensional space should meet the intent of demonstrating three-dimensional uniformity and compliance with product requirements. For both facility and trailer/container temperature mapping, the ambient conditions should be recorded and correlations between ambient conditions and potential thermal risks inside the controlled space should be identified. Drug products should not be stored in areas where a thermal risk has been identified as a result of the temperature mapping. Areas identified as being unsuitable for storage should be clearly labeled as such to ensure that they are not used.

Temperature data loggers should be used for temperature mapping and Performance Qualification (PQ) testing of facilities, equipment, and transportation containers used for storage or transportation of temperature-sensitive medicinal products. Temperature data loggers and any associated
software applications should be appropriately validated. Further, temperature data loggers should be calibrated to an accuracy specification of ±0.5°. Certificates of calibration to a NIST or other international traceable standard should be available for individual monitoring devices.

EXCURSIONS

The mapping process will help determine when excursions could occur and are useful when pharmaceutical manufacturers develop a plan for dealing with them. Alarms should be used to reveal environmental excursions during operations. Temperature excursions for brief periods outside of respective storage label conditions may be acceptable provided stability data and scientific/technical justification exists demonstrating that product quality is not affected (see Health Canada’s GUI 0069 entitled, Guidelines for Temperature Control of Drug Products During Storage and Transportation, 2011).

MEAN KINETIC TEMPERATURE (MKT) CALCULATION

The MKT is 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. 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.

The temperatures used 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. Software to compute the MKT is available commercially.

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 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):

$$T_k = \frac{\Delta H/R}{-\ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)}$$

where $T_k$ is the mean kinetic temperature; $\Delta H$ 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 during the
The holding of a drug may occur as part of storage and distribution practices. Drug products in the distribution supply chain may be held at temperatures outside their labeled storage requirements as determined by an appropriate stability study. Drug products stored either in warehouse conditions or in transportation modes may experience excursions from their acceptable temperature ranges. Each product excursion must be evaluated to determine the final product effect. The means of evaluation must be scientifically sound with documented technical justification that the integrity of the drug product has not been affected. One method of analysis for drug product stored outside its respective label storage conditions is the use of a Mean Kinetic Temperature (MKT) calculation.

Because MKT expresses the cumulative thermal stress a drug product experiences, it is considered an acceptable practice for storage, and it follows that it should be considered for transit excursions in the process of distribution. The calculation must be justified for use with distribution excursions. The ICH stability-testing guidelines define MKT as a “single” derived temperature, which, if maintained over a defined period, would afford the same thermal challenge to a pharmaceutical product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period.

The MKT analysis must be based on good science and should take into account the integrity of the product. The calculated mean kinetic temperature is not sensitive to the impact of excursions that may occur if the baseline is a long period of time such as a storage segment or the entire lifetime of the drug product. For shorter baseline periods of time, such as transport segments, an excursion can have a significant impact on the resulting MKT for that segment; however, this would not necessarily have a significant impact on product quality.

Knowing the MKT for an excursion is useful for evaluating the potential impact on product quality. However, it is also essential to know the upper and lower temperature limits of any excursion. If these extreme temperatures are outside available stability data, it may not be possible to predict the quality impact of the excursion with any confidence regardless of the MKT. Although higher temperatures are given greater weight in the calculation, the calculation of MKT for nonfrozen product that becomes frozen for any amount of time may not result in an acceptable temperature although the product may not be adulterated. At higher temperatures the kinetics of degradation may change or new degradation reactions may occur; at lower temperatures (near freezing) a phase change may occur which is known to have a negative impact on the quality of some drug products (e.g., some proteins and vaccines). For an example of a calculation, see *Pharmaceutical Calculations in Prescription Compounding* (1160).

**Emergency Medical Service Vehicles, Automobiles, and Van Transportation**—Road vehicles
used to transport drug products (e.g., ambulances and other emergency response vehicles, vans, or automobiles, including those used by sales representatives to transport physicians’ samples) should be suitable for their purpose. Monitoring devices should be placed in different areas of the trunk or cabin where the drug product will be positioned during seasonal extremes (e.g., summer and winter). The monitor should be secured so that it is immobile, and there should be no ambiguity about its exact position within the payload so that the monitor is always placed in the same position. Monitoring devices used on or in packages or on containers may also be used. Suitable measures should be taken to maintain the drug product within the allowable limits of the labeled storage requirements. Storage of physician drug product samples by sales representatives is regulated under 21 CFR Part 203.34(b)(4).

Mail Delivery Distribution—Delivery staff should be trained on how drug products should be delivered to end-user locations. In the event that the package cannot be delivered as scheduled, the package should be returned to the mailing pharmacy. If the drug product was stored outside of the labeled storage requirements, the delivery staff should notify the recipient of the drug package.

Risk Management System

Risk Management System strategies should ensure that each organization’s best interests are served by adhering to proper practices, controls, and procedures, including but not limited to the following: the nature of the drug products; distribution requirements on the readable container labeling; exposure to adverse environmental conditions; number of stages/receipts in the supply chain; manufacturer’s written instructions; contractors; and drugs at risk from freezing (vaccines, insulin, and biological products) or elevated temperatures (fatty-based suppositories, vaccines, insulin, and biological products). Examples of risks that should be assessed include (1) vibration that can cause aggregation of some drug products such as proteins and peptide-based drugs; (2) temperature excursions that may lead to phase changes (melting or freezing); (3) loss of container–closure integrity in transit that could cause glass fractures in sterile drug product containers or cracks in the release-controlling polymer layer of modified-release solid oral dosage forms; and (4) ingress of water or oxygen that could lead to an increase in degradation products. Appropriate firms such as applicant holders are recommended to convey relevant environmental requirements when needed to support deviations or excursions. There may be alternate ways of determining acceptable environmental conditions and these should be documented and justified.

Pharmaceutical manufacturers should ensure that suppliers of drug product transportation are monitored. Auditing transportation firms should be carried out routinely to ensure adequate product handling. The manufacturer’s change control system should capture and evaluate changes in logistic factors such as warehouse or receiving areas and vehicle changes.
CONCLUSION

The practices and processes set forth in this general information chapter apply to storage and distribution as part of the life-cycle management of drug products. All involved should ensure the product to its point of use, creating a contiguous supply network that is collaborative and emphasizes preventive measures to protect drug product quality. The increase in global processes coupled with products requiring special environmental controls highlights the need for a strong QM program. QM should provide the foundation for maintaining the storage and distribution practices in a continual improvement program and part of an overall management system review by each entity, as appropriate, in the supply chain.

It is equally important to stay current and be ready to change as new solutions evolve (e.g., proactive approaches to implement strategies such as track and trace technologies, industry standards, and on-demand visible technologies). Pharmaceutical scientists will create new technologies to meet world needs. These new technologies should be considered in developing strategies for good distribution practices, controls, and procedures.

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**Auxiliary Information** - Please check for your question in the FAQs before contacting USP.

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