# Excerpted USP-NF Standards Referenced in the USP COVID-19 Vaccine Handling Toolkit

**Operational Considerations for Healthcare Practitioners** 



Not official text. Please refer to the currently official version of the applicable USP–NF standard for compliance purposes. For more information about reference material related to these chapters or other questions, email <u>COVID-19@usp.org</u>.

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## (659) PACKAGING AND STORAGE REQUIREMENTS

#### Change to read:

(A portion of the *Packaging* section of this chapter will become official on  $\triangle$  December 1, 2025 (USP 1-Dec-2020) as indicated. Early adoption of the requirements in this chapter and *Plastic Materials of Construction* (661.1) and *Plastic Packaging Systems* for *Pharmaceutical Use* (661.2) is permitted by USP.)

#### Change to read:

#### INTRODUCTION

The purpose of this chapter is to provide packaging definitions, auxiliary packaging information, and storage condition definitions relevant to the storage and distribution of active ingredients, excipients, and medical products, such as pharmaceuticals,  $A_{\text{(USP 1-Dec-2020)}}$  combination products, and, when labeled as being USP compliant,  $A_{\text{(USP 1-Dec-2020)}}$  dietary supplements.

#### Change to read:

## PACKAGING

Packaging materials must not interact physically or chemically with a packaged article in a manner that causes its safety, identity, strength, quality, or purity to fail to conform to established requirements. Any plastic material used to construct a *Packaging system* must meet the applicable requirements of *Plastic Materials of Construction* (661.1). (Official 1-Dec-2025) All *Packaging systems* must meet the applicable requirements specified in *Containers*—*Glass* (660), *Plastic Packaging Systems and Their Materials of Construction* (661.2), (Official 1-Dec-2025) All *Packaging Components* (670). All elastomeric closures must meet the applicable requirements in *Plastic Packaging Systems* (381) (CN 1-Dec-2020).

Every monograph in USP–NF must have packaging and storage requirements. For the packaging portion of the statement, the choice of containers is provided in this chapter. For active pharmaceutical ingredients (APIs), the choice would be a tight or well-closed  $\triangle$  container (as specified in the monograph), and,  $\triangle$  (USP 1-Dec-2020) where needed, a light-resistant container. For excipients, given their typical presentation as large-volume commodity items (*Packaging systems* ranging from drums to tank cars), a well-closed container is an appropriate default requirement. Articles must be protected from moisture, freezing, and excessive heat (see *General Definitions*) when no specific directions or limitations are provided.

The compendial requirements for the use of specified containers apply also to articles packaged by *Dispensers*, *Repackagers*, or other individuals, unless otherwise indicated in the individual drug product monograph.

#### Change to read:

#### **POISON PREVENTION PACKAGING ACT**

This act, which is administered by the US Consumer Product Safety Commission (CPSC), requires special packaging for most human oral prescription drugs, oral controlled drugs, certain non-oral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations, to protect the public from personal injury or illness from misuse of these preparations [16 Code of Federal Regulations (CFR) §1700 (USP 1-Dec-2020)].

The primary packaging of substances regulated under the Poison Prevention Packaging Act (PPPA) must comply with the special packaging standards.  $\triangle$  (USP 1-Dec-2020) These apply to all packaging types, including reclosable, non-reclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Also, special packaging does not need to be used by manufacturers and packagers of bulk-packaged prescription drugs that will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in non-*Child-resistant packaging* upon the request of the purchaser or when directed in a legitimate prescription.

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in non-Child-resistant packaging as long as popular-size, special packages are also supplied. The non-Child-resistant packaging requires special labeling. (USP 1-Dec-2020)

#### Change to read:

#### **TEMPERATURE AND STORAGE**

Specific directions are stated in some monographs with respect to storage conditions (e.g., the temperature or humidity) at which an article must be stored and shipped.  $\triangle$  Storage and shipping  $\triangle$  (USP 1-Dec-2020) directions apply except where the label on the article  $\triangle$  or its prescribing information  $\triangle$  (USP 1-Dec-2020) has different storage conditions that are based on stability studies. Where no specific directions or limitations are provided in the article's labeling  $\triangle$  or prescribing information  $\triangle$  (USP 1-Dec-2020), articles must

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be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution; drug substances are exempt from this <sup>▲</sup>requirement. (USP 1-Dec-2020)

#### Change to read:

#### **GENERAL DEFINITIONS**

#### **Packaging Definitions**

**Packaging system** (also referred to as a Container–closure system): The sum of *Packaging components* and materials that together contain and protect the article. This includes *Primary packaging components* as well as *Secondary packaging components* when such components are required to provide additional protection.

**Container:** A receptacle that holds an intermediate compound, API, excipient, or dosage form, and is in direct contact with the article (e.g., ampules, vials, bottles, syringes, and pen injectors).

**Closure:** A material that seals an otherwise open space of a *Container* and provides protection for the contents. It also provides access to the contents of the *Container* (e.g., screw caps and stoppers).

**Packaging component:** Any single part of the *Package* or *Container–closure system*, including: the

*Container*, (USP 1-Dec-2020) *Closures* (USP 1-Dec-2020); ferrules and overseals; *Closure* liners; *Container* liners, (USP 1-Dec-2020) (e.g., tube cartridge liners); inner seals; administration ports; overwraps; administration accessories; labels; cardboard boxes; and shrink wrap.

**Primary packaging component:** A *Packaging component* that is in direct contact with or may come into direct contact with the article.

**Secondary packaging component:** A *Packaging component* that is in direct contact with a *Primary packaging component* and may provide additional protection for the article.

**Tertiary packaging component:** A *Packaging component* that is in direct contact with a *Secondary packaging component* and may provide additional protection for the article during transportation and/or storage.

**Ancillary component:** A component or entity that may come into contact with a *Tertiary packaging component* during the distribution, storage, and/or transportation of the packaged article (e.g., pallets, skids, and shrink wrap).

**Associated component:** A *Packaging component* that is typically intended to deliver the drug article to the patient but is not stored in contact with the article for its entire shelf life (e.g., spoons, *Dosing cups*, and dosing syringes).

**Materials of construction:** The materials (e.g., glass, plastic, elastomers, and metal) of which a *Packaging component* consists.

**Small-volume injection** (also referred to as Small-volume parenteral): An injectable dosage form that is packaged in *Containers* labeled as containing 100 mL or less.

**Large-volume injection** (also referred to as Large-volume parenteral): An injectable dosage form that is packaged in *Containers* labeled as containing more than 100 mL.

**Child-resistant packaging:** A *Packaging system* designed or constructed to meet CPSC standards pertaining to opening by children (16 CFR §1700.20 et seq. and 16 CFR §1700.15).

Senior-friendly packaging: A *Packaging system* designed or constructed to meet CPSC standards pertaining to opening by senior adults (16 CFR §1700.15 and 16 CFR §1700.20).

**Restricted delivery system:** A *Packaging system* designed or constructed to restrict (control) the amount of the drug product that may be delivered in order to limit unintended access by children and other similarly vulnerable populations. *Restricted delivery systems* should meet and may exceed CPSC standards for special packaging [*Child-resistant* and *Senior-friendly packaging* (16 CFR §1700.15 et seq.)]. For oral medicinal liquids, surface and flow characteristics vary. It is the responsibility of the manufacturer to ensure that all components of the *Restricted delivery system* provide the intended safety protection. One component of the *Restricted delivery system* is the flow restrictor, which is a *Packaging component* that restricts the flow of liquid. The flow restrictor may be used as part of a *Restricted delivery system* or as an adapter to facilitate use of a measuring device for oral medicinal liquids. A flow restrictor should not compromise CPSC standards for special packaging [*Child-resistant* and *Senior-friendly packaging* (16 CFR §1700.15 et seq.)].

**Tamper-evident packaging:** A Packaging system that may not be accessed without obvious destruction of the seal or some portion of the Packaging system. Tamper-evident packaging must be used for sterile drug products intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription. Drug products intended for sale without prescription are also required to comply with the Tamper-evident packaging and labeling requirements of the FDA where applicable (21 CFR §<sup>4</sup>211.132). (USP 1-Dec-2020)</sup> Preferably, the immediate Container and/or the outer Container or protective packaging used by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed to show evidence of any tampering with the contents.

**Reclosable packaging:** A package that after it has been initially opened is capable of being reclosed with a similar degree of security and is capable of being used a sufficient number of times to dispense the total contents without loss of security. *Reclosable packaging* may incorporate child-resistance capabilities.

**Non-reclosable packaging:** A package or part of a package that cannot be closed again after all or part of the contents have been removed. Examples of *Non-reclosable packaging* are blisters, sachets, strips, and other *Single-unit containers*. *Non-reclosable packaging* may include cold-formed foil blisters, foil strip packs, and polyvinyl chloride (PVC)/Aclar combining multilayer materials that are thermo-formed or cold-formed foil blisters. *Non-reclosable packaging* may be child resistant depending on the intended use and place of use. Household non-reclosables are subject to the PPPA as defined in 16 CFR §1700.14.

**Hermetic container:** A Container–closure system that is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

**Tight container:** A *Container–closure system* that protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary

conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article. [NOTE—Where packaging and storage in a tight container or well-closed container is specified in the individual monograph, the container used for an article when dispensed on prescription meets the requirements in *Containers—Performance Testing* (671).]

Well-closed container: A *Container–closure system* that protects the content's from contamination by extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution. See (671).

**Light-resistant container:** A Container–closure system that protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. A clear and colorless or a translucent container may be made light-resistant by means of an opaque covering or by use of secondary packaging, in which case the label of the container bears a statement that the opaque covering or secondary packaging is needed until the articles are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended. See  $\triangleq$  (671), Spectral Transmission or  $\_(USP 1-Dec-2020)$  (661.2), Functionality, Spectral Transmission Requirements for Light-Resistant Components and Systems.

**Equivalent container–closure system:** A *Container–closure system* that is as protective as or more protective than the original manufacturer's *Packaging system* in terms of moisture vapor transmission rate, oxygen transmission, light transmission, and compatibility. System equivalency extends to any special protective materials, such as those for seals or desiccants associated with the original *Packaging system*.

Injection	Noninjection
Multiple-dose	Multiple-unit
Single-dose	Single-unit
_	Unit-dose
_	Unit-of-use
Pharmacy bulk package	_

Imaging bulk package

#### **Table 1. Packaging Systems Definitions: Injection versus Noninjection**

#### **Injection Packaging Systems**

**Multiple-dose container** (also referred to as Multi-dose): A Container–closure system that holds a sterile medication for parenteral administration (injection or infusion) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation. A *Multiple-dose container* is intended to contain more than one dose of a drug product. When space permits, a *Multiple-dose container* is labeled as such. *Multiple-dose containers* are generally expected to contain 30 mL or less of medications. The beyond-use date for an opened or entered (e.g., needle-punctured) *Multiple-dose container* is 28 days unless otherwise specified by the manufacturer on the label. An example of a *Multiple-dose container* is a vial.

**Single-dose container:** A Container–closure system that holds a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A *Single-dose container* is designed for use with a single patient as a single injection/infusion.<sup>1</sup> When space permits, a *Single-dose container* is labeled as such and should include on the label appropriate discard statements. Examples of *Single-dose containers* are vials, ampules, and prefilled syringes.

**Pharmacy bulk package:** A *Container–closure system* of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The *Closure* must be penetrated only one time after constitution, if necessary, with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents. The *Pharmacy bulk package* is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean-air compounding area). Designation as a *Pharmacy bulk package* is limited to injection, for injection, or injectable emulsion dosage forms as defined in *Nomenclature* (1121), *General Nomenclature Forms*.

*Pharmacy bulk packages,* although containing more than one single dose, are exempt from the *Multiple-dose container* volume limit of 30 mL and the requirement that they contain a substance or suitable mixture of substances to prevent the growth of microorganisms. See *Labeling*  $\langle 7 \rangle$  for labeling requirements.

**Imaging bulk package:** A container of a sterile preparation for parenteral use that contains many single doses of a contrast agent (medical imaging drug product) for use with a medical imaging device. The contents are restricted to use in direct conjunction with a device with features to mitigate the risk of cross-contamination (i.e., an automated contrast injection system, A (USP 1-Dec-2020) contrast management system, A or contrast media transfer set (USP 1-Dec-2020) approved or cleared for use with an *Imaging bulk package*). The sterility assurance of the *Imaging bulk package* contents in part is dependent upon the automated contrast injection system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set. (USP 1-Dec-2020) the contrast management system, A or the contrast media transfer set.

The *Imaging bulk package* is to be used only in a room designated for radiological procedures that involve intravascular administration of a contrast agent. Using aseptic technique, the *Imaging bulk package* closure must be penetrated only one time with a suitable sterile component of the automated contrast injection system, A the A (USP 1-Dec-2020) contrast management system, A or the contrast media transfer set. A (USP 1-Dec-2020) If the integrity of the *Imaging bulk package* and the delivery system cannot be assured through direct continuous supervision, the *Imaging bulk package* and all associated disposables for the

<sup>&</sup>lt;sup>1</sup> Exceptions may be considered only under conditions described in *Pharmaceutical Compounding*—Sterile Preparations (797).

automated contrast injection system,  $\wedge$  the (USP 1-Dec-2020) contrast management system,  $\wedge$  or the contrast media transfer set (USP 1-Dec-2020) should be discarded.

Designation as an *Imaging bulk package* is limited to injection, for injection, or injectable emulsion dosage forms as defined in (1121), *General Nomenclature Forms. Imaging bulk packages*, although containing more than one single dose, are exempt from the multiple-dose container volume limit of 30 mL. The contents of the *Imaging bulk package* must have demonstrated the ability to limit the growth of microorganisms over the labeled period of use.

Where a container is offered as an *Imaging bulk package*, the label must: 1) state prominently "Imaging Bulk Package" and, in juxtaposition with this statement, include the following use statement: "For use only with an automated contrast injection system,  $A_{(USP 1-Dec-2020)}$  contrast management system, or contrast media transfer set  $_{(USP 1-Dec-2020)}$  approved or cleared for use with this contrast agent in this Imaging Bulk Package"; 2) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions; and 3) bear the statement, "See drug and device labeling for information on devices indicated for use with this Imaging Bulk Package and techniques to help assure safe use".

## **Noninjection Packaging Systems**

**Multiple-unit container:** A Container–closure system that permits withdrawal of successive portions of a noninjection article without changing the safety, strength, quality, or purity of the remaining portion (e.g., bottle of capsules, tablets, oral or topical liquids, A and semisolids (USP 1-Dec-2020).

Single-unit container: A Container-closure system that holds a quantity of a noninjection article intended for

administration as a single dose or a single finished device intended for use promptly after the *Packaging system* is opened. **Unit-dose container:** A single-unit *Container–closure system* for an article intended for administration by other than the parenteral route as a single dose.

**Unit-of-use container:** A Container–closure system that contains a specific quantity of an article that is intended to be dispensed as such without further modification except for the addition of appropriate labeling (see  $\langle 7 \rangle$ ). It is not permitted to repackage *Unit-of-use containers* for sale.

#### Miscellaneous

**Repackaging:** The act of removing a drug product from the original manufacturer's *Packaging system* and placing it into another *Packaging system*, usually one of smaller size.

**Repackager:** A firm that repackages drug products ▲ (USP 1-Dec-2020) for distribution (e.g., for resale to distributors, hospitals, or pharmacies). For drug products, this applies to a function that is beyond the regular practice of a pharmacy. The distribution is not patient-specific, in that there are no prescriptions. ▲ (USP 1-Dec-2020) **Contract packager/contract repackager:** A firm that is contracted by another organization, such as a manufacturer,

**Contract packager/contract repackager:** A firm that is contracted by another organization, such as a manufacturer, to package bulk into a marketed *Container* of a drug product. A *Contract packager* does not take ownership from the manufacturer and generally receives the assigned expiration date from the manufacturer.

**Dispenser:** A licensed or registered practitioner who is legally responsible for providing the patient with a preparation that is in compliance with a prescription or a medication order and contains a specific patient label. In addition, dispensers may prepare limited quantities in anticipation of a prescription or medication order from a physician. *Dispensers* are governed by the board of pharmacy of the individual state. The terms "dispenser" and "pharmacy" are used interchangeably.

**Beyond-use date:** See  $\langle 7 \rangle$ .

**Expiration date:** See  $\langle 7 \rangle$ .

**Black closure system or black bands:** The use of a *Black closure system* on a vial (e.g., a black cap overseal and a black ferrule to hold the elastomeric closure) or the use of a *Black band* or series of bands above the constriction on an ampule is prohibited, except for  $\langle 7 \rangle$ , Labels and Labeling for Injectable Products, Potassium Chloride for Injection Concentrate.

#### Change to read:

#### **INJECTION PACKAGING**

Packaging for sterile products intended for injection must be validated as meeting the containment, protection, and  $compatibility_{(USP 1-Dec-2020)}$  requirements that are essential for maintaining the article's  $strength_{(USP 1-Dec-2020)}$ , quality, andpurity\_(USP 1-Dec-2020). Refer to Package Integrity Evaluation—Sterile Products (1207), Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation (1207.1), Package Integrity Leak Test Technologies (1207.2), and Package Seal Quality Test Technologies (1207.3) for further information regarding sterile product container–closure integrity testing and validation. Closures for Multiple-dose containers permit the withdrawal of the contents without removal or destruction of the Closure. The Closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the contents against contamination. Refer to (381) for Closure reseal tests that are useful for screening multiple-dose Closures for their reseal properties. Additional testing may be needed to ensure that the specific Closure selected for a product package is able to prevent loss of product contents and microbial contamination under anticipated conditions of multiple entry and use. Piggyback Packaging systems are usually intravenous infusion Container–closure systems that are used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback Packaging systems also are known as secondary infusion containers.

The volume of injection in a *Single-dose container* provides the amount specified for one-time parenteral administration, and in no case is more than sufficient to permit the withdrawal and administration of 1 L. Preparations intended for intraspinal, intracisternal, or peridural administration are packaged in *Single-dose containers* only. Unless otherwise specified in the individual monograph, a *Multiple-dose container* contains a volume of injection sufficient to permit the withdrawal of NMT 30 mL.

The following injections are exempt from the 1-L restriction of the foregoing requirements relating to packaging:

- Injections packaged for extravascular use as irrigation solutions or peritoneal dialysis solutions
- Injections packaged for intravascular use as parenteral nutrition or as replacement or substitution fluid to be administered continuously during hemofiltration

Injections packaged for intravascular use that may be used for intermittent, continuous, or bolus replacement fluid administration during hemodialysis or other procedures, unless excepted above, must conform to the 1-L restriction. Injections labeled for veterinary use are exempt from the packaging and storage requirements concerning the limitation to single-dose Packaging systems and the limitation on the volume of Multiple-dose containers.

## Packaging for Constitution

Containers, including the Closures, for dry solids intended for injection must not interact physically or chemically with the preparation in any manner that alters the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. A Packaging system for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained. Where the assay in a monograph provides a procedure for the sample solution, in which the total withdrawable contents are to be withdrawn from a Single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding 3 times the volume to be withdrawn and fitted with a 21-gauge needle NLT 2.5 cm (1 inch) in length. Care must be taken to expel any air bubbles, and the contents are then discharged into a Container for dilution and assay.

#### Change to read:

#### **MEDICAL GAS PACKAGING**

Gas cylinder: A metallic Packaging system constructed of steel or aluminum and designed to hold medical gases under pressure; these gases may include: Carbon Dioxide USP, Helium USP, Medical Air USP, A (USP 1-Dec-2020) Nitrogen NF, and Oxygen USP. As a safety measure, for carbon dioxide, helium, medical air, nitrous oxide, and oxygen, the Pin Index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

#### Change to read:

#### ASSOCIATED COMPONENTS

Many Associated Components are graduated for measurement and dose administration. Associated Components can be packaged with the drug product or sold and purchased separately. It is the responsibility of the manufacturer to ensure that the appropriate measurement and dosing component is provided or that a general purpose component, such as those described in this section, is specified for delivering the appropriate amount/dose with the intended accuracy. Liquid preparations have unique surface and flow characteristics. Consequently, the volume delivered from a measurement/dosing component may vary for each preparation.

The graduated Associated Components described in this section are for general use and should be composed of safe materials. Graduated markings should be legible And (USP 1-Dec-2020) indelible, and on an extraoral surface that does not contact the product.

The  $A_{USP 1-Dec-2020}$  markings A on associated components (USP 1-Dec-2020) must be in metric units only and limited to a single measurement scale that corresponds with the dosing instructions on the OTC or prescription container label (see Prescription Container Labeling (17)). Under expected conditions of use, the volume error incurred in measuring ▲an<sub>▲ (USP 1-Dec-2020)</sub> individual dose A (USP 1-Dec-2020) by means of such graduated components should be NMT 10% of the indicated amount of the (USP 1-Dec-2020) preparation with which the graduated component will be used.

**Dosing cup:** A measuring device consisting of a small cup that may be packaged with oral liquid articles.

**Dosing spoon:** A measuring device consisting of a bowl and handle that may be packaged with oral liquid articles. The handle may be a graduated tube.

Medicine dropper: A measuring device consisting of a transparent or translucent barrel or tube that is generally fitted with a collapsible bulb. It may be packaged with A (USP 1-Dec-2020) liquid articles.

Oral syringe: A measuring device consisting of a plunger and barrel made of transparent or translucent plastic material and a seal on the end. It may be packaged with oral liquid articles. The syringe should deliver a measured amount of a liquid drug product.

#### Change to read:

### **TEMPERATURE AND STORAGE DEFINITIONS**

**Freezer:** A place in which the temperature is controlled between  $-25^{\circ}$  and  $-10^{\circ}$  ( $-13^{\circ}$  and  $14^{\circ}$  F). It is noted that, in some instances, articles may have a recommended storage condition below  $-20^{\circ}$  ( $-4^{\circ}$  F). In such cases, the temperature of the storage location should be controlled to ±10°<sup>▲</sup> of the recommended storage condition<sub>▲ (USP 1-Dec-2020)</sub>. **Refrigerator:** A cold place in which the temperature is controlled between 2° and 8° (36° and 46° F).

**Cold:** Any temperature not exceeding 8° (46° F).

Cool: Any temperature between 8° and 15° (46° and 59° F). [NOTE—An article for which storage in a cool place is directed may, alternatively, be stored and shipped as refrigerated, unless otherwise specified by the individual monograph.]

**Room temperature** (also referred to as Ambient temperature): The temperature prevailing in a working environment. **Controlled cold temperature**: The temperature maintained thermostatically between 2° and 8° (36° and 46° F), which allows for temperature excursions between 2° and 15° (36° and 59° F) that may be experienced during storage, shipping, and

distribution, but not to exceed 24 h, such that the allowable calculated mean kinetic temperature (MKT) is NMT 8° (46° F) with no excursions below 2° (36° F) or above 15° (59° F). These limits (time and temperature) and the calculated MKT must be documented (see Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products (1079.2)). Additionally, controlled cold excursions may only occur one time during the possession of the product within the supply chain unless directed otherwise by the manufacturer. The length of time the product is held at 2° and 15° (36° and 59° F) should be supported by stability data. Other limits may be permitted if the manufacturer so instructs as supported by the manufacturer's stability data and/or thermal cycling studies. (USP 1-Dec-2020)

Controlled room temperature: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F).

▲MKT may be used during an excursion provided: 1) MKT does not exceed 25° (77° F); 2) excursion between 15° and 30° (59° and 86° F); 3) transient excursions are NMT 40° (104° F); and 4) excursion time is NMT 24 h.<sup>2</sup> These limits (time and temperature) and the calculated MKT must be documented. (USP 1-Dec-2020) Articles may be labeled for storage at "controlled room temperature" or at "20°–25°", or other wording based on the same

MKT. ▲(See (1079.2).) (USP 1-Dec-2020)

An article for which storage at Controlled room temperature is directed may, alternatively, be stored and shipped in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label. A Storage time in controlled cold or cool place cannot be used to calculate excursion temperature outside of controlled room temperature ranges. (USP 1-Dec-2020)

Warm: Any temperature between 30° and 40° (86° and 104° F).

Excessive heat: Any temperature above 40° (104° F).

Dry place: A place that does not exceed 40% average relative humidity at 20° (68° F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT 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 does not exceed 40% relative humidity. Storage in a *Container* validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry place.

**Do not refrigerate:** The Container label will bear an appropriate instruction to protect the article from refrigeration in cases where refrigeration exposes the article to loss of strength or potency or destructive alteration of its characteristics (e.g., precipitation, cloudiness). These risks are increased when a drug product with the storage temperature of 20°-25° (68°-77° F) is formulated at near-maximum solubility. (USP 1-Dec-2020)

Protect from freezing: The Container label will bear an appropriate instruction to protect the article from freezing in cases where freezing exposes an article to loss of strength or potency or to destructive alteration of its characteristics. These risks are present in addition to the risk that the Container may break if exposed to freezing temperatures.

Protect from light: Where light 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 light. The article must be packaged in a light-resistant Container.

## (1079) RISKS AND MITIGATION STRATEGIES FOR THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS

1. INTRODUCTION

2. SCOPE

3. RISK-BASED APPROACH TO THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS

4. RISK MITIGATION CATEGORIES AS QMS ELEMENTS

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GLOSSARY

ADDITIONAL SOURCES OF INFORMATION

## 1. INTRODUCTION

Proper storage and transportation of finished drug products are critical activities in an integrated supply chain. These finished drug products include but are not limited to temperature-sensitive small molecules, vaccines, biologics, biotechnological products, radiopharmaceuticals, and combination products. With the globalization of the pharmaceutical industry, various individuals and organizations from locations around the world can come into contact with the finished drug product. The storage and transportation processes for a drug product may involve complex movements with differences in documentation, handling requirements, and communication between the various entities throughout the supply chain.

Environmental controls play a key role in maintaining drug safety, quality, and efficacy. Temperature is one of the most important parameters to control. Drugs must be stored and transported according to predetermined conditions (e.g.,

<sup>&</sup>lt;sup>2</sup> Anderson C, Seevers R, Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions: proper and improper application. Pharm Forum. 2018;44(4). www.usppf.com/pf/pub/index.html.

temperature) as supported by stability data. Temperature excursions outside of their respective labeled storage conditions, for brief periods, may be acceptable provided that stability data and scientific/technical justification exist, demonstrating that product safety, quality, and efficacy is not affected.

To maintain the original quality, every party involved in the storage and transportation of a finished product should have an in-depth understanding of the storage and transportation risks and have the appropriate mitigation strategies in place to control these risks. The intent of this chapter is to identify common risks in the storage and transportation of drug products and to recommend mitigation strategies. The chapter is not meant to prescribe specific approaches or discuss regulatory frameworks currently in place, but rather to focus on risks and mitigation strategies for quality processes to maintain product and supply chain integrity. The principles of this chapter can be used to facilitate the storage and transportation of drug products throughout a supply chain that is controlled, measured, and analyzed for continuous improvements while also maintaining the integrity of the drug product in its packaging during distribution.

## 2. SCOPE

This chapter applies to organizations and individuals involved in the storage and transportation of drug products, including but not limited to the following:

- Manufacturers of drug products, radiopharmaceuticals, biological products, and biotechnological products
- Repackaging operations in which the product may be owned by a company other than the primary manufacturer
  Healthcare providers and institutions such as hospitals; outpatient, ambulatory, and urgent care centers; home health
- providers; vaccine clinics; emergency departments; and medical, dental, and veterinary offices
- Pharmacies, including but not limited to retail, compounding (sterile and nonsterile), specialty, mail order, hospital, nursing home, and hospice
- Importers and exporters
- Wholesale distributors
- Third-party logistics providers, brokers, freight forwarders, consolidators, and other organizations involved in storage; road, rail, sea, and/or air transport services, or mail distributors that offer expedited or controlled-temperature shipping services

Manufacturers of active pharmaceutical ingredients, excipients, packaging materials, medical devices, and dietary supplements are not within the scope of this chapter. However, the concepts, risks, and mitigation strategies discussed in this chapter may be useful and can be applied in these cases, if desired.

## 3. RISK-BASED APPROACH TO THE STORAGE AND TRANSPORTATION OF FINISHED DRUG PRODUCTS

*Figure 1* illustrates the risk-based approach of a quality management system (QMS). It represents how product knowledge and process knowledge facilitate the identification of risk. The figure also illustrates how mitigation strategies that are planned to reduce the identified risks, categorized in clusters, form the pillars of a QMS.



Figure 1. Risk-based approach for a QMS.

Product and process knowledge is the starting point in identifying risks related to the storage and transportation of drug products. Product knowledge includes but is not limited to the following: intended use; storage conditions; potential hazards to environment and personnel (e.g., hormones, cytotoxic drug products, and radiopharmaceuticals); and inherent vulnerability

(e.g., high potential for abuse, high-value drugs, attractiveness cargo theft, counterfeiting, and diversion). Process knowledge includes but is not limited to the following: knowledge of supply chain partners; physical modes of transportation (air, sea, rail, road, or a combination of modes); transportation routes; and national and international regulation. Understanding these factors helps an organization identify their associated risks. Process mapping is a useful tool for organizations to gain further understanding of a particular process and/or operation (e.g., transport lane selection or loading/unloading patterns of warehouses and vehicles).

Risk identification is the systematic use of information to identify potential sources of harm (hazards). Information can include historical data, theoretical analysis, informed opinions, product and process knowledge, and the concerns of stakeholders. Risk identification addresses the question: "What might go wrong?" Mitigation strategies are part of the risk control process, specifically risk reduction. Risk reduction addresses the question: "What can be done to reduce or eliminate risks?" In this way, risk reduction can include actions taken to mitigate the severity or probability of harm. Processes that improve the detectability of hazards and quality risks can also be used as part of a risk control strategy.

Different stakeholders perceive risks differently; for example, they may assign different levels of risk based on their experience and knowledge or they may estimate the probability of risk to product differently. Regardless of where your organization fits into the supply chain, consideration of risks and mitigation actions taken should consider potential impact throughout the supply chain. The mitigation strategies can be divided into four categories that are fundamentals (or pillars) of a QMS (see *Figure 1*). These strategies, when implemented, give an organization the autonomy to plan, implement, measure, and improve their processes according to current regulations and associated risks. Generally, mitigation strategies fall within four categories related to: 1) documentation, i.e., providing instructions for a specific operation or process to standardize it and establish consistency; 2) training, i.e., ensuring competence; 3) resources, i.e., providing capability through infrastructure and human resources; and 4) qualification and validation, i.e., assurance that the resources and processes are reliable, reproducible, and robust.

Several informal and formal tools can be used to conduct risk assessments and control risk. Examples of tools used to perform risk identification include (but are not limited to): flow charts, process mapping, trends, historical data records (such as temperature records over a particular route), and observations. Other tools—such as failure mode effects analysis (FMEA), fault tree analysis (FTA), hazard analysis and critical control points (HACCP), hazard operability analysis (HAZOP), and preliminary hazard analysis (PHA)—can also be used for conducting risk management [see International Council for Harmonisation (ICH) in *Additional Sources of Information*].

Table 1 contains illustrative examples of the risks related to drug product storage and transportation, along with their mitigation strategies. The list presented below is not exhaustive and is meant to stimulate discussion and provide examples.

Hazard	Effect	Mitigation Strategy	Mitigation Category				
General Risk							
Human error due to excessive duties or lack of training or competence	Mishandling along the supply chain, which can affect product quality and integrity and patient safety	<ul> <li>Evaluate training effectiveness [are trainees competent in key aspects of the standard operating procedures (SOPs)?]</li> <li>Assign appropriate number of personnel to avoid excessive duties placed on one individual</li> <li>Assign employees to duties that they are qualified for based on education, experience, and competence</li> </ul>	Training and Resources				
	Procureme	nt and Sales					
Buy from or sell to unlicensed trading partners	Legal sanctions; patient safety	<ul> <li>Supplier qualification</li> <li>Customer qualification</li> <li>Checks to ensure license is current and appropriate</li> <li>Quality agreements between sup- plier and trading partners</li> </ul>	Documentation and Resources				
	Receiving a	nd Shipping					
Receive adulterated, falsified, or recal- led product	Patient safety; introduction into legiti- mate supply chain of a product that is potentially substandard, illegal, or counterfeited	<ul> <li>Quarantine</li> <li>Quality control test</li> <li>Packaging identification finger- prints</li> <li>Recall awareness</li> <li>Notify regulatory authorities or trading partners</li> <li>Qualification of supply chain part- ners and on-going performance qualifications</li> </ul>	Documentation and Training				
Receive product that was not ordered	Unmatched transaction (e.g., wrong paperwork or transaction data sent); introduction into legitimate supply chain of a product that is potentially substandard, illegal, or counterfeited	Adhere to receiving SOP	Documentation and Training				

#### Table 1. Storage and Transportation Risks and Mitigation Strategies

Table 1. Stora	ge and Transportation	n Risks and Mitigation	<b>Strategies</b> (continued)
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Hazard	Effect	Mitigation Strategy	Mitigation Category		
General Risk					
Mix products with different status (re- jected, recalled, or returned)	Patient safety; shipping or selling of in- appropriate product	<ul> <li>Product segregation, physical in the location and/or system</li> <li>Warehouse layout (logical flow and holding areas in order to avoid mix-ups)</li> <li>Adhere to receiving SOP</li> </ul>	Storage, Documentation, and Resour- ces		
Shipping and receiving delays due to inclement weather, natural disasters, traffic disruption	Patient safety; arrival delays; tempera- ture out of specification (temperature excursions, e.g., product freezes acci- dentally)	<ul> <li>Reschedule the delivery</li> <li>Temporary parking (waiting for opportunity to unload) or off-loading to a temperature-controlled facility or vehicle</li> <li>Recondition materials to ensure temperature maintenance during delay</li> <li>Rescue services</li> <li>Monitoring to demonstrate that the product integrity was not compromised; in cases when monitoring was not implemented due to qualifications and risk assessments, these delays might be out of scope due to the qualification parameters</li> </ul>	Documentation, Training, and Resour- ces		
	Stor	rage			
Improper entry into a materials man- agement system: wrong batch num- ber, wrong expiration date, wrong status (e.g., product was approved but should be quarantined), or wrong amount	Inaccurate stock; picking and/or ship- ping product that should have been quarantined but was marked ap- proved	<ul><li>Adhere to stocking SOP</li><li>Software validation</li></ul>	Documentation and Validation		
	Patient safety because of picking error (software shows location, but staff can pick the wrong product if there is no check of the physical location)	<ul><li>Adhere to stocking SOP</li><li>Automated checking system</li></ul>	Documentation, Training, and Valida- tion		
	Product exposed to temperature ex- cursions	Refer to SOP showing list of prod- ucts and their temperature specifi- cations	Documentation		
Product stored in wrong physical loca- tion	Legal sanctions for controlled sub- stance; risk of diversion for control- led substance	Refer to SOP showing list of prod- ucts and their license category (e.g., controlled, radiopharma- ceutical)	Documentation		
	Affects product quality, product integ- rity, and patient safety (e.g., freezing of vaccine or biologic product); prod- uct loss causing financial loss	<ul> <li>Warehouse, packaging, and transportation qualification (temperature mapping)</li> <li>Product storage identification</li> </ul>	Qualification and Validation, Training, and Documentation		
Environmental conditions out of spec- ification	Out-of-range cold or hot areas; prod- uct storage temperature excursion product loss; financial loss; patient product availability	<ul> <li>Qualification (temperature mapping)</li> <li>Storage temperature monitoring program</li> <li>Homogenous airflow</li> <li>Monitoring and alarms</li> <li>Adhere to excursion-handling SOP</li> </ul>	Documentation, Resources, and Qual- ification and Validation		
Temperature monitoring device failure	Out-of-range cold or hot areas; prod- uct storage temperature excursion; product loss	<ul> <li>Backup monitoring devices with independent power source</li> <li>Adhere to excursion-handling SOP</li> </ul>	Documentation and Resources		
<ul> <li>Storage or temperature system failure due to:</li> <li>Loss of electrical power</li> <li>Failure of temperature control or air circulation systems</li> <li>Unusual weather event</li> </ul>	Out-of-range cold, warm, or hot areas; product storage temperature excur- sion; product loss	<ul> <li>Temperature and power alarms</li> <li>Backup power and coolant systems (redundant) and/or contingency storage</li> <li>Adhere to excursion-handling SOP</li> </ul>	Documentation and Resources		
Fear of reporting nonconformance and exception conditions	Affects product integrity and patient safety due to serious conditions not communicated	<ul> <li>Independent quality reporting structure</li> <li>Education on product integrity and impact on patients and the supply chain</li> </ul>	Training and Resources		

Hazard Effect **Mitigation Strategy Mitigation Category General Risk** Patient safety; wrong item shipped (product availability); product returns • Automated checking system or Documentation, Training, and Qualifi-Picking (human) error second-person verification cation and Validation

#### Table 1. Storage and Transportation Risks and Mitigation Strategies (continued)

[NOTE—The effect of a hazard, if not mitigated, could impact product integrity and ultimately patient safety.]

#### Change to read:

## 4. RISK MITIGATION CATEGORIES AS QMS ELEMENTS

A QMS is necessary to implement, monitor, and maintain a robust storage and transportation process. Key elements of a QMS are management responsibility, documentation, training, resource management, complaint handling, deviation/ excursion handling, returns and recalls management, qualification/validation, monitoring, audit, corrective action, preventive action, and continuous improvement. This chapter does not intend to provide a QMS framework; rather this chapter highlights how risk mitigation strategies are pillars of a QMS and how QMS elements ensure the quality and security of drug products throughout storage and transport.

The four categories of risk mitigation strategies are discussed in Table 2, with a matrix that links the mitigation strategy to the role that an organization plays within the supply chain.

Applicable Mitigation Strategies	Role of Organization within Supply Chain					
	Manufactur- er	Wholesaler and Distributor	Pharmacy or Compound- ing Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Pro- vider (LSP)
Documentatio	on (Manuals, Pr	ocedures, Proto	cols, Records)			
Quality manual	Yes	Yes	Yes	Yes	Yes	Yes
Labeling	Yes	Yes	Yes	Yes	No	Yes
Procurement	Yes	Yes	Yes	Yes	Yes	Yes
Receiving	Yes	Yes	Yes	Yes	No	Yes
Picking	Yes	Yes	Yes	Yes	No	Yes
Packing	Yes	Yes	Yes	Yes	No	No
Sales	Yes	Yes	Yes	Yes	Yes	No
Storage	Yes	Yes	Yes	Yes	No	Yes
Transportation	Yes	Yes	Yes	Yes <sup>a</sup>	No	Yes
Supplier qualification	Yes	Yes	Yes	Yes	Yes	Yes
Customer qualification	Yes	Yes	No	No	Yes	No
Quality agreements	Yes	Yes	Yes	Yes	Yes	Yes
Licenses and authorizations	Yes	Yes	Yes	Yes	Yes	Yes
Recall	Yes	Yes	Yes	Yes	Yes	Yes
Return	Yes	Yes	Yes	Yes	No	No
Temporary parking	Yes	No <sup>b</sup>	Yes	No	No	Yes
Excursion handling	Yes	Yes	Yes	Yes	No	Yes
Disposal of expired and nonconforming drug products (e.g., suspect, expired, recalled, quarantined)	Yes	Yes	Yes	Yes	Yes	No
Pest control and pallet conservation	Yes	Yes	Yes	Yes	No	Yes
	Trai	ning				
Training	Yes	Yes	Yes	Yes	Yes	Yes
Resources						
Product segregation	Yes	Yes	Yes	Yes	No	Yes
Storage area (layout/logical flow)	Yes	Yes	Yes	Yes	No	Yes <sup>c</sup>
Maintenance	Yes	Yes	Yes	Yes	No	Yes

#### Table 2. Mitigation Strategies Used by Organizations within Supply Chain

Applicable Mitigation Strategies	Role of Organization within Supply Chain					
	Manufactur- er	Wholesaler and Distributor	Pharmacy or Compound- ing Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Pro- vider (LSP)
Documentatio	on (Manuals, Pro	ocedures, Proto	cols, Records)			
Calibration	Yes	Yes	Yes	Yes	No	Yes
Monitoring systems and alarms	Yes	Yes	Yes	Yes	No	Yes
Appropriate number of personnel	Yes	Yes	Yes	Yes	Yes	Yes
Organizational chart and job descriptions	Yes	Yes	Yes	Yes	Yes	Yes
	Qualification a	and Validation				
Temperature mapping	Yes	Yes	Yes	Yes	No	Yes
Shipping packaging qualification	Yes	Yes	Yes	Noª	No	No
Software validation (automated checking systems, inventory management system)	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Mitigation Strategies Used by Organizations within Supply Chain (continued)

<sup>a</sup> Unless the healthcare entity ships between owned facilities or to the patient.

<sup>b</sup> If the ownership of the product has already transferred to the distributors, then temporary parking could be the responsibility of the distributors/wholesaler.

<sup>c</sup> Applied only if the logistics service provider has a temporary storage area.

## 4.1 Documentation and Procedures

Documentation provides written information that allows for consistency and traceability of actions. For this reason, documentation is a fundamental part of any quality system. In a risk-based approach, documentation is a category of risk mitigation. Some examples of documentation include quality manuals; standard operating procedures (SOPs); labeling; records pertaining to procurement, receiving, storage, and transportation; supplier qualification records; quality agreements; recalls; and excursion-handling records.

The sections that follow describe key types of documents that are fundamental for a QMS supply chain system. These documents can be used in a range of different organizations (see *Table 2*).

## 4.1.1 QUALITY MANUAL

A quality manual is a top-level quality document for all areas of the business affected by the quality system. The quality manual contains the quality policy, quality objectives, quality system structure, and information related to the management of a specific organization. The content may also include information on inspection management, customer complaints, recalls, withdrawals and holds, corrective and preventive actions, nonconformance and change control, information about regulatory issues, and performance evaluation through quality indicators.

## 4.1.2 STANDARD OPERATING PROCEDURES

SOPs are controlled documents, with document owners and approvers, effective dates, revision management, and scheduled reviews. Procedures should cover areas governed by the quality manual and should cover all aspects of the operation that may affect product quality, including handling, distribution, and all regulated activities in relation to the specific business (e.g., national and international laws). SOPs should also address actions that are performed to identify and mitigate risks.

Some key components are, but not limited to, the following:

- Corrective action/preventive action (CAPA)
- Documentation
- Record keeping
- Inventory management
- Licensing
- Management reviews
- Nonconforming product (for example, but not limited to, damaged or adulterated, expired, recall, suspect or illegitimate product, and temperature deviation)
- Order processing
- Purchasing
- Picking
- Packing and shipping
- Receiving
- Returns
- Storage
- Training

#### Not official text. Please refer to the currently official version of the applicable USP-NF standard for compliance purposes.

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**Procurement:** One of the risks in procurement is buying and selling for transport with an unlicensed trading partner, leading to legal sanctions. A procurement procedure ensures that a product is purchased according to product specifications and that purchases are made from qualified partners that are licensed as appropriate.

**Receiving:** One potential risk when moving a product forward and backward along the supply chain is the introduction of substandard, illegal, or counterfeit products into the legitimate supply chain. Receiving is the operation related to the entrance of cargo into the operation's facility, starting with unloading the cargo from vehicles and then receiving, checking, and stocking the operation's facility. Each organization should have a receiving procedure that determines the appropriate checks for this operation. A checklist can be used as a reminder of what to inspect and what to record. Where appropriate, the transport vehicle can be inspected before unloading to verify that adequate protection from contamination was maintained during transit. To avoid the risk of receiving a product that was not ordered, all deliveries should be verified at the time of receipt in order to check that containers were not damaged and that the consignment corresponds to the order.

All incoming products should be segregated from salable inventory and identified. Products should be transferred to their respective storage areas according to their classification and storage specification. When products arrive at warehouse loading docks and other arrival areas, they should be transferred as quickly as possible to a designated storage area within a time period that is consistent with the organization's receiving SOP.

Inclement weather, natural disasters, and traffic disruption can cause receiving delays and potential temperature excursions. Rescheduling the delivery, temporarily parking while waiting for an opportunity to unload, rescue services, or even reconditioning materials to ensure temperature maintenance during delays are all mitigation strategies that can be implemented. Procedures to follow for these contingencies should be written, and personnel should be trained on them. **Storage and transportation:** During storage and transportation, two approaches can be used to keep the product within its required labeled specifications:

- 1. Controlling the environmental conditions within equipment, storage rooms, and transportation vehicles; and when applicable, using thermostatically controlled devices such as a heating, ventilation, and air conditioning (HVAC) system or refrigerators
- 2. Using packaging materials that allow for the control of environmental conditions (e.g., passive/thermal packaging, thermal blankets, temperature stabilizers, desiccants, and light-resistant material)

The organization should have written procedures for qualification of storage, shipping containers, and transportation (in-transit storage) of drug products, taking into account at a minimum:

- Product category (e.g., narcotics, medical devices, temperature-sensitive or hazardous products)
- Layout of the area [e.g., floor-standing pallets, pallet racking, and boxes inside refrigerators where practical and applicable (not feasible for air freight)]
- Volume of stored product (including peaks of storage)
- Air circulation and environmental conditions (e.g., temperature, relative humidity, pressure, shock, and vibration)
- Contingency plan for outages and employee breaks

The procedure should be written based on a risk assessment of factors that can impact product quality during storage and transportation. This procedure will be a measure to mitigate this risk.

If there are problems with vehicles during the transportation process (e.g., breakdowns, accidents, and loss of fuel), a product should be protected against environmental factors, theft, and diversion. The risk assessment and written procedures should take these situations into consideration. Depending on the probability of occurrence and the level of risk, an organization may consider backup systems or access to backup systems in the event of logistics disruption (e.g., severe weather). **Recalls:** All supply chain partners are responsible for maintaining the quality and integrity of products under their control. Anytime a deviation is found that likely affects the safety or efficacy of a marketed product, an appropriate action should be taken, including a potential recall. A challenge involved in recalling a product is ensuring that the amount of product that was initially distributed is returned. Thus, sharing information on product recall increases the efficacy of the recall procedure, provides transparency to supply chain partners, and mitigates the risk of reintroducing a recalled product into the supply chain. The organization should have a written procedure that establishes the steps for recalling products and the control of recalled product, such as product identification and segregation. The extent of the recall needs to correspond to the level of risk. The extent of the recall may change if the risk is re-evaluated.

**Returns:** Accepting a returned product for restocking poses the risk that the product may not be authentic or its quality may have decreased. A risk-based evaluation should be performed to determine if the product will be acceptable for restocking and resale or if it needs to be destroyed. During the evaluations, returned products should be kept in a segregated area designated specifically for returns until final disposition. A written procedure for handling returns should be in place, taking into account:

- Reasons for return
- Appearance and integrity of the original packaging
- Evidence of conditions in which the cargo was transported and stored throughout the entire time span
- Duration of time between the original shipment and its return
- Authenticity of the product, to include product identifier verification covered by applicable traceability and serialization laws and evidence of proper storage while in possession of the entity returning the product (e.g., ongoing assurance)
- Representative sampling for quality control analysis (if applicable and following regulation)
- Expiry date and batch number
- Batch trace history of excursion
- Information from any track-and-trace system in place

Supplier qualification (logistics service provider, third party logistics provider, material suppliers, maintenance providers, etc.): Supplier qualification is a process in which the organization assesses its suppliers regarding their licenses, authorizations, and compliance with regulatory requirements for the distribution of drug products. The organization should

establish a written procedure for how suppliers are selected and evaluated, including the criteria for qualification and the period for requalification on a risk-based approach.

#### 4.1.3 LABELS

Labels are fundamental to material identification. For this reason, any label change should be communicated to downstream supply chain partners. Labels applied, even to small containers, should be clear, indelible, unambiguous, and permanently fixed in the format established by the manufacturer, packager, or repackager. The shipping label should include wording or icons to emphasize storage and transportation conditions, handling requirements, and hazards. The use of symbols that are recognized by international organizations is strongly recommended. Asee *General Notices*, *10.20. Labeling*. (ERR 1-Feb-2021)

#### 4.1.4 QUALITY AGREEMENTS

Written agreements (e.g., quality agreement, technical agreement, service level agreement) should be in place between applicable organizations involved in the supply chain. Each supply chain partner should ensure that its respective service level agreements and supporting documents cover delivery and receiving responsibilities. The use of written agreements ensures clarity and transparency, while delineating the responsibilities of each organization in the supply chain.

#### 4.1.5 EXCURSION HANDLING

Short-term temperature excursions can occur during distribution, storage, and transportation (see *Packaging and Storage Requirements* (659)). Each excursion should be documented and handled with a deviation or appropriate risk assessment. Product disposition should be established on the basis of an assessment of the excursion (i.e., the temperature to which the material or product was exposed, and for how long), the stability data obtained from traditional stability studies (under accelerated, intermediate, if appropriate, and long-term conditions and performed in accordance with ICH guidelines), and distribution stability studies (e.g., extremes of temperature, thermal cycling, and freeze–thaw studies, as appropriate). Combining stability data from long-term and accelerated studies with mean kinetic temperature (MKT), temperature-excursion, and thermal-cycling studies should provide the information necessary to evaluate the effects of excursions. Excursions out of temperature range defined by thermostability data or (659) should be addressed/corrected in order to prevent recurrence using a risk-based approach. Downstream handlers of finished drug products may rely on the manufacturer's product disposition instructions. See (659) for excursion allowances and MKT limits and *Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products* (1079.2) for MKT. MKT should be calculated for the period of time that a drug is in residence at a warehouse and/or in transit on a truck to avoid the problem of diluting the impact of excursions by calculating annual MKT values.<sup>1, 2</sup>

#### 4.2 Training

Training is a teaching-learning process used in the workplace to provide knowledge and develop skills and behaviors. The objective of training is to reduce the gap between the existing competencies and those required for performing the work. Training comprises knowledge of the topic to be taught and the types of training practices such as class-like, on-the-job training, web-based, blind sample analysis, mocks, and simulations. The type of training can influence the effectiveness of that training.

A written training procedure is necessary to establish who can be the trainer, how training needs are identified, and how training effectiveness will be evaluated. Selection of trainers must adhere to applicable laws as appropriate. Training needs could be identified and linked to job descriptions, complexity of duties, types of product handled, management reviews, and any kind of human resources program for competence development.

SOPs are the foundation of a quality system, and training must be provided for each SOP to the appropriate job roles responsible for executing the processes outlined in each SOP. Frequency of training and when training or retraining should occur should also be outlined in the overarching training SOP. Training records should be maintained either as hard copies or electronically.

The effectiveness of training should be considered and evaluated to determine its impact on task execution and quality. Evaluation of training effectiveness is not necessarily a separate document, but it may include a review of written or performance tests, observation, error rates, non-conformance or CAPAs, customer complaints, and internal and external audits. Any identified training effectiveness gaps should be corrected and evaluated. This may include retraining or evaluation and modification of SOPs, training materials, training method, or the instructor.

As a risk mitigation strategy, training should be performed before the SOP becomes effective. All employees whose actions have an impact on product quality and security should have initial and ongoing training based on an approved schedule. Basic training should be provided regarding risks and mitigation for storage and transportation of drug products so that employees will better understand how individual and collective actions impact product quality, and so they will develop awareness and a risk-based mindset.

#### 4.3 Resources for Storage, Transportation, and Personnel

In the context of this chapter, resources are warehouses, vehicles, and organizational personnel. Facilities, equipment, and transportation vehicles are emphasized as systems that function to control environmental conditions in accordance with product

<sup>&</sup>lt;sup>1</sup> Seevers RH, Hofer J, Harber P, Ulrich DA, Bishara R. The use of mean kinetic temperature (MKT) in the handling, storage and distribution of temperature sensitive pharmaceuticals. *Pharmaceutical Outsourcing*. May/June 2009;12–17.

<sup>&</sup>lt;sup>2</sup> Anderson C, Seevers R, Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions: proper and improper application. *Pharm Forum*. 2018;44(4).

specifications. Evaluation of facilities, equipment, packaging, and transportation systems should be part of the quality system of the organization. Sampling family or type of equipment/vehicles (e.g., shipping containers or trailers) should be part of the risk assessment, when evaluation of individual systems is not feasible. Additionally, trading partner facilities/vehicles can be evaluated by risk by family or type, which may include sample lane mapping to evaluate the exposure of product through the transportation system.

#### 4.3.1 STORAGE

The facility should be designed to maintain the quality and integrity of the stored drug product. Buildings should be constructed in such a way that they are appropriate for the intended operations, taking into account:

- Security
- Product characteristics (e.g., narcotics, radiopharmaceuticals, fire/explosion risk)
- Product status (e.g., approved, recalled, returned, rejected, quarantined, falsified)
- Product required storage temperature
- Ease of cleaning and maintenance
- Logical flow of personnel and materials
- Means of preventing mix-ups and cross-contamination
- Ergonomic measures
- Product demand in order to prevent capacity constraints
- Any local, national, or international requirements
- Necessary environmental controls

Product segregation and proper identification can reduce the risk of mixing up products with different statuses, such as quarantined (rejected, expired, recalled, returned, or falsified) and released/salable. Products with special handling authorization, such as narcotics, should be segregated and locked in a secure area per applicable regulations. Radiopharmaceuticals should be contained in dedicated, locked storage areas. Hazardous products should be managed per applicable regulations for each supply chain partner. Other products that require special storage conditions such as hazardous products (see *Hazardous Drugs—Handling in Healthcare Settings* (800)) should also be segregated per applicable safety standards. Any system used to replace physical segregation should offer the same level of security and protection.

Buildings and facilities used for the warehousing, storage, and/or holding of drug products should be of adequate size for their intended use to prevent product overcrowding. The building and facility should be designed to control environmental conditions, where necessary, and should be made of materials that are readily or easily cleaned. Sanitation and pest control procedures should be written, indicating the frequency of cleaning and the materials and methods to be used. The pest-control program should prevent contamination and ensure the safe use of pesticides. Records of all cleaning and pest-control activities should be maintained.

Storage facilities themselves, unless thermostatically controlled, cannot be validated. However, they can be qualified via a mapping process, with appropriate attention to geography and seasons. The generator backup power supply should be qualified.

Drug product storage areas are required to maintain the product temperature between the limits defined on the product label (see (659)). Product storage areas/units should utilize recording systems to log and track temperatures. Alarm systems should be an integral part of the monitoring system for product temperatures. Although automated systems monitor units continuously, manual checks should be performed as appropriate to ensure functionality. When automated systems are not available, manual systems may be used. A risk-based approach should be applied when using a manual system.

Controlled access to warehouses and vehicles is a measure used to prevent unauthorized personnel from coming into contact with the product. Access control can be accomplished with automated systems or by procedure. Adequate precautions should be taken to prevent theft and diversion of products.

#### 4.3.2 TRANSPORTATION

All vehicles used in supply chain activities—such as trucks, vans, trains, airplanes, sea vessels, mail delivery vehicles, and emergency medical services vehicles—should be suitable for the intended purpose because they are providing in-transit storage and should prevent exposure to conditions that affect stability and package integrity. Thus, all of the precautions needed to maintain product quality, integrity, and security should be taken. Risk identification and mitigation strategies should be applied to determine whether the transportation method adequately protects the product from environmental exposures such as temperature and vibration without the need for additional packaging, or if additional packaging is necessary to mitigate the risk.

#### 4.3.3 PERSONNEL

Organizations should hire personnel and contractors who meet the requirements for handling drugs safely and securely per applicable laws and regulations. Job descriptions and individual profiles should be reviewed to ensure that all experience and training requirements are met and maintained.

## 4.4 Qualification and Validation

Qualification and validation for storage and transportation of drugs focus on the assurance that the storage and transportation methods meet predetermined criteria and that processes and procedures produce the desired outcome. Calibration is necessary for instruments used in qualification studies. Organizations need to include appropriate qualification, validation, and calibration activities in their master plan and SOPs, as well as schedules and the use of approved protocols to conduct these activities and

produce final reports. The sections below provide brief explanations of calibration, qualification, and validation, focusing on storage and transportation. The scope for each stakeholder within the supply chain is described in *Table 3*.

#### 4.4.1 CALIBRATION OF INSTRUMENT OR DEVICE

Calibration ensures that measurements such as temperature and humidity meet recognized standards. Calibration frequency may be determined by the device manufacturer, device workload, operational demands, and/or damage that require repairs. Instruments or devices used for qualification or monitoring of set criteria must be calibrated to recognized standards such as those from the National Institute of Standards and Technology (NIST) and those found in *Monitoring Devices—Time, Temperature, and Humidity* (1118).

	Role of Organization within Supply Chain					
Calibration, Qualification, and Validation Activities	Manufactur- er	Wholesaler and Distributor	Pharma- cy and Compound- ing Pharmacy	Hospital and Healthcare Provider	Broker	Logistics Service Pro- vider (LSP)
	Calibi	ation				
Temperature recording devices used for temperature mapping or monitoring during storage and transportation	Yes	Yes	Yes	Yes	No	Yes
	Qualifi	cation				
Temperature mapping of warehouse and equipment (freezers, refrigerators)	Yes	Yes	Yes	Yes	No	Yes
Shipping packaging performance qualification	Yes	Yes	Yes	Yes	No	No
Transportation vehicle performance qualification	Yes	Yes	Yes	Yes	Yes	Yes
	Valid	ation				
Software validation for systems that make quality decisions	Yes	Yes	Yes	Yes	Yes	Yes

#### Table 3. Calibration, Qualification, and Validation Activities of Organizations

#### 4.4.2 QUALIFICATION

For the purposes of this chapter, performance qualification is defined as all tests designed and executed to evaluate whether the storage rooms and areas, warehouse facilities, utilities, equipment, transport vehicles, and shipping containers are suitable for their intended purpose. Qualification studies should reflect actual load configurations and environmental conditions. Testing should be performed on both active and passive thermal packaging systems.

During the qualification process, temperature mapping is performed to provide information relative to temperature consistency throughout a product area. This information may confirm a uniform temperature over the mapped area or it may identify areas that need mitigation. Such mitigation may include the movement or installation of insulation, HVAC units, or fans, or the need to modify the relevant SOPs. The identification, documentation, and rationale for the mapping procedure are the foundation of temperature mapping of any temperature-controlled space (e.g., facility, vehicle, shipping containers, refrigerator, and freezer). Temperature variability in mapped locations and the level of thermal risk to the product should both be defined, unless another process to ensure environmental control has been put in place (see (1118)).

**Temperature mapping in facilities and equipment:** The following factors, which may contribute to temperature variability in a facility, should be considered during the process of temperature mapping for 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 duration of temperature recordings during the thermal mapping of a warehouse or cold room should capture workflow variation that may impact airflow and the resulting temperature fluctuation; for example, this process could last from 1 day to 1 week, depending on the workflow cycle. **Temperature mapping for shipping packaging and vehicles**: Pharmaceutical manufacturers should consider primary, secondary, and tertiary packaging that best protects the drug product during storage and distribution. Shipping package performance testing should be documented as part of a QMS. Several standard test procedures are available to evaluate package performance for factors such as shock, vibration, pressure, compression, and other transit events. (See Additional Sources of Information for standards for test methods.)

Packaging at the tertiary level (e.g., outer, external, or shipping package) or thereafter for the distribution of the drug product should be selected and tested to ensure that product quality is maintained and to protect the contents from the rigors of distribution, including environmental or physical damage. Active, passive, or semi-active shippers and transport systems are typically subjected to operation performance qualification by the manufacturers or suppliers of such equipment.

Thermal packaging and vehicles used for transporting the drug product for pharmaceutical manufacturers, wholesalers, and pharmacies should be evaluated based on the labeled storage or transport conditions of the product as well as anticipated environmental conditions. Special consideration should be made for seasonal temperature differences, transportation between hemispheres, and the routes and modes of transport.

Identification of risks and mitigation strategies to protect the product should be based on documented studies of specific distribution environments, including domestic and international lanes (as appropriate), mode(s) of transport, duration, temperature, and other potential environmental exposures or sensitivities that may impact product quality. If risks to product

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integrity have been identified by using historical data, observation of current practices, or operational changes, mitigation strategies may be employed to address the identified risks. Strategies include temperature-controlled vehicles, active or passive thermal containers or packaging, or ambient conditions based upon identified risks (product storage labeling, time, temperature, and geography).

Temperature monitors/indicators may include calibrated monitoring or recording devices, real-time monitors such as GPS, and chemical indicators of temperature. Monitoring devices may include an alert mechanism if the preset ranges are breached (see (1118)).

Thermal packaging and vehicles may be qualified based on historical data that are relevant to the process. If qualified thermal packaging is used without a temperature verification method (monitors or indicators), a plan should be in place to schedule transport within qualifying times and to mitigate and respond to exceptions. However, it may be acceptable to use product stability data from manufacturers and supply chain risk assessment to justify shipping without either continuous monitoring or qualification of the shipping system.

Operational and performance shipping studies should 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 configuration conditions and expected environmental extremes. Testing should be performed on both active and passive thermal packaging systems.

When developing a thermal package qualification protocol, the following factors and actions should be considered:

- Transportation temperature profile for the shipping lane(s)
- Delivery cycle time, accounting for reasonable delays due to weather, traffic, or customs
- Testing beyond qualification time to obtain worst-case data for excursion dispositioning
- Seasonal changes in the environment
- Use of seasonal (warm/summer and cool/winter) configurations versus universal configuration
- Testing with actual payload, worst case configuration, or a representative sample
- Variable order sizes, making it difficult to select a representative sample; testing for the minimum and maximum payload possible in each package may be necessary
- Probe placement should be inside or directly attached to the product (or representative samples) or in the most vulnerable temperature locations within the package; scientific justification should be given for the differences between monitoring for qualification and operation
- Perform at least 3 replicate tests on a representative package containing a representative thermal payload per season; tests may be performed at the same time in an environmental chamber
- Allow the product payload as well as coolant to condition before beginning testing per protocol
- Utilize a recognized standard to conduct thermal qualification (see *Additional Sources of Information*) or develop a written rationale for a qualification

#### 4.4.3 VALIDATION OF INFORMATION SYSTEMS

In the context of this chapter, before an information system that can impact the quality of the product in storage or in transportation is brought into use, it should be demonstrated through appropriate validation or verification studies that the system is capable of achieving the desired results accurately, consistently, and reproducibly. (See Pharmaceutical Inspection Convention in *Additional Sources of Information*). The following are considerations for using validation as a mitigation strategy. These considerations do not suggest replacing or enforcing any existing regulatory standards in place for various members of the supply chain [e.g., current good manufacturing practices (cGMP) for manufacturers, wholesale distributors, or pharmacies].

Prior to their use, information systems should be tested according to approved protocols. The extent of the study depends on the risk or impact the software can have on product or service quality. Validation or verification is not applied to systems that have no impact on quality. An inventory of information systems should be done periodically and include at least:

- Information system identification (name, version)
- System supplier
- Processes where system is used
- Process owner
- Risk assessment

• Status (validated, not validated, validation in progress, verified, not verified, verification in progress, not applicable)

A multidisciplinary team with representatives from information technology, quality, and operations should be responsible for protocols and report approvals. Responsibilities for the tests should be assigned in the protocols. Validation or verification tests should cover the following:

- Security (e.g., access levels, profiles, responsibilities inclusion, exclusion, or changing profiles)
- Data validity (e.g., challenge the software with entries above and below specification and with entry value errors)
- Documentation (e.g., system design in accordance with user requirements and other documents)
- Functionality (e.g., calculations, operations) [most of the functionality tests for embedded software are covered during equipment qualification (installation, operation, and performance qualifications]
- Data integrity (e.g., changes, traceability, backup, recovery, and protection)

After validation or verification studies, any modification to the system should be done according to change control procedures, and records of these changes should be kept.

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#### GLOSSARY

**Calibration:** A process that typically focuses on instruments or devices to provide assurance that they produce results within specified limits. Organizations need to include the appropriate qualification, validation, and calibration activities in their SOPs and master schedules and should follow protocols to conduct these activities and final reports.

**Qualification:** Qualification is the assurance that systems or equipment meet predetermined acceptance criteria. This process typically focuses on equipment and utilities such as refrigerators and HVAC systems, as well as packaging. There are several different types of qualification, and an organization should determine which to use and when. Some of these include design qualification, installation qualification, operational qualification, and performance qualification.

**Service level agreement** (SLA): An SLA or contract is a negotiated 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 either be a legally binding document or an information agreement. The SLA may also specify the target and minimum-level performance, operation, or other service attributes.

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

**Validation:** Validation typically focuses on processes and procedures, to provide assurance that the processes or equipment produce the desired outcome.

## **ADDITIONAL SOURCES OF INFORMATION**

American Society for Testing and Materials International. ASTM D3103-14. Standard Test Method for Thermal Insulation Performance of Distribution Packages.

American Society for Testing and Materials International. ASTM D4169-16. Standard Practice for Performance Testing of Shipping Containers and Systems.

American Society for Testing and Materials International. ASTM D4332-14. Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing.

Health Canada. National Guidelines for Vaccine Storage and Transportation. In: Canada Communicable Disease Report. June 15, 1995; Vol 21-11:93–97.

European Commission. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01).

International Council for Harmonisation. Quality Risk Management (ICH Q9).

International Council for Harmonisation. Pharmaceutical Quality System (ICH Q10).

International Council for Harmonisation. Good manufacturing practice guide for active pharmaceutical ingredients (ICH Q7), Chapter 10—Storage and Distribution, p 22; November 10, 2000.

International Organization for Standardization. Quality management systems—Fundamentals and vocabulary (ISO 9000:2015).

International Organization for Standardization. Risk management (ISO 31000).

International Organization for Standardization. Quality management systems—Requirements (ISO 9001:2015).

International Safe Transit Association. Testing Standard for Thermal Transport Packaging Used in Parcel Delivery System Shipment (ISTA STD-7E).

Parenteral Drug Association. Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment (PDA Technical Report 39); 2007. Parenteral Drug Association. Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User (PDA Technical Report 46); 2009.

Parenteral Drug Association. Active Temperature-Controlled Systems: Qualification Guidance (PDA Technical Report 64); 2013.

Parenteral Drug Association. Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance (PDA Technical Report 72); 2015.

Pharmaceutical Inspection Convention. PIC/S Guide to Good Distribution Practice (GDP) for Medicinal Products (PE-011-1); June 1, 2014.

International Air Transport Association. IATA Temperature Control Regulations, Chapter 17—Air Transport Logistics for Time and Temperature Sensitive Healthcare Products; July 1, 2009.

World Health Organization. Model Guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, Annex 9); 2011.

World Health Organization. Supplement 7—Qualification of temperature-controlled storage areas (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 8—Temperature mapping of storage areas (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 11—Qualification of refrigerated road vehicles (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 12—Temperature-controlled transport operations by road and by air (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 13—Qualification of shipping containers (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. Supplement 14—Transport route profiling qualification (Technical supplement to WHO Technical Report Series, No. 961, 2011); 2015.

World Health Organization. WHO good distribution practices for pharmaceutical products (WHO Technical Report Series, No. 957, Annex 5); 2010.

#### Add the following:

## ▲ (1079.2) MEAN KINETIC TEMPERATURE IN THE EVALUATION OF TEMPERATURE EXCURSIONS DURING STORAGE AND TRANSPORTATION OF DRUG PRODUCTS

## **1. INTRODUCTION**

The extent of physicochemical degradation of drug products depends on factors such as product stability, how a product is stored and shipped, and how it is packaged. Temperature at which a product is stored or shipped is likely to vary during the life of the product, which can impact its stability and degradation pathways and kinetics, thereby leading to the product failing to maintain its critical quality attributes.

Mean kinetic temperature (MKT) is a way to summarize the time history of a product's temperature exposure with a single "effective" or "virtual" temperature. It 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. MKT integrates the time–temperature history by making assumptions about the kinetics of a product's chemical degradation. Therefore, MKT takes into account the fact that long temperature excursions at slightly elevated temperatures can be just as, or more, impactful than short temperature excursions at elevated temperatures.

## 2. SCOPE

This chapter applies to every link in the supply chain from the manufacturer through any entity that transports or stores a finished drug product, with the sole exception of the patient. Examples:

- · Manufacturers of drug products, radiopharmaceuticals, biological products, and biotechnological products
- Repackaging operations in which the product may be owned by a company other than the primary manufacturer
- Healthcare providers and institutions such as hospitals; outpatient, ambulatory, and urgent care centers; home health providers; vaccine clinics; emergency departments; and medical, dental, and veterinary offices
- Pharmacies including but not limited to retail, infusion/compounding (sterile and nonsterile), specialty, mail order, hospital, nursing home, and hospice
- Importers and exporters
- Wholesale distributors

• Third-party logistics providers, brokers, freight forwarders, consolidators, and other organizations involved in storage; road, rail, sea, and/or air transport services; or mail distributors that offer expedited or controlled-temperature shipping services

Manufacturers of active pharmaceutical ingredients, excipients, medical devices (with the exception of drug combination devices), and dietary supplements are not within the scope of this chapter. However, the principles and mitigation strategies presented in this chapter may be useful for materials other than finished drug products.

## 3. MEAN KINETIC TEMPERATURE

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.<sup>1</sup> Seevers et al. demonstrated that the choice of activation energy doesn't change the MKT significantly. It is not a simple arithmetic mean. The use of MKT is considered an acceptable practice for storage and can be considered for excursions during transit.

The temperatures used for calculating MKT can be conveniently collected using electronic devices that measure temperatures at frequent intervals (e.g., every 15 min). MKT can be calculated directly or the data can be downloaded to a computer for processing. Software to compute the MKT is available commercially.

The arithmetic mean of the high and low temperatures of the observation period is then used in the calculation of MKT. MKT is calculated by the following equation (derived from the Arrhenius equation):

<sup>&</sup>lt;sup>1</sup> Seevers RH, Hofer J, Harber P, Ulrich D, Bishara R. The Use of Mean Kinetic Temperature (MKT) in the Handling, Storage, and Distribution of Temperature Sensitive Pharmaceuticals in *Pharmaceutical Outsourcing*; May–June 2009, 10(3); 30–35.



- = mean kinetic temperature
- $\Delta H$ = heat of activation, 83.144 kilojoules · mole<sup>-1</sup> (unless more accurate information is available from experimental studies)
- R = universal gas constant, 8.3144  $\times$  10<sup>-3</sup> kj  $\cdot$  mole<sup>-1</sup>  $\cdot$  K<sup>-1</sup>
- = total number of storage temperatures recorded during the observation period
- = value for the temperature recorded during the first time period
- n T<sub>1</sub> T<sub>2</sub> T<sub>n</sub> = value for the temperature recorded during the second time period
- = value for the temperature recorded during the *n*th time period

[NOTE—All temperatures, T, are absolute temperatures in degrees Kelvin (K).]

Drug products in the distribution supply chain may be held at temperatures outside of their labeled storage requirements as determined by the appropriate stability data. Drug products stored either in warehouse conditions or during transportation may experience excursions from their acceptable temperature ranges. Each product excursion outside of USP excursion limits must be evaluated and its impact on the final product determined. The means of evaluation must be scientifically sound with documented justification that the integrity and quality of the drug product have not been affected. One method of analysis for examining temperature excursion is the use of MKT.

Because MKT expresses the cumulative thermal stress that a drug product experiences, it is considered an acceptable practice for storage and can be considered for excursions during transit. The calculation must be justified for use with distribution excursions by confirming that the stability-limiting characteristic of the product follows zero-order or first-order kinetics over the temperature range encountered.

## 4. APPLICATION OF MKT

Mean kinetic temperature has been misunderstood and/or misused. The most significant misuse has been utilizing 52 weeks of temperature data to calculate MKT during a temperature excursion. Drug products typically do not spend 52 weeks in a single storage location. Thus, the 52 weeks of data used in the MKT calculation would not be a true reflection of the storage time. This approach skews results and could lead a company to overlook the impact of an excursion on the drug product.<sup>1,2</sup> A closely related concern is the idea that a temperature excursion above a product's storage temperature can be "fixed" just by lowering the temperature of a warehouse for an appropriate period of time so that the resulting MKT calculation would provide an acceptable value. This ignores the fact that any degradation due to the higher temperature is not reversible.<sup>3</sup>

Mean kinetic temperature is referenced in the controlled room temperature (CRT) and controlled cold temperature (CCT) definitions in Packaging and Storage Requirements (659). Within the definitions, the temperature range for an excursion and the maximum excursion time are defined, but the time frame used for calculating MKT is not mentioned. For CRT excursions, USP recommends using 30 days for calculating MKT or the average number of days that a product remains in the holder's possession. This recommendation is based on temperature data presented by Anderson et al.<sup>3</sup> and the fact that products, on average, spend 30 days in warehouse storage in the United States.<sup>4</sup>

For CCT excursions, USP recommends using 24 h for calculating MKT. While specific products may have stability data to support excursions within wider temperature and time frames, operations involved with storage and distribution (shipping) throughout the supply chain typically do not have access to information beyond the product labeling. This includes dispensing and healthcare providers. Excursions occur and these guidelines are intended to manage these excursions while being conscious of the impact of temperature and time excursions. It is important to note that an excursion is a nonconforming event (except as previously noted when provided by the manufacturer). MKT should not be used to justify a system out of control (e.g., repeated temperature and time excursions).

	Storage Range	Acceptable Excur- sion Range	Maximum Temper- ature	Maximum Excur- sion Time (NMT)	MKT (NMT)	Time Period of Cal- culation
CRT <sup>b</sup>	20°–25°	15°-30°	40°	24 h	25°	30 days
CCT <sup>c</sup>	2°–8°	8°–15°	15°	24 h	8°	24 h

Table 1.	Use of MK	T for CRT	and CCT	<b>Excursions</b> <sup>a</sup>
Table L.				LACUISIONS

<sup>a</sup> Exposure to higher and/or lower temperatures beyond what is recommended in this chapter should be evaluated using monographs, product labels, or stability data provided by the manufacturer.

<sup>b</sup> Some CRT- labeled products may have stability issues with the higher and/or lower excursion limits. These products must be evaluated and shipped within the stability limits provided by the manufacturer.

<sup>2</sup> Anderson C, Seevers R, Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions: Proper and improper application. Pharm. Forum 2018;44(4).

<sup>3</sup> Anderson C, Seevers R, Hunt D. The use of mean kinetic temperature to aid evaluation of temperature excursions for controlled cold temperature drugs: Proper and improper application. Pharm. Forum 2019;45(5).

<sup>4</sup> Center for Healthcare Supply Chain Research. Factbook: The Facts, Figures and Trends in Healthcare (2015–2016). 86th ed. Arlington, VA: Center for Healthcare Supply Chain Research; 2016:15.

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<sup>c</sup> An article for which storage at CCT is directed may, alternatively, be stored and shipped in a cool place or refrigerated unless otherwise specified in the monograph or on the label (see (659)).

In CRT storage environments, temperature monitoring (see *Monitoring Devices—Time, Temperature, and Humidity* (1118)) captures the temperatures throughout the day (e.g., every 15 min). MKT can be calculated on an ongoing basis or anytime that there has been a temperature excursion using data going back 30 days from (and including) the high excursion temperature. 30 days must be from, and including, the high excursion temperature for the entire period of the excursion.

## Use of MKT for Controlled Cold Temperature Excursions

In CCT storage environments, temperature monitoring (see (1118)) captures the temperatures throughout the day (e.g., every 15 min). MKT can be calculated on an ongoing basis or anytime that there has been a temperature excursion using data going back 24 h from the (and including) high excursion temperature. Excursion ranges, time, and MKT within allowances should be documented and can be reviewed for compliance and trending. The excursion temperature and time allowances for CCT products are much more restrictive than for most CRT products due to the more sensitive nature of these products to temperature excursions. Each excursion should be considered a separate event. A storage or transportation system that has repeated excursions should be considered a system out of control that needs to be corrected.

Excursion ranges, time, and MKT within allowances should be documented and can be reviewed for compliance and trending. Transportation systems that are monitored may also use MKT as outlined in this chapter. For transportation systems that are not monitored (a risk-based decision), lane temperature profile mapping may include the use of MKT when evaluating risks (see *Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products* (1079)).

## 5. CONCLUSION

While every effort should be made to store and distribute drugs within their labeled temperature range, excursions may occur. The use of MKT in evaluating a short-term excursion (as defined in (659)) and the time period used for calculating MKT as recommended by USP will allow responsible management of excursions. It is important to note that excursions outside of USP allowable limits must be evaluated by the manufacturer, where conveying the excursion temperatures and time is critical to determining product disposition. MKT may not be used to justify a storage or transportation system that has repeated excursions; such a system is not in control and needs to be corrected. (USP 1-Dec-2020)

# $\langle 1118 \rangle$ monitoring devices—time, temperature, and humidity

## INTRODUCTION

This chapter provides background information about the science and technology of temperature and humidity monitoring over time. It describes the available technologies and performance characteristics, and provides recommendations for qualifying performance. The shelf life of a drug product is a function of the temperature and humidity conditions during storage and transportation, as well as the drug product's chemical and physical properties. For this reason, the ability to monitor those conditions is important in the shipping and storage of temperature- and humidity-sensitive drug products. This chapter focuses strictly on supply chain temperature- and humidity-monitoring devices, both electronic and chemical.

The storage and distribution temperatures may be different if justified by appropriate stability studies and as indicated in the labeling. The effects of humidity are typically observed over longer time periods of exposure than are temperature effects due to the barrier to moisture ingress presented by the primary and secondary drug product packaging.

The devices described in this chapter are those most commonly used to monitor the controlled storage and established distribution of drug products following Good Distribution Practices (GDP).<sup>1</sup> The chapter does not address measurement of temperature at extremes, which are temperatures above those that drugs are reasonably expected to experience in the supply chain. The types of devices described are already used in the worldwide distribution of pharmaceuticals and by other similar industries that require temperature control in distribution (for example, the perishable food, blood component, and medical device industries). Devices also may be attached to individual items for the end user (for example, vaccine vials in the World Health Organization (WHO)/UNICEF global immunization program).<sup>2</sup> Appropriate recycling practices should be followed for all devices as required by local regulations.

<sup>&</sup>lt;sup>1</sup> PDA Technical Report 52 (TR 52) Guidance for Good Distribution Practices (GDPs) For the Pharmaceutical Supply Chain.

<sup>&</sup>lt;sup>2</sup> World Health Organization (WHO)-UNICEF Policy Statement on the Implementation of Vaccine Vial Monitors: The Role of Vaccine Vial Monitors in Improving Access to Immunization, http://whqlibdoc.who.int/hq/2007/WHO\_IVB\_07.04\_eng.pdf.

## **TEMPERATURE-MEASUREMENT DEVICES**

## **Alcohol or Mercury Thermometers**

These devices are based on the change in volume of a liquid as a function of temperature. Both types of thermometers can be designed to indicate the maximum and minimum temperatures (see *General Notices, 6.80.30. Temperature Reading Devices* for more information). Historically, these types of thermometers are used in a laboratory setting or in a pharmacy, rather than during supply chain monitoring. Alcohol thermometers can have a precision as good as 0.01°, but they must be quite large to measure temperatures in ranges of more than a few degrees.

Mercury thermometers are typically used in the ranges from 0° to 50° with a precision of about 0.1°. Some local regulations apply to mercury-based thermometers, and many states and local agencies have legislated or developed collection or exchange programs for mercury-containing devices. The U.S. Environmental Protection Agency also issues regulations requiring industry to reduce mercury releases to air and water, and to properly treat and dispose of mercury wastes to avoid potential health hazards.<sup>3</sup> Globally, Health Care Without Harm and WHO are co-leading a Health Care Initiative Products Partnership to reduce demand for mercury-containing devices by at least 70% by 2017 and to shift production to accurate, affordable, and safer nonmercury alternatives.<sup>4</sup>

Both alcohol and mercury thermometers are more fragile than other temperature-measuring devices described in this chapter.

#### **Infrared Devices**

This device is used for measuring the infrared (IR) radiant heat from the article whose temperature is being determined, and the IR reading varies as a function of the object's temperature. The advantage of this type of device is that the article may be at some distance from the IR sensor. IR devices may give inaccurate higher or lower temperature readings because of the surface characteristics of packages (e.g., black vs. white surfaces), and they also have the potential for operator error because of incorrect use of the IR reader (improper angle).

#### **Resistance Temperature Detectors**

The resistance temperature detector (RTD) is based on the change in electrical resistance of a material as a function of temperature. The precision and accuracy of an RTD depend on the quality of the electronics used to measure the resistance. Although RTDs are among the most stable and accurate temperature sensors, their accuracy may change with the age and temperature of the device because its electronic components are affected by age and use. Although all temperature-measurement devices should be placed on an appropriate calibration program as recommended by the manufacturer or user of the device, this calibration is particularly important for RTDs.

#### Solid-State Devices

Solid-state devices are based on the effect of temperature on either an integrated circuit (see *Thermistors*) or a micromechanical or microelectrical system. These devices are commonly referred to as data loggers, and can attain high precision and have the advantage of producing a digital output.

#### Thermistors

A thermistor is a semiconductor device whose resistance varies with temperature. Thermistors are able to detect very small changes in temperature and are accurate over a broad range of temperatures.

#### Thermocouples

Thermocouples are based on the change in the junction potential of two dissimilar metals as a function of temperature. Many metal pairs can be used, and each pair provides a unique range, accuracy, and precision. Precision and accuracy depend on the quality of the electronics used to measure the voltage across both metals and the type of temperature reference used.

#### **Thermomechanical Devices**

Thermomechanical devices are based on the change in length of a solid material as a function of temperature. An example of such a device is a mechanical spring, which expands or contracts as a function of temperature, thus opening and closing an electrical circuit or moving a chart pen. Typical examples are chart recorders used in cold rooms.

<sup>&</sup>lt;sup>3</sup> http://www.epa.gov/mercury/.

<sup>&</sup>lt;sup>4</sup> http://www.noharm.org/.

## **ELECTRONIC TIME-TEMPERATURE HISTORY RECORDERS**

These recorders use one of the electronic temperature-measurement technologies described above and create a record of the temperature history experienced.

#### **Electronic Time-Temperature Indicators**

Electronic time-temperature indicators (TTIs) can be designed to alarm after a cold excursion, heat excursion, or after multiple temperature excursions and can provide a visual alarm by a colored light or LCD. The alarm(s) are generally programmable and can display conditions such as date, time, temperature, and duration of the alarm. A certificate of calibration is issued for individual units or lots. Multiple-use devices should have a calibration schedule, but single-use devices can rely on manufacturers' certificates of calibration.

## **Electronic Temperature-Data Loggers**

Electronic temperature-data loggers are recorders that monitor the temperature at programmable intervals and save the temperature history to a peripheral system, such as a personal computer. In addition, data loggers can record humidity using sensors described below. Electronic recorders monitor and save temperature values representative of the cumulative temperature history over a period of time and therefore have the advantage of being able to calculate the mean kinetic temperature (MKT)<sup>5</sup> based on the measurements. Data loggers equipped with transmitting devices (hardwired or radio transmission) can be used to monitor the temperature and humidity of a product while in transit and can download the recorded data when the data loggers arrive at a destination. Data loggers are increasingly required by worldwide ministries of health as part of a standard quality system for GDPs. Based on their communication capabilities, data loggers can be grouped into several different categories.

## **Radio-Frequency Data Loggers**

In addition to data loggers that require a hardwired connection to a base unit or a computer, in recent years companies have adapted wireless (radio-frequency or RF-enabled) temperature and humidity recorders. The effects of radio-frequency identification (RFID) use on biologics have been studied on a variety of blood, blood components, monoclonal antibodies, and vaccines, and have demonstrated no effect.<sup>6</sup> These loggers are integrated with chips capable of wireless RF communications that constitute the RFID sensor tags. The RFID chip inside the tag can be either active, which requires battery power for operation, or passive, which requires a nonzero RF field created by the RFID interrogator host unit (commonly called the reader) in the vicinity of the tag. RFID-enabled sensor tags (temperature and/or humidity) have the added capability of conveying recorded temperature history wirelessly to a host computer or database for seamless downstream processing. Multiple passive and active standards exist to control the communication between the tag and the host unit, including ISO-18000-6C,<sup>7</sup> ISO-18000-7,<sup>8</sup> ZigBee,<sup>9</sup> IEEE 802.11,<sup>10</sup> and many proprietary standards.

When choosing between active and passive technologies, one needs to know that active technologies typically have extended communication range and memory capabilities at the expense of a higher price. Currently, reading ranges extend to 100 m and with repeaters longer distances can be achieved. Whether the communications circuitry is passive or active, these RF loggers still are electronic temperature recorders, which means their sensor circuitry uses external power from batteries or other sources.

A completely passive wireless RFID tag with an antenna capable of functioning as a sensor has been developed. The tag uses resonant antenna structures of RFID tags that are coated with specific sensor films. The passive wireless RFID tags act like analog sensors that, when interrogated by a wireless reader, show the instantaneous temperature. The film changes the antenna's reflection characteristics based on the monitored environmental variable (such as temperature and/or humidity), which then is decoded by the reader. The sensor film can be designed to work with different variables such as temperature, humidity, and various gas and chemical vapors. Although they lack some of the memory functionality included in electronic recorders, passive wireless sensors are relatively cost effective compared to data loggers and can be considered for item-level applications.

## **CHEMICAL TEMPERATURE INDICATORS**

Chemical temperature indicators are relatively cost effective compared to electronic data loggers and can be considered for item-level applications. There are two basic types of chemical temperature indicators: 1) a threshold indicator that responds at a specific temperature and 2) a TTI that responds to cumulative heat exposure.

<sup>&</sup>lt;sup>5</sup> The Use of Mean Kinetic Temperature (MKT) in the Handling, Storage, and Distribution of Temperature Sensitive Molecules. R. H. Seevers, J. Hofer, P. Haber, D. A. Ulrich, R. Bishara. Pharmaceutical Outsourcing, May/June, 30–37, 2009.

<sup>&</sup>lt;sup>6</sup> Effects of Radio Frequency Identification-Related Radiation on In Vitro Biologics. I. Uysal, C. Hohberger, R. S. Rasmussen, D. A. Ulrich, J. P. Emond, A. Gutierrez. PDA Journal of Pharmaceutical Science and Technology, Vol. 66(4), July/Aug, 333–345, 2012.

<sup>&</sup>lt;sup>7</sup> ISO/IEC 18000-6:2010–ISO/IEC 18000-6:2010—Information technology– Radio frequency identification for item management–Part 6: Parameters for air interface communications at 860 MHz to 960 MHz.

<sup>&</sup>lt;sup>8</sup> ISO/IEC 18000-7:2009—Information technology–Radio frequency identification for item management–Part 7: Parameters for active air interface communications at 433 MHz.

<sup>&</sup>lt;sup>9</sup> IEEE 802.15.4—Wireless Medium Access Control (MAC) and Physical Layer (PHY) Specifications for Low-Rate Wireless Personal Area Networks (LR-WPANs), 2003.

<sup>&</sup>lt;sup>10</sup> IEEE 802.11—Wireless Local Area Networks (LANs), 2007.

#### **Chemical Temperature Threshold Indicators**

These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are reversible or irreversible and are suitable for high or low temperatures. Temperature threshold indicators do not include any specified time delay to show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature.

Ascending-Temperature Threshold Indicators—Ascending-temperature threshold indicators are supplied as self-adhesive labels or cards and are normally composed of a heat-fusible compound that melts at the critical temperature. Melting of the compound gives rise to a color change or color development. Other types are provided as inks, lacquers, pellets, or crayons. Ascending-temperature threshold indicators are available from 0° to more than 200° and as many as 10 temperatures on a single unit. Some ascending-temperature threshold indicators used to monitor frozen or refrigerated temperatures require an activation step (such as a pull tab or a reservoir that is ruptured by pressure).

**Descending-Temperature Threshold Indicators**—Descending-temperature threshold indicators show a response when exposed to temperatures below a threshold. These indicators do not include a specific time delay to show a response, and the response is typically caused by the time required for solidification of a liquid at the threshold temperature. Solidification of a liquid causes a visual change in the indicator. Examples include: 1) the expansion of the liquid to crack an ampule and release a colorant, 2) contraction of the liquid to mix components to develop color, or 3) aggregation of colloidal particles to change color.

#### Chemical Time–Temperature Indicators

These indicators, sometimes referred to as time-temperature integrators (TTIs), include systems in which a reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (discussed above). The reactions generally are irreversible—once a color change, color development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state, but lower temperatures (refrigeration) will slow the color change. The accuracy and precision of these indicators depend, to some extent, on human interpretation. Some versions of chemical indicators have been prepared in a bar code format and can be read with bar code readers. Other developments include reading a chemical indicator with an imaging device such as a camera in a smart phone.

TTIs do not directly reflect the status of the drugs to which they are attached. In actual practice, the characteristics for degradation of a particular drug are known from accelerated and real-time stability studies that follow internationally accepted guidelines such as PDA TR 53<sup>11</sup> to guide selection of a suitable TTI.<sup>12</sup> The activation energy of the TTI is not required to exactly match the activation energy of the degradation of the drug being monitored, and the latter, in fact, may not be known precisely. Therefore, the TTI should be chosen to provide an early warning if the drug is exposed to an excessive heat load before the expiration date.

An important characteristic of chemical TTIs is the precision with which the end point can be determined. For TTIs that change color, a reference color normally brackets the active portion of the TTI to show the end point color, which simplifies TTI interpretation. Accuracy can vary widely with the control and quality of the manufacturing process. Some TTIs are manufactured by procedures that comply with Quality System Regulations for Medical Devices. As discussed below in *Calibration of Temperature- and Humidity-Monitoring Devices*, it is not possible to calibrate any individual single-use device because the test is, by the nature of the TTI, necessarily destructive. This is analogous to any pharmaceutical product because each dose cannot be calibrated or validated, but validated processes should be used in the manufacturing process.

The two types of TTIs are partial-history indicators and full-history indicators. Partial-history TTIs provide a time- and temperature-dependent response when the temperature exceeds a predetermined value. A partial-history indicator normally is composed of a dyed, heat-fusible compound that diffuses along a porous strip or wick when the temperature exceeds the melting point of the compound. The diffusion process of the compound down the wick is temperature dependent, and therefore the partial-history TTI provides a time and temperature response above the melting point of the compound. Migration of the compound down the wick is temperature dependent, and therefore the partial-history TTI provides a time and temperature response above the melting point of the compound. Migration of the compound down the wick stops when the indicator is moved to a lower temperature at which point the compound solidifies. These TTIs normally have one or more viewing windows to monitor the length the dyed compound from the wick or rupturing a reservoir that contains the dyed compound. Other indicators do not require activation and must be stored below the melting point of the compound before use. These partial-history TTIs can have durations (service life) anywhere from several hours to several years. Full-history TTIs provide a continuous response to temperature. They change color or physical appearance as a result of exposure to time, and the rate of change increases with temperature so they are sensitive to cumulative heat exposure. Full-history TTIs are responsive to MKT (Ref 1079) and typically are single use, irreversible, and disposable because once the color changes it will not revert to the original color.

#### Chemical–Physical Time–Temperature Indicators

This type of TTI is based on a temperature-dependent diffusion or chemical reaction process. It consists of a pressure-sensitive tape device that is composed of an indicator tape and an activator tape. In one example, the indicator tape contains a dye precursor dispersed in a polymer carrier. The activator is incorporated into an adhesive on the activator tape. Laminating the activator tape over the indicator tape causes activation. A color change or readable message occurs as the activator migrates

<sup>&</sup>lt;sup>11</sup> PDA Technical Report 53 (TR 53) Guidance for Industry: Stability Testing to Support Distribution of New Drug Products, https://store.pda.org. <sup>12</sup> ASTM F1416–96 (2008) Standard Guide for Selection of Time Temperature Indicators.

into the indicator as a function of temperature and time. Other approaches to develop color changes include the use of a pH indicator or the etching of aluminum by the activator tape.

#### **Chemical Polymerization–Based Time–Temperature Indicators**

This type of TTI uses a solid-state polymerization process in which a color develops intensity as a function of time and temperature. The color evolution is caused by the polymerization of a colorless monomer to a highly colored polymer. These TTIs can be applied by a print process that permits direct integration into a product label or stand-alone label. Because this type of TTI does not require activation, it must be shipped from the manufacturer on dry ice or under frozen conditions and stored at temperatures according to the manufacturer's instructions, normally below  $-24^{\circ}$  before use. Chemical polymerization–based TTIs can be designed to reach the end point as quickly as weeks at refrigerated temperature or as long as years at controlled room temperature.

#### Chemical Enzyme–Based Time–Temperature Indicators

This type of TTI uses an enzyme-catalyzed color-generating reaction that occurs as a function of time and temperature. The color change is caused by an enzyme reacting with a substrate, accompanied by a change in pH. The enzyme and substrate are in separate solutions in adjacent compartments. Breaking the barrier between the two compartments and mixing the two solutions activates the TTI.

## Chemical-Organic Pigment–Based Time–Temperature Indicators

This type of TTI uses an organic pigment that is activated by exposure to ultraviolet light to develop a dark blue starting color. A filter is then placed over the label to protect it from deliberate or accidental reactivation. The colored pigment fades over time as a function of temperature.

## **RELATIVE HUMIDITY MEASUREMENT TECHNOLOGIES**

Relative humidity is the ratio of the partial pressure of water vapor in air to the vapor pressure of saturated air at a given temperature. In other words, the relative humidity is the amount of water vapor present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature. Extensive tables of relative humidity data are available. Devices for measuring relative humidity are called hygrometers. Several different technologies exist for measuring relative humidity.

## **Sling Psychrometer**

The simplest type of hygrometer is based on the temperature difference observed between two identical thermometers, one ordinary and one with a wet cloth wick over its bulb. The two thermometers are whirled at the end of a chain, and the evaporation of water from the wick cools (based on evaporative cooling) the wet-bulb thermometer. The temperature difference between the wet and dry thermometers then is compared to a table specific to that psychrometer based on dry-bulb temperature, and the relative humidity is determined.

### **Hair Hygrometer**

This type of device is based on the fact that the length of a synthetic or human hair increases as a function of the relative humidity. This change is used to move an indicator or affect a strain gauge. A hair hygrometer can be accurate to  $\pm 3\%$ , but it is unable to respond to rapid changes in humidity and loses accuracy at very high or very low levels of relative humidity.

#### Infrared Hygrometer

This type of hygrometer determines relative humidity by comparing the absorption of two different wavelengths of IR radiation through air. One wavelength is absorbed by water vapor and the other is not. This type of hygrometer can accurately measure relative humidity in large or small volumes of air. It is sensitive to rapid changes of humidity and can be integrated with an electronic data-handling system.

## **Dew Point Hygrometer**

This type of device uses a chilled mirror to determine the dew point of an air sample. The dew point is the temperature at which water vapor in the air begins to condense; that is, the temperature at which the relative humidity is 100%. The relative humidity can be calculated from this measurement and an accurate measurement of the ambient temperature. The dew point hygrometer is the standard against which most commercially available instruments are calibrated.

#### **Capacitive Thin-Film Hygrometer**

The principle of this type of hygrometer is that the dielectric of a nonconductive polymer changes in direct proportion to the relative humidity. This change is measured as a change in capacitance. This type of hygrometer is accurate to  $\pm 3\%$ .

#### **Resistive Thin-Film Hygrometer**

This type of hygrometer is similar to the capacitive thin-film type because it uses the effect of changing relative humidity on an electric circuit. In the resistive thin-film hygrometer the sensor is an organic polymer whose electrical resistance changes in logarithmic proportion to the relative humidity. This type of hygrometer is accurate to  $\pm 5\%$ .

### **CALIBRATION OF TEMPERATURE- AND HUMIDITY-MONITORING DEVICES**

Thermometers and hygrometers that are used to provide data about the temperature and humidity exposure of a product must be suitable for their intended use. Specifically, they must be appropriately calibrated. A calibration program assures the user of the monitoring device that the device has been tested before use either by the manufacturer or the user to assess the suitability for its intended use. Calibrations should be performed with appropriate frequencies to support ongoing use. Monitors used in manufacturing, storage, and transport of drug products should be properly qualified by their users to ensure that the monitors have been received and maintained in proper working order. It is acceptable to use the calibration performed by the device's manufacturer based on the certificate of calibration and expiration date.

For temperature- and humidity-monitoring devices, measurement accuracy refers to the closeness of the value obtained with a particular device and the true value of the object or environment under measurement. In practice, this is determined by comparison with a device that has been calibrated against a standard that is obtained from or is traceable to the National Institute of Standards and Technology or a comparable national metrology organization.

Any monitor takes time to respond to a change in the temperature or humidity. Measurement responsiveness typically is defined in a device's specifications for its operating range. Different data recording intervals are appropriate for different monitoring applications and should be based on supply chain length (for example, transportation via ocean may require 30-min intervals, but 15-min intervals may be suitable for air transport). Most commonly, time accuracy is expressed as a  $\pm$  percentage of total duration of the recording period. For pharmaceutical applications, a  $\pm 0.5\%$  time accuracy is adequate.

Single-use electronic and chemical indicators should follow Good Manufacturing Practices with appropriate testing controls. Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots. For TTIs that calculate MKT, the performance of a batch can be assessed statistically by subjecting an appropriately sized sample to elevated temperature conditions for a set period of time and observing the results. Manufacturers should adopt appropriate acceptance criteria. It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or gualification.

## THE USE OF HISTORICAL TEMPERATURE DATA

Although historical geographic and seasonal trends may be used as a planning tool in selecting among the types of temperature- and humidity-monitoring devices, outside ambient temperatures are not necessarily reliable indicators of the temperatures experienced by different items in the distribution chain. For example, studies have reported important departures from ambient temperatures on summer days for mailboxes, trucks, and warehouses.<sup>13</sup> Therefore, using lane-specific temperature monitoring is beneficial when manufacturers and shippers develop an ambient profile and can be a valuable consideration for a risk-based approach to maintain product quality.<sup>14</sup>

A drug product's quality (identity, strength, and purity) may be notably influenced by variations in temperature and humidity over the course of its shelf life, so manufacturers should appropriately monitor those environmental conditions. Pharmaceutical manufacturers perform stability testing to carefully evaluate the effects of temperature and humidity on their products. The packaging, shelf life, and storage and transportation conditions recommended for a product are chosen based on the results of these stability studies. Temperature effects can happen rapidly; therefore, temperature monitoring should be implemented on a risk-based approach taking the product stability, distribution route, mode of transportation and potential risks that may compromise the quality of the product into account. Relative humidity effects occur over a much longer time frame; humidity monitoring can be omitted when the drug product is sufficiently protected by the primary container proven by sound stability studies. Humidity monitoring is recommended when special environmental restrictions concerning the humidity are defined for the drug product.

<sup>&</sup>lt;sup>13</sup> Okeke, C.C. Medwick, T., Bailey, L.C., and Grady L.T. Temperature and Humidity Conditions During Shipment in International Commerce, *PF* 25(2) Mar.–Apr. 1999.

<sup>&</sup>lt;sup>14</sup> ISTA 7E Standard, http://www.ista.org.

Not official text. Please refer to the currently official version of the applicable USP–NF standard for compliance purposes.