

Technical Report No. 46

Last Mile: Guidance
for Good Distribution

Practices for
Pharmaceutical Products
to the End User



PDATM

2009

Last Mile: Guidance For Good Distribution Practices For Pharmaceutical Products To The End User TaskForce

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Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User

Technical Report No. 46

ISBN: 978-0-939459-26-1

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1.0 Introduction

Medicinal products and devices requiring controlled temperature storage are subject to highly variable distribution environments. The manufacturer distributes in a well-controlled shipping lane that is routinely monitored for temperature excursions and is subject to uniform, stringent Good Distribution Practices (GDP). Conversely, shipping/distribution regulations vary widely from location to location, and uniform guidelines are lacking. This divergence has proved challenging for the pharmaceutical industry.

Good Distribution Practices are a natural extension of Good Manufacturing Practices, Good Clinical Practices and Good Laboratory Practices, among other requirements for manufacturers of medicinal products and devices. Regulations and guidance for each different custodian in the supply chain can vary by country, state and province. For example:

- The United States Pharmacopeia (USP) Chapter <1079> Good Storage and Shipping Practices offers guidance and procedures on maintaining pharmaceutical integrity throughout the supply chain to the patient.
- The World Health Organization (WHO) provides *Good Distribution Practices for Pharmaceutical Products* (WHO Technical Report Series, No. 937, 2006, Annex 5).
- The European Union issued *Guidelines on Good Distribution Practice of Medicinal Products for Human Use* (94.C 83/03) and Council Directive on the *Wholesale Distribution of Medicinal Products for Human Use* (EEC 9225).
- Canada developed *Guidelines for Temperature Control of Drug Products during Storage and Transportation* (Guide 0069). Additional guidance has been prepared in Ireland, Singapore, Brazil and Austria.
- *PDA Technical Report No. 39, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment* (TR-39) provides global and industry perspectives with further documentation of quality systems.
- Argentina passed Law # 26492, *Regulación de la cadena de frío de los medicamentos*, requiring all pharmaceutical products for human or veterinary use containing temperature-sensitive active ingredients to have a temperature indicator attached by the manufacturer to verify that the cold chain for the product has not broken when it is received by the consumer.

“Last mile” is an often-used logistical term, and in the shipping of pharmaceutical products, is considered to start from the manufacturing facility handoff to the wholesaler or pharmacy and continue to delivery to the end user. This may include thousands of miles or the last few feet until the product is administered. The “last mile” to the point of patient administration can prove difficult to manage. Healthcare professionals, patients and most retailers are, by and large, unaware of the challenges experienced during the “last mile.” Invariably, detailed and practical knowledge and information related to any product excursions beyond compendial ranges are unknown or unavailable to the end user.

This guidance document serves to complement the information provided in TR-39 by going beyond manufacturer-focused issues and addressing those issues specifically encountered within the “last mile.”

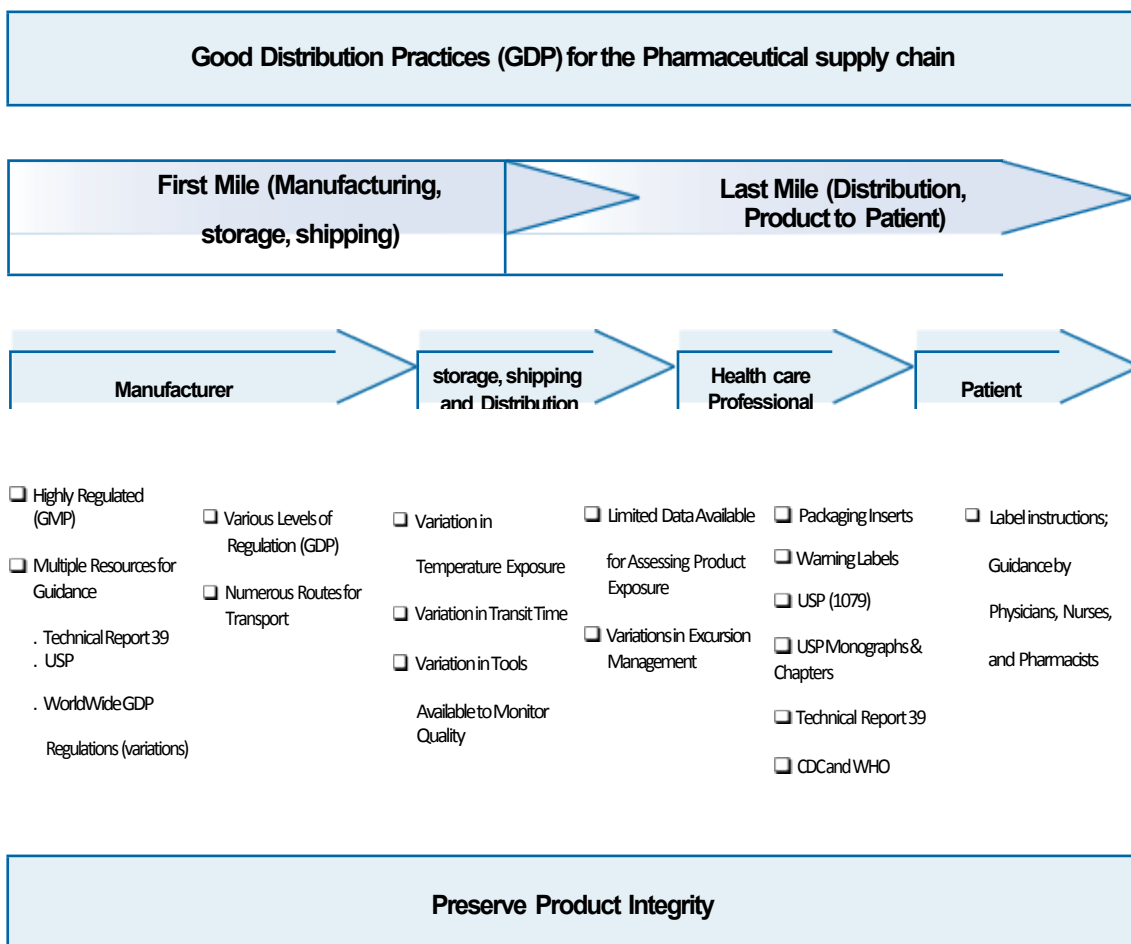
1.1 Purpose

The purpose of this document is to provide guidance to all involved in the “last mile” regarding the proper handling and storage of controlled-temperature medicinal products and devices.

1.2 scope

This document is designed to provide best practices related to the preservation of controlled-temperature and humidity requirements of pharmaceutical products and devices up to, and including, administration by the end user. The diagram below outlines the challenges faced in maintaining product integrity through the pharmaceutical supply chain.

Figure 1.2 Quality system Distribution Practices: From the First Mile to the Last Mile



2.0 Glossary of Terms

For the purposes of this technical report, the following terms are used and are accompanied by their synonyms, where applicable.

cold chain Tolerance Groups

This concept expands the “normal” definition of cold chain to include all products that need to be stored below 25°C and also introduces the ancillary terms “ambient temperatures” and “controlled ambient.”

common carrier

Transportation available to the public that does not provide special treatment to any one party and is regulated as to the rates charged, the liability assumed, and the service provided. A common carrier must obtain a certificate of public convenience and necessity from the Federal Trade Commission for interstate traffic. *(I)*

continuous Monitoring

A mechanism by which temperature is regulated and recorded without interruption. It is recommended that if the system is not alarmed, it must be checked at predetermined time intervals. The time intervals should be determined by the facility but should be adequate enough to provide meaningful data of the temperature change overtime.

customer

1) In distribution, the trading partner or reseller, and 2) Indirect-to-consumer, the end customer or user. *(I)*

Downstream

Refers to the demand side of the supply chain. Downstream consists of one or more companies or individuals who participate in the flow of goods and services moving from the manufacturer to the final user or consumer. This is the opposite of upstream. *(I)*

Extended Producer Responsibility (EPR)

Refers to a legislative requirement that packaging manufacturers “take back” their packaging, or otherwise ensure (through a tax) that it is collected and properly disposed of.

International standards organization (Iso) container

ISO containers are shipping containers manufactured according to specifications from the International Standards Organization. They may

also be referred to as “sea containers” or “inter- modal containers. (2)

The Last Mile

This is a multidimensional cross-industry term that defines a point in the supply chain where the product or service directly faces the customer, end user or patient.

Mean Kinetic Temperature (MKT)

The single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation. It is not a simple arithmetic mean.

Pedigree, e-pedigree

A pedigree is a record, containing information regarding each transaction, resulting in a change of ownership of a prescription drug, from sale by a manufacturer, through acquisition and sale by a wholesaler, until final sale to a pharmacy or person furnishing, administering or dispensing the prescription drug.

Peltier Device

Peltier devices are small, solid-state ceramic and doped-semiconductor sandwiches designed to function in small cooling and heating applications. The devices can be “stacked” for greater cooling/heating but do draw considerable power. The advantage of these devices is that there are no moving parts, no maintenance, no refrigerant gasses, no noise, and no vibration. Disadvantages may include: high cost, fragility, and scalability, in addition to the aforementioned high power draw.

Phase change Material (PcM)

A physical material that stores and releases thermal energy when freezing or melting. A PCM releases energy when freezing [latent heat energy] and absorbs energy when melting.

Qualified shipping Packaging

Packaging that has been subjected to documented testing that demonstrates with a high

degree of assurance that a specific process will meet its predetermined acceptance criteria. Due to the “real world” nature of transportation, a qualified process may change overtime, requiring appropriate monitoring. (3)

Radio Frequency Identification (RFID)

Is an automatic technique for identifying objects using radio frequency transmissions. An RFID system generally consists of a tag, reader, antenna and software. An RFID tag is simply another type of data carrier. Essentially, tags comprise a semiconductor chip with memory, processing capability and a transmitter connected to an antenna (aerial).

Reverse Logistics

The process of planning, implementing and controlling the efficient, cost-effective flow of raw materials, in-process inventory, finished goods and related information from the point of consumption to the point of origin for the purpose of recapturing value or proper disposal. (4)

shipping Lane

An established route of transportation between a specific point of origin to a specific destination. More defined routes will consistently use the same combination and types of transportation vehicles and transfer procedures, but this may not be observed through all shipping lanes throughout the last mile.

supply chain

The chain of events or process which includes all

storage and movement of raw materials, work-in-process inventory, and finished goods from point-of-origin to point-of-consumption.

Upstream

Refers to the supply side of the supply chain.

Upstream partners are the suppliers who provide goods and services to the organization that are to satisfy demands, which originate at the point of demand or use, as well as other flows, such as return product movements, payments for purchases, etc. This is the opposite of downstream. *(1)*

3.0 Distribution of Temperature-sensitive Pharmaceutical Products

The distribution of temperature sensitive pharmaceutical products is a critical link in the chain of processes required to move products from early discovery to patient use. Factors that impact the distribution are discussed below.

3.1 Transportation conditions for Last Mile Logistics

Transportation conditions are dependent upon many factors, including available technology, seasonal hot/cold and random, severe weather events. There are several layers of protection that should be considered when shipping that are related to time and mode, as well as monitoring and intervention capability. Generally, there are four modes for transportation: air, truck, ocean vessel and rail. The three modes of transportation considered most pertinent to the last mile are: air, truck, and sea and are discussed below.

3.1.1 aircraft

Currently, while many aircraft are equipped with air conditioning ability, standard passenger and cargo aircraft are not designed for temperature control. Air temperature inside the cargo holds on properly equipped aircraft can be monitored and influenced, but not controlled in the way that a Temperature Control Unit (TCU) can control the temperatures in a truck or compressor-powered container. The aircraft does, however, have some ability to warm the cargo holds using engine heat.

Pressure in aircraft cargo holds during flight can be set to a comfortable level for living creatures. At the standard altitude of 20,000 feet, the outside weather-ambient pressure is roughly 2 psi. Internal pressure is set at a level consistent with 8,000 feet. In particular, the cargo holds in many commonly used aircraft types can be pressurized throughout flight to a “cabin altitude” of no higher than 8,000 feet, which corresponds to a pressure of approximately 11 psi (compared to 14.7 psi at sea level). This pressure difference may be significant for the seal integrity of certain packages.

Due to the tremendous mass of an airframe, generating enough heat to sufficiently warm each entire cargo hold and maintain a narrow stabilized temperature range (e.g., 2-8°C) within the entire hold is costly in terms of fuel and time. Thus, an aircraft can be conditioned during the ongoing conduct of its flight operations, not prior to loading/departure, as is common with other modes of transport. For mixed-use aircraft, temperatures within aircraft cargo holds below the main deck may also vary front to back, top to bottom, in proximity to doors, and in proximity to the skin of the aircraft.

Generally, aircraft that are equipped with some temperature-control capability are able to warm the cargo areas with enough speed to minimize impact on active dry-ice containers and passive packaging, so that the product within them is protected for the duration of the flight. New, active container technology that is controlled by battery-powered compressors has been shown to be able to maintain a stable temperature within the container without regard to the variations of temperature within the cargo hold of the aircraft.

3.1.1.1 The 2009 Transportation security administration cargo screening Requirement

To implement the recommendations of the 9/11 Commission Act of 2007, the U.S. Transportation Security Administration is required to establish a system to screen 50% of air cargo transported on passenger aircraft by February 2009 and 100% of air cargo transported on passenger aircraft by August 2010. All cargo must be broken down, and the individual pieces must be screened prior to being loaded onto a passenger aircraft. Supply chain partners should work closely with each other to fully understand the impact of this program on existing processes and systems and should take the necessary measures to ensure continual product integrity.

3.1.2 Truck

Areas of consideration specific to ground-truck transportation are: the type of truck (temperature control [refrigerated] dry van) versus the expenses associated with protective packaging, refrigerated truck specifications/qualifications, monitoring methods, and cargo load configuration, as well as route, length of shipment and contingency plans.

When a refrigerated truck is used, it is important to ensure that it is well maintained and qualified to be able to control temperatures within the required range. When practical, also consider the truck's ability to operate in the ambient conditions it will encounter on the specified route. Then, select a monitoring technique to ensure that accurate temperature data is obtained. Coordinate monitoring and shipment procedures carefully with the selected carrier. Load planning is essential. The efficient operation of truck refrigeration systems depends on unimpeded airflow around the entire load, including both sides, underneath, in front and at the rear of the cargo hold. Without constant and unimpeded airflow to all areas around the cargo, the truck's ability to control air temperature stability is reduced. This increases the likelihood of unplanned variations of temperature within the cargo area and the chances of impact to the freight itself. A well-planned route can reduce the extremes of ambient heat and cold that might otherwise be encountered. In seasons of peak heat or cold, consider timing routes, including load and unload events, so that the truck avoids the peak heat / cold of the day. Another option to consider is routing around desert or high mountain environments, when appropriate. Finally, to complete due diligence, prior to beginning a movement, plan for contingencies along the route. Predefine contingency events; for example, vehicle breakdown, TCU malfunction, or temperature excursions. Consider how decision makers will know when a contingency event has occurred and what options are available for responding, depending on where the event occurred along the route. Depending on the level of risk, consider precoordinating with service locations along the route, when possible, to ensure a complete understanding of the service they offer and to obtain contact information, particularly for after-hour events, to enable timely action.

3.1.2.1 shipping containers

Two major categories of shipping containers available for use in air or ground transports are: passive containers/packaging systems and active containers/packaging systems. Passive systems consist of an insulated container and a finite amount of coolant in the form of chilled or frozen gel packs or dry ice. Since the amount of coolant is finite, passive systems will keep products at the desired temperature for a certain amount of time, which is dependant upon the temperature of the environment to which the system is exposed. Active systems use a variable and a renewable source of energy to maintain the

temperature inside an insulated container. In addition, active systems are thermostatically controlled and are able to respond to the temperature of the environment by producing more or less cooling and/or heating, when required. Examples of active systems are those using compressors (refrigerated trucks, refrigerated ocean containers and some new airline containers with battery-powered cooling

and heating units, or solid state, "Peltier devices") and those using thermostatically controlled fans to regulate the amount of cooled air produced by dry ice heat exchangers, which are used to cool the insulated container.

Any of these can be used effectively when their use is considered within the context of the chosen transportation plan and the product requirements. Active or passive wraps/blankets can also be used, as required, to protect against the effects of a particular weather condition, or when exposure cannot be sufficiently reduced.

3.1.3 sea

Sea containers (also referred as ISO containers or intermodal containers) can now be equipped with powerful heating/refrigeration equipment and efficient bottom-air delivery systems that offer better temperature control. By conducting efficient loading practices, a uniform temperature throughout the payload can be achieved and maintained for any outside environmental conditions. This mode of transport also makes door-to-door shipments possible with minimal handling of the payload, reducing the risk of physically damaged products and exposures to temperatures outside of the required range.

The main downside of sea container transport is the lack of visibility during the ocean transport portion of the trip, or oftentimes the entire trip. Sometimes, information regarding the status of the refrigeration unit, the temperature inside the container, and even the location of the container is not available for weeks, thus putting the payload at risk if a failure of the equipment or a human error occurs during transport.

Sea containers rely on external power to run the refrigeration unit; consequently a break in the cold chain may occur each time the box is moved from one mode of transport to another. Even though these containers are insulated, the temperature can quickly go out of the required range, because of the containers' high surface-area-to-volume ratio. Loading and unloading the ship should be performed according to the SOPs designed to document and limit the amount of time that the container is disconnected from a power source. The effect of this maximum amount of time, based on historical extreme temperature conditions for the ports being utilized, should be understood to assure that proper temperatures are maintained during this critical step in the process.

Some factors to consider when shipping by sea are: the shape of the equipment, the procedures in place for all the parties involved, and the ability to track and monitor the shipment for quick corrective action when needed.

3.1.4 Implications of Weather

Freight shipped by air may experience different conditions due to the chosen transportation system's vulnerability to the impacts of weather. The most common challenges are in the transfer of freight between modes of transport during the course of the shipment from the shipper to the consignee. For example: a truck will pickup the product, then move the product to the airport, and then freight is processed and loaded onto an airplane. At the destination port, the freight is removed from the airplane, processed, loaded onto a truck, and moved to final delivery. Conditions including weather condition exposure time must be considered for all of the following events:

- Loading/pickup – the conditions on the dock/loading area
- Truck movement – can be controlled by using a properly qualified refrigerated truck

- Processing (export) – may include open inspections or extended wait times. These can often be reduced with prior planning and coordination.
- Processing (loading aircraft) – weather exposure
- Flight – consider route/duration of transport and temperature, depending on the container system being used. Time of flight may also be a factor for the leg of the shipment where the product is placed. The temperature within an aircraft cargo hold being used for the first time that day will be at the same temperature as the external environment. For example, during the winter, it may take several hours of flight time to condition the airframe to stabilize at a comfortable temperature, as the warm air from the conditioning system works to warm the existing cold air and the cold aircraft.
- Unloading – weather exposure
- Processing (import) – may include open inspections or extended wait times. These can often be reduced with prior planning and coordination.
- Processing (loading truck) – weather exposure
- Truck movement – during the last mile, a properly qualified refrigerated truck may not be available.
- Unloading/delivery – for the last mile, this may often involve exposure to weather or worse, left inside a mailbox or other unprotected container for several hours.

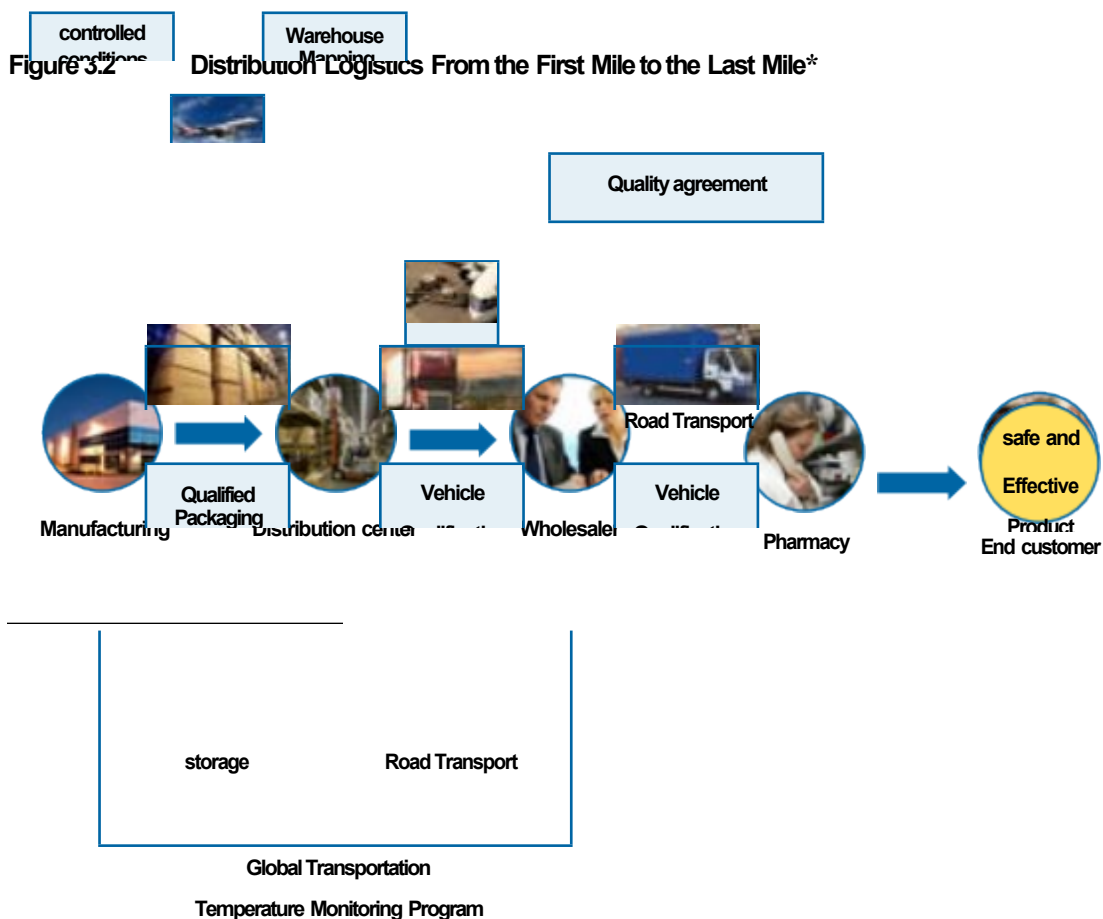
The length of time outside a controlled environment as well as the ambient conditions at each of these stages must be considered and planned for in order to successfully transport temperature-sensitive products by air. Transport systems can be designed to eliminate or significantly reduce the risks to the freight at each stage. Contingency plans can be developed to effectively address risk if it cannot be sufficiently removed by design.

It is important to note that the International Air Transport Association (IATA), a global organization of more than 230 airlines, has regulatory requirements for the safe handling and transport of perishable cargo, of which healthcare products are a part. The IATA Perishable Cargo Regulations, Chapter 17, “Air Transport Logistics for Time- and Temperature-Sensitive Healthcare Products” should be referenced as a resource for shippers involved in last mile distribution.

3.2 Wholesaler Distribution for Refrigerated Pharmaceutical shipments

In the United States, most prescription drugs travel through a complex system that includes: large primary wholesalers, approximately 6,000 smaller secondary wholesalers, plus a small number of specialty wholesalers. (7) In addition to purchasing overstock from manufacturers and primary wholesalers, secondary wholesalers buy and sell drugs among themselves, as well as sell to pharmacies. (8) Thus, cold chain prescription drug products may undergo multiple handoffs within

a supply chain. For a particular drug product, it is possible for a pharmacy to receive shipments which had a minimal number of handoffs (e.g., manufacturer to chain pharmacy warehouse to pharmacy) or which had multiple handoffs, as determined by the extent of selling and reselling among wholesalers. (See **Figure 3.2**)



***Note:** The process-flow diagram presented here is not intended to fully represent the complexity of the pharmaceutical supply chain. A pharmaceutical product may take many more routes to reach the patient.

Some additional routes for consideration include, but are not limited to, manufacturer to patient, manufacturer to pharmacy to patient, and manufacturer to physician to patient.

Wholesalers of pharmaceuticals are defined within the regulations. In the United States, the Food and Drug Administration (FDA) defines wholesale distribution as, “distribution of prescription drugs to persons other than a consumer or patient...” [21 CFR, Part 205.3 (f)] and defines a wholesale distributor as “...any one engaged in wholesale distribution of prescription drugs...” [21 CFR, Part 205.3 (g)]. Additionally, the Code of Federal Regulations defines an authorized distributor as, “...a distributor with whom a manufacturer has established an ongoing relationship to distribute such manufacturer’s products.” [21 CFR, part 203.3 (b)]. Wholesalers must have a method to ensure that shipments of prescription drugs are only sold and delivered to licensed entities.

The European Union and the Japanese Authority maintain similar definitions for wholesalers, describing that a wholesaler must be licensed to distribute an approved product into the region to which it will sell. (9, 10)

Title 21 of the Code of Federal Regulations, Parts 203 and 205, does not address packaging and shipping requirements for temperature-controlled products. The U.S. Pharmacopeia (USP) General Guidance Chapter <1079>: “Good Storage and Shipping Practices” (hereafter referred to as USP <1079>) is very clear in its guidance for the storage, monitoring, calibration, training and qualification of “cold chain”

equipment. The guidance for packing and shipping provides more detail, but it is still lacking detail for the wholesale level. Under the “Distribution and Shipment of Pharmacopeial Articles,” it states, “Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer.” Later in this section it states, “The manufacturers and distributors should work together to establish proper distribution and product-handling requirements for the purpose of ensuring appropriate product maintenance in transit.” Additionally, under “Temperature Challenges,” it states, “Storage temperature ranges may not be indicative of the allowable tolerances during shipping. Articles labeled for special

storage conditions (between 2° and 8°C) vary widely in their tolerance of short-term exposure to heat and cold.” In addition, the manufacturer ships refrigerated pharmaceuticals in a variety of ways, ranging from protective packaging or temperature-controlled trailers to no temperature protection or control at all. The decision of how a manufacturer will ship a product is dependent upon the stability data a manufacturer has, that may not be included in the product labeling.

USP <1079> offers some detail on managing the distribution of temperature- controlled products, however, the regulations and guidelines for packaging and shipping are not clear insofar as shipping temperature ranges, time and thermal packaging material are concerned. Shipments from wholesalers are made via private fleet (vehicles owned by the wholesaler), commercial carriers (UPS, FedEx, etc.) and local courier services. Typically, the duration of these shipments from the wholesaler’s distribution centers to the provider’s facilities ranges from several hours to the next day.

The National Association of Boards of Pharmacy’s Verified Accredited Wholesale Distributors (VAWD) accreditation program is designed to protect the public from counterfeit drugs entering the U.S. drug supply. This program involves background checks and on-site third-party audits of a facility’s procedures and practices (National Association of Boards of Pharmacy Fact Sheet 3/05). Nearly half of the states require VAWD for distributors that are licensed to distribute in their states (whether they have facilities in their state or not). All of the three large primary wholesalers have a number of their distribution centers with VAWD accreditation. While this is not a requirement in every state, and some states, such as Florida, have a more rigorous licensing process that also involves passing state certification exams, this may be criteria for manufacturers to use in evaluating the relationships they have with wholesale distributors.

At the time of publication, only five U.S. states have promulgated requirements specifically for wholesale distributors’ storage, packaging and shipping of drugs. **(11-15)** All other states refer to federal regulations, official compendia and/or the labeling of the drug product. **(16-61)** The five states that specifically address the shipping of refrigerated drugs by wholesalers provide vague guidance, using terms such as “adequate,” “appropriate,” and “proper,” to describe packaging and shipping temperature ranges to maintain product integrity, stability and potency. Without specific requirements, wholesale distributors have no way of knowing if they are providing adequate, appropriate, and proper packaging and shipping temperature ranges in order to maintain product integrity, stability and potency. In the absence of specific packaging requirements or stability data provided by a manufacturer, the distributor should use qualified packaging or transportation to maintain product storage labeling requirements for refrigerated or frozen product for the duration of the shipping time, from the removal of the distributors’ temperature-controlled environment until delivery at their customer’s location. In the event that a manufacturer provides specific packaging requirements or stability data for the wholesaler to qualify their packaging configurations, the distributor would have data that must support conditions outside of labeled storage temperature ranges, but within specified time and temperature parameters. It should be noted that, if available, manufacturers should be encouraged to provide information that supports shipping within parameters outside of storage labeling requirements, since this would reduce environmental packaging waste and costs that are passed on to the consumers. Manufacturers may want to consider VAWD accreditation as one criterion to share packaging requirements or stability data with wholesalers.

3.3 Pedigree and Unit serialization

Pedigree requirements currently vary from state to state, and where unit serialization maybe used, it is seldom linked to a pedigree. While many pedigrees are paper based, there are various types of electronic pedigrees currently being used, including the GS1 Drug Pedigree Messaging Standard. GS1 is a leading

global organization dedicated to the design and implementation of global standards and solutions to improve the efficiency and visibility of supply and demand chains globally and across sectors.

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) was signed into law. Section 913 of this legislation created section 505D of the Federal Food, Drug, and Cosmetic Act, which requires the Secretary of Health and Human Services to develop standards as well as identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded or expired drugs.

While the Food and Drug Administration Amendments Act of 2007, the January 2009 FDA Standardized Numerical Identifiers guidance, and the House Resolution 5839 (HR 5839) draft bill are separate initiatives, there may be convergence within FDA on using electronic track-and-trace technology with serialization down to the unit of sale level for prescription drugs. While Radio Frequency Identification (RFID) and barcodes can carry the same product identification and serial number data, RFID has the advantage of being read remotely. Regardless of the data carrier, when the product ID and serial number are linked, the supply chain will be further secured, down to the last handoff to the patient through authentication of the product and its pedigree via a database that contains appropriate manufacturer, distributor and pharmacy transaction data.

HR 5839, Safeguarding America's Pharmaceuticals Act of 2008, was introduced to the House of Representatives in April 2008. This draft bill lays the groundwork for identifying a standardized numerical identifier, developing a drug tracking system, and licensing wholesalers.

In January 2009, the FDA published guidance for identifying package-level standardized numerical identifiers (SNIs) as an initial step to facilitating other measures for securing the drug supply chain. Although the FDA does not specify a particular means of incorporating the SNI onto the unit package, the SNI is compatible with machine-readable forms of data carriers, such as the 2D Matrix barcode and RFID. In addition to containing the SNI, the 2D Matrix barcode and the RFID tag may also contain the batch ID number, as well as the batch expiration date. The implementation of serialized numbers, coupled with the data carrier technologies and electronic pedigrees will certainly strengthen supply chain integrity.

In addition to verifying the shipment and receipt of products, RFID tags may record temperature and vibration within the supply chain. Other possible enhancements include detecting the opening and closing of packing containers. The degree to which these devices may replace or supplement temperature monitors and recorders remains to be determined.

3.4. stability Data

As indicated earlier, the distribution chain for pharmaceuticals is complex, and there are multiple points in the supply chain in which excursions outside the label long-term storage temperature range may occur. There is often a deficiency in the stability information that is necessary for managing temperature excursions experienced throughout the distribution process. This can be resolved when the logistics group openly communicates the stability needs to the research and development area of a company in which stability studies are executed. Comprehensive stability data is essential for managing temperature excursions that are likely to occur during transit. (62, 63)

Products requiring storage at defined temperatures may experience exposure to temperatures outside of the defined range for a period of time during filling, labeling, inspection, packaging, shipping and distribution. It is essential for proper management to achieve an understanding of the potential

temperature exposures a product may experience as it is transported to the point of use. Some example situations that may arise include:

- Transit within a refrigerated truck: even though a truck has reached the correct set temperature, the temperature will rise temporarily in warm environments or fall in cool environments as the doors are opened for loading and unloading. Temperature monitoring devices, located on the outside of product containers, will record this change in temperature, and some monitors may go outside the labeled storage claim of the product.
- Storing prescription drugs within a hospital or pharmacy: the refrigeration unit used to store temperature-sensitive pharmaceuticals stops cooling overnight or during the weekend.
- Dispensing prescription drugs within a pharmacy: a pharmacy will remove a product from the refrigerator to place a patient label on the product and check that the medication is suitable for dispensing (e.g., it hasn't expired, or that the correct product was removed from the inventory, etc.).
- Shipment of drug product from a pharmacy to an enduser: a product requiring storage at a controlled room temperature (USP definition) is mailed to a patient's home and remains in a mailbox or on a doorstep for several hours where it is exposed to ambient summer or winter temperatures.

In the examples listed above, it would be important to know if the exposures would be problematic to the product. USP <1079> and the World Health Organization (64) state that deviations or variances in exposure to temperatures outside of the product's label range should be addressed with the manufacturer or market authorization holder in order to determine if the exposure is acceptable and if the product may be used.

When the product is within the manufacturer's control, it is easier for the manufacturer to identify potential excursions in the cold chain and to prepare stability and to support exposures, as outlined in PDA TR-39. Commonly, a manufacturer will map all of the transport steps, from filling to the point of distribution and assign exposure temperatures and times to all steps. The product is then exposed to these conditions, or more commonly "exaggerated" conditions, before it is placed on long-term stability at the label storage temperature (please see Appendix 6.4 for compendia definitions for storage conditions). This type of stability study will take into account all temperature exposures within the manufacturer's control.

To account for exposure outside the manufacturer's control, (e.g., in shipping, storage, and distribution by other parties, and that used by hospitals, pharmacies and patients), accelerated stability studies are executed. For a 2–8°C product, these tests include storage at a constant high temperature (25°C or, even better, 40°C) for six months or more. The test protocol also includes a temperature-cycling study. For refrigerated products that may be frozen, the exposure consists of three cycles of two days at freezer temperature (-10–-20°C) followed by two days under accelerated storage conditions (40°C). For refrigerated products that cannot be frozen, the product is cycled between 5–40°C.

Even though comprehensive stability studies that support handling both within and outside of the manufacturer's control have been executed, the resulting stability data is shared with other parties, e.g., distributors, caregivers, and patients in a very limited way. Typically, product labels and inserts contain only long-term storage conditions, such as, "Store between 2–8°C (36–46°F). Do not freeze!" When excursions outside the label storage temperatures do occur, the manufacturer instructs that they should be contacted regarding the ultimate disposition of the drug product. Manufacturers are reluctant to provide expanded standard stability information to other parties, since the same allowable excursions

could be used multiple times by those possessing the product without knowledge of the manufacturer. The cumulative effects of multiple excursions could impact the quality of the product.

Drug manufacturers can facilitate the use of their temperature-controlled products, when product stability data allow, by providing a wider range of label storage temperatures (i.e., 2–15°C rather than 2–8°C), providing separate long-term storage and transport temperatures, providing specific storage and/or handling temperatures for patient use only, and/or by utilizing Mean Kinetic Temperature (MKT).

It is appropriate to use the calculated MKT(65, 66) for a drug product to approximate the effects of storage temperature variations that may occur during product transport in the absence of product-specific kinetic data. MKT calculations for each portion of the distribution process may be used to estimate the impact of temperature excursions on the quality of the drug product.

- For brief segments, such as transport, the MKT for the segment is best used in conjunction with upper and lower temperature limits from the manufacturer.
- For longer segments, such as storage, calculating the MKT of only the excursion may be preferable to using the MKT of the entire segment for evaluating the impact of the excursion.
- Within these limitations, MKT and the controlled room temperature and cold temperature as defined by USP are useful in understanding the impact of temperature excursions on product quality over the lifetime of a drug.
- Each successive owner of the material (manufacturer, wholesaler, pharmacy and patient) can, at best, be responsible for only his or her particular segment, including the storage and transport temperatures and the interpretation of the resulting partial MKT values.

Others in the distribution chain will have access only to what is provided in the drug's labeling*, typically storage statements (e.g., "Store at Controlled Room Temperature," "Excursions permitted 15–30°C," or "Do Not Freeze"), and therefore, the inclusion of MKT excursion data in the labeling is useful. The manufacturer of a drug product has a unique responsibility, since it is the manufacturer who performs the stability studies to determine the expiration dating of the drug. It is those stability studies, plus any additional ones that the manufacturer may choose to do, such as freeze-thaw and temperature excursion studies beyond the standard ICH data package, that enable informed decisions to be made about the use of MKT to evaluate the impact of temperature excursions on the product. For this reason, when questions arise during the distribution process about such temperature excursions, they are best raised with the manufacturer who can use the stability data to interpret the MKT.

3.5 Distribution from Point of Dispensing to End Use in Mail service Pharmacy

Pharmacists' traditional dispensing role in the practice of medicine has shifted to include a clinical focus in monitoring the appropriateness of prescribing and patient care. Automated programs, including mail-service pharmacies, allow the time for these additional clinical responsibilities. Given the shift in dispensing trends, quality programs used throughout the pharmaceutical industry to transport medications must also be implemented at a local pharmacy level.

* **Note:** An example of a model that maybe suitable for products requiring refrigerated storage maybe stated

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