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Guidance for Temperature-
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Products: Maintaining the
Quality of Temperature-
Sensitive Medicinal Products
through the Transportation
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Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment

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Cold Chain Guidance for Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment

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Table of Contents

1.0 INTRODUCTION	2	9.0 QUALITY SYSTEMS	13
1.1 Purpose.....	2	10.0 HANDLING	13
1.2 Scope	2	10.1 Scope	13
2.0 GLOSSARY	4	10.2 Responsibilities.....	13
3.0 PRINCIPLES OF QUALIFICATION FOR TRANSPORT	6	10.2.1 Shipper's Obligations	13
4.0 PRODUCT STABILITY PROFILE	6	10.2.2 Transport Service Provider's Obligations	14
5.0 TRANSPORTATION PROCESS FLOW CONSIDERATIONS	8	10.3 Specific Aspects for Transportation in Vehicles/Containers Providing an Active Temperature-Controlled Environment	14
5.1 Development of Temperature Profiles for Use in Qualification Studies	8	10.4 Specific Aspects for Transportation in Passive Cooling Systems.....	14
5.2 Packaging (Passive) and Transportation (Active) Systems	8	11.0 CONCLUSION	15
5.2.1 Packages/Components/Systems	8	12.0 GLOBAL REGULATIONS AND PHAMACOPOEIAL STANDARDS	16
6.0 DESIGN AND DEVELOPMENT	9	13.0 PUBLICATIONS FROM OFFICIAL BODIES	17
6.1 Functional Requirements Document.....	9	14.0 TABLES	18
6.2 Component/System Specification (CS)	9	14.1 Table I. Long-Term Stability Study.....	18
6.3 Design Qualification (DQ).....	10	14.2 Table II. Accelerated Stability Study	18
7.0 OPERATIONAL AND PERFORMANCE QUALIFICATION TESTING	11	14.3 Table III. Temperature Excursion Study	18
7.1 Qualification Protocol	11	14.4 Table IV. Thermal Cycling Study	19
7.1.1 OQ Testing	11	14.5 Table V. Example of a Comprehensive Study Design for a Refrigerated Product	19
7.1.2 PQ Testing	12	14.6 Table VI. Example of a Transportation Control Strategy Document Based On Product-Specific Stability Data To Determine the Effect of Temperature Excursions	19
8.0 PROCESS IMPLEMENTATION AND TRAINING	12		

This document is a guidance to help minimize the risk to temperature-sensitive medicinal products during transport. It is not intended to establish any mandatory or implied standard. The original version was published in 2005. This is a revised version to harmonize with European Union (EU) regulatory expectations.

1.0 Introduction

Some medicinal products require storage under controlled temperature in order to maintain product quality. In addition to those labeled for refrigerator or freezer storage, some products are stable at controlled room temperature but may suffer degradation at temperatures of 30°C or above or at temperatures below 0°C due to freezing. Such products, where a limited temperature range is necessary to maintain quality, may be termed *temperature-controlled pharmaceuticals* (TCP). All such products requiring special temperature handling should be transported by appropriately specialized means to ensure product quality is not adversely affected during transport. These products may be shipped outside of their respective label storage conditions provided stability data or scientific/technical justifications exist demonstrating that product quality is not affected and meets the national and international requirements.

This document presents an approach to develop and implement specialized packages and systems that will protect temperature-sensitive products during transport. The design approach is comprised of three elements. These elements are (1) Identification of Requirements, (2) Development, and (3) Implementation.

The distribution environment can vary greatly, especially when transporting medicinal products between climatic zones. Seasonal changes, mode of transportation, and regional regulations and capabilities are also variables that must be considered within the transportation environment. These variables should be evaluated on a case-by-case basis.

Global regulatory expectations, guidelines (e.g., Good Distribution Practices) and compendial standards (e.g., USP <1079>) regarding good storage and transportation practices, and the use of time, temperature, and humidity monitoring devices have been put forth by the World Health Organization (WHO), EU, Canada, Ireland, Australia, Brazil, United States Pharmacopeia (USP), and other government and non-government organizations.

1.1 Purpose

The purpose of this document is to provide guidance to industry on the essential principles and practices of transporting temperature-sensitive medicinal products through the transportation environment. This process is commonly referred to as “temperature-controlled”. This guidance has necessarily been written at a high level. As befits a guidance document, it enunciates the what without providing prescriptive detail on the how. Quality systems should be developed by pharmaceutical companies and extended into the supply chain where appropriate.

1.2 Scope

The process defined in this document is for temperature-controlled transportation of medicinal products. The same principles may also be applicable for investigational medicinal products, intermediates, excipients, active pharmaceutical ingredients (APIs), and diagnostic products that require temperature-controlled transportation.

The level of guidance provided herein should allow firms to develop their own processes and also be aligned with the Center for Drug Evaluation and Research (CDER) **Guideline on General**

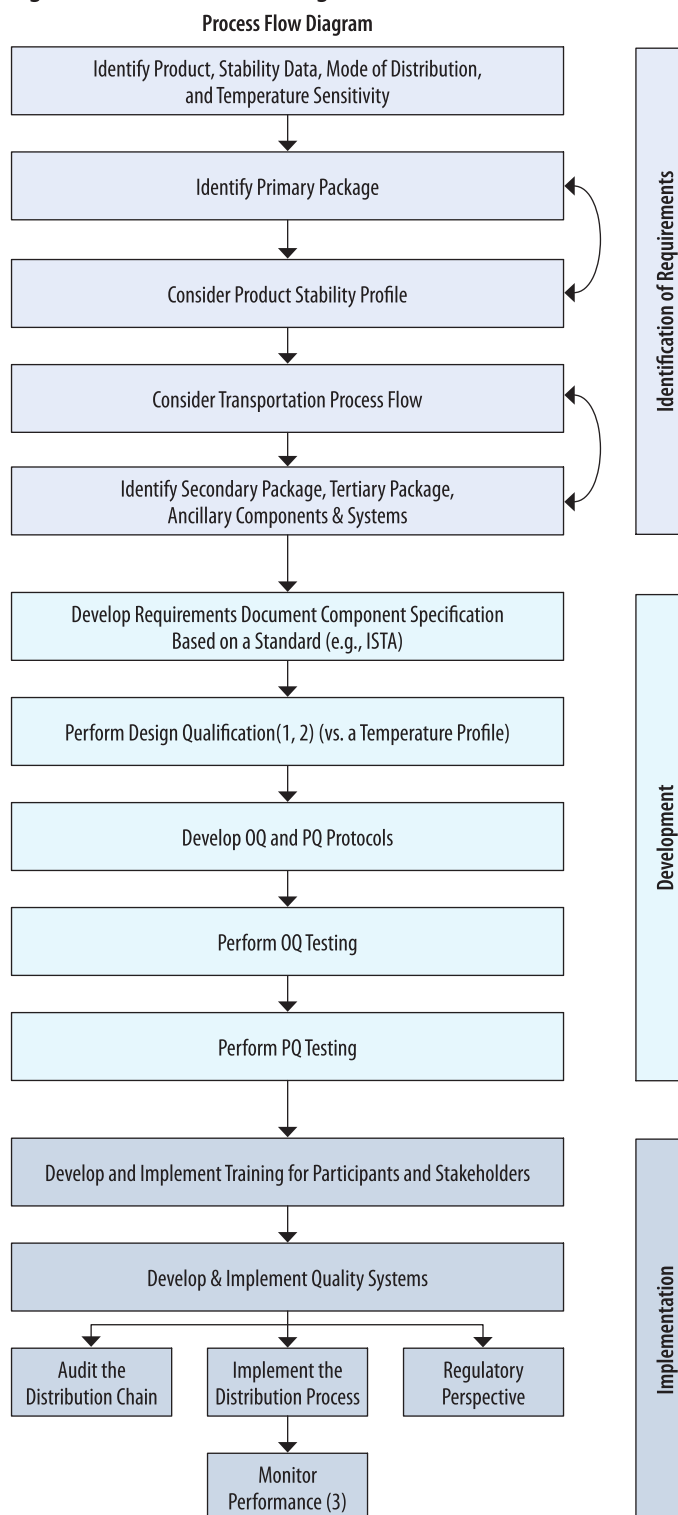
Principles of Process Validation as adapted in this guidance. Generally speaking, the supply chain cannot be “validated”; however, the principles can be used to qualify portions of the supply chain. Where qualification does not add value, change control can be utilized:

- **Component/System Qualification (CQ; later referred to as Design Qualification, DQ)**
 - Establishing confidence that ancillary component systems are capable of consistently operating within established limits and tolerances
- **Operating Qualification (OQ)**
 - Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges
- **Performance Qualification (PQ)**
 - Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

The above principles may be used to reliably qualify the temperature-controlled distribution process. Even a qualified process is subject to change over time. Therefore, periodic and appropriate monitoring is recommended. The frequency and type of monitoring will be based on the specific conditions of a given distribution process. While the qualification process is a typical quality system for manufacturing, it should be noted that it may be a relatively new concept for logistics service providers, e.g. distributors, wholesalers, transportation companies, etc.).

The diagram in **Figure 1** shows an overview of the medicinal temperature-controlled management process flow.

Figure 1.2-1 ■ Process flow diagram.



Note 1: Temperature profiles should be reviewed periodically and updated as seen appropriate.

Note 2: If a vendor is used, the vendor should be part of the firm supplier audit program.

Note 3: A quality system including change control should be used on the implemented process.

2.0 Glossary of Terms

Active Systems: Systems with active temperature control (e.g., air/sea freight containers, refrigerated trucks/cars).

Ancillary Packaging Components/Systems: Additional means used in combination with the basic transportation unit to maintain the required temperature during transport. Examples include active systems and passive systems.

API: Active pharmaceutical ingredient.

Bulk Packaged Product: Consists of solid, liquid, or frozen product in a bulk container configuration such as a bag, tank, or drum. The product may be in these container configurations between process steps or prior to filling into vials, ampoules, cartridges, or syringes.

Change control: The processes and procedures to manage changes being made.

Critical Quality Attributes: Attributes that describe a parameter or item that must be controlled within predetermined criteria to ensure that the medicinal product meets its specification (ICH Q7A).

Design Qualification (DQ): Documented verification that the proposed design of the systems is suitable for the intended purpose. Also establishing confidence that ancillary component systems are capable of consistently operating within established limits and tolerances.

Distribution: Transport of a medicinal product from a drug manufacturer's warehouse/storage facility to distribution centers, commercial customers, or clinical facilities. Subsequent distribution may also occur.

Distribution Temperature: The temperature range, supported by stability studies, within which a medicinal product can be transported for a short duration of time without adverse effect on quality parameters.

Intermediate: Material resulting from a pre-step in the manufacture of an active pharmaceutical ingredient (API).

ISTA: International Safe Transit Association. World-wide organization that supports its membership in designing and developing effective preshipment packaging performance standards, guides, and best practices for product distribution.

Market Package: The package presentation intended for the end user (e.g., bottle + cap liner + screw cap + label + dose cup + carton; may contain multiple units of product) but not including packaging used solely for transportation (e.g., corrugated boxes or insulated containers).

Medicinal Product: Any product intended for the diagnosis, treatment, or prevention of disease.

Operational Qualification (OQ): Transport tests that are conducted in a temperature-controlled chamber or by other simulated test protocols. Generally, simulated testing is conducted using a temperature profile that contains the anticipated extremes for the transportation duration and temperature.

Passive Systems: Systems without active temperature control (e.g., insulated containers with or without refrigerants).

Performance Qualification (PQ): Transport tests of product or representative product that is conducted during actual transportation or distribution.

Primary Packaging Component: A component that is (or may be) in direct contact with the dosage form. Some examples of primary components are glass vials, syringe barrels, bottles, rubber closures, and container or closure liners.

Qualification: Documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria.

Quality Management (QM) System for Transport Service Providers: A QM system that may cover topics such as, but not limited to

- GMP/GDP-relevant processes identified and described in standard procedures
- A procedure to identify the main functions of individuals, roles and responsibilities, and contact information of relevant individuals in the case of a deviation
- An adequate change control system
- An adequate deviation management system, including procedures for corrective actions

Secondary Packaging Component: A component that is not nor will not be in direct contact with the drug

product (e.g., vial seals, overwraps, container labels). The purpose of secondary packaging is to identify, protect, market, and communicate information about the product. Examples of secondary packaging include labels, cartons/folding boxes, and leaflets.

Shipper: An individual or company who tenders products for transportation.

Shipping: The transit of any material by land, sea, or air from one site to another. This may include intra-plant movements.

Stability: The capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.

Stability Profile: The physical, chemical, biological, and microbiological behavior of a drug substance or drug product as a function of time when stored under the defined environmental conditions of an approved protocol.

Transportation Study: Study performed to generate data to evaluate the effect of temperature variation on the product during transportation on product quality. Other tests, such as vibration, pressure, and drop tests, may also be considered.

Storage Temperature: The temperature range listed on the medicinal product label specified for long-term storage.

Sub-Contractor: An individual or company hired by the transport service provider to perform the actual shipment. The shipper and the sub-contractor do not necessarily have a contractual agreement.

Supply Chain: The process by which a drug product is shipped and distributed from the manufacturer to the end user.

Temperature-Controlled: The sequence of transportation events, from the manufacture of the API up to the receipt of the final packaged product by the end-user, which maintains temperature-sensitive products within approved temperature specifications. Maintaining temperature control during these transportation events assures that product quality is maintained.

Temperature Excursion: Any event in which product is exposed to temperatures outside of the recommended storage and/or transport temperature range.

Temperature-Sensitive Products: Products whose quality may be adversely affected by temperature extremes (e.g., frozen, refrigerated, and certain controlled room temperature products).

Tertiary Packaging Component: A component that is used to assemble secondary or primary packages in the form of the basic transportation unit and to provide protection against mechanical impact. Examples are corrugated cardboard boxes, but corresponding plastic boxes/containers are also used.

Transportation: Movement of medicinal product within a designated supply chain including activities from preparation for shipment up to the point of receiving at the final destination.

Transport Duration: The time from preparing goods for transport until receipt of goods. This includes, but is not limited to

- Preparation
- Loading
- Transit
- Intermediate storage
- Unloading

Transport Service Provider: Contracting party who mediates or executes the transportation of medicinal products on behalf of the shipper.

Transport Service Agreement: A contractual agreement that describes the legal, logistical, technical and quality terms or contractual arrangements between shippers and transport service providers. Different names might be used for this type of agreement in different companies.

Temperature Profile: Anticipated ambient temperature variation and duration to which product may be exposed during transportation.

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria.