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GOOD DISTRIBUTION AND STORAGE FOR PHARMACEUTICALS IN UNITED STATES

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ABSTRACT

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Various people and entities are generally responsible for the handling, storage and distribution of such products. The Storage and distribution processes may involve a complex movement of product around the world differences in documentation, handling requirement and communication among various entities in the supply chain.The objective is to facilitate the movement of drug products throughout a supply chain that is controlled, measured, and analysed for continuous improvements and should maintain the integrity of the drug product in its packaging during storage and distribution. This article intended to provide general guidance concerning storing, distribution of pharmaceutical preparations. It describes requirements and key principles to maintain proper storage environments for individual products and to ensure a preparation's integrity, including its appearance, until it reaches the user.

INTRODUCTION

The Good Distribution Practices (GDP) is part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products. The Good Storage Practices (GSP) That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.The quality of pharmaceutical products and the integrity of the distribution chain should be maintained throughout the distribution process from the site of the manufacturer to the entity responsible for dispensing or providing the product to the patient. Good storage and distribution practices should ensure that drug products (medicines) reach the end user (Practitioners and patient/consumers) with quality intact.

US Guidelines: To help protect product quality, USP is developing a series of informational general chapters on good

distribution practices that will appear in the United States Pharmacopeia--National Formulary (USP-NF), USP's compendia of public quality standards.

Key principles for good distribution practice: Quality management system: documentation control and resources management; non-conformances, complaints, and corrective actions; and the role of continuous improvements.

- Good importation and exportation practices: audits and supply agreements, container seals, cargo inspection, customers, and brokers; and verifying product and firm compliance with regulations.
- Supply-chain integrity and security: adulteration and counterfeiting; diversion and productrecall procedures.

Environmental control management: building/facility (storage), transportation vehicles (shipping), and controlled-temperature environments.

Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer. For particular cases, such as shipment of vaccines or other special care products, manufacturers may require special shipping and storage conditions generally referred to as "cold-chain management". For example, manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution. A drug can take a variety of paths from the manufacturer to the patient as given in a Fig 1. In the simplest form of the distribution system, the manufacturer ships directly to the customer, such as a doctor's office, clinic, or hospital. However, more often, the article leaves the manufacturer's chain of control and enters a complex system of handoffs that involve the distribution chain to the patient. Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer. For particular cases, such as shipment of vaccines or other special care products, manufacturers may require special shipping and storage conditions generally referred to as "cold-chain management". For example, manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution. Validated, available temperature- and/or humidity-monitoring technologies can be used to monitor the overall environmental effect on compendial articles during shipment and distribution. The Prescription Drug Marketing Act of 1987 and the ensuing regulations in 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors, provide the necessary regulations and guidance for several legs of the distribution chain for the prescription drug. Information that may be considered in determining the ability of pharmaceutical articles to maintain their Pharmacopeial requirements of identity, strength, quality, and purity through the distribution channel may include, but is not limited to the following: ICH stability studies, temperature cycling studies, stability shipping studies, ongoing regulatory stability commitment studies, market experience portfolio (i.e., product complaint files, historical product performance data, product development data), and product labeling commitments.

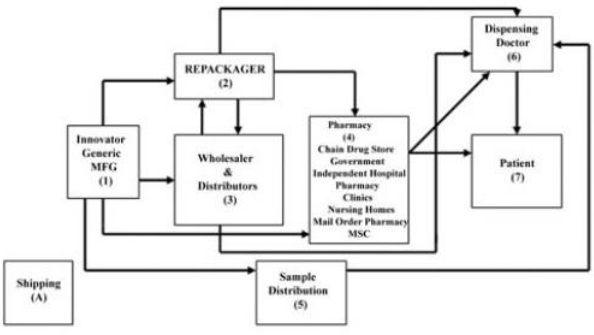

Figure 1: Good Distribution Practice for Pharmaceuticals in US

Distribution or Shipping Vehicles

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

Temperature Challenges

- Shipping of temperature-sensitive articles requiring thermally controlled packaging presents a special challenge. Unlike shock, vibration, and other physical hazards, thermal hazards tend to be unique to a given system.
- Except for temperature controlled trucks, the distribution environment is widely variable and depends upon a range of factors, including points of origin and destination, article and container sensitivities to cold, accidental freezing or heat, transit mode (e.g., air, truck, combination), time, weather or season, and carrier type (e.g., small package carrier or integrator, freight forwarder, U.S. Postal Service).
- The shippers should know and understand the systems they use and should design the protective package accordingly. Storage temperature ranges may not be indicative of the allowable tolerances during shipping.
- Products labeled for special storage conditions (between 2 and 8) vary widely in their tolerance of short-term exposure to heat and cold.

Wholesale Distribution:

Requirements for wholesale distribution of drugs

(a) Identifying statement for sales by unauthorized distributors. Before the completion of any wholesale distribution by a wholesale distributor of a prescription drug for which the seller is not an authorized distributor of record to another wholesale distributor or retail pharmacy, the seller shall provide to the purchaser a statement identifying each prior sale, purchase, or trade of such drug. This identifying statement shall include:
(1) The proprietary and established name of the drug
(2) Dosage
(3) Container size
(4) Number of containers
(5) The drug's lot or control number(s)
(6) The business name and address of all parties to each prior transaction involving the drug, starting with the manufacturer; and
(7) The date of each previous transaction.

(b) The drug origin statement is subject to the record retention requirements of §203.60 and must be retained by all wholesale distributors involved in the distribution of the drug product, whether authorized or unauthorized, for 3 years.

(c) Identifying statement not required when additional manufacturing processes are completed. A manufacturer that subjects a drug to any additional manufacturing processes to produce a different drug is not required to provide to a purchaser a statement identifying the previous sales of the component drug or drugs.

(d) List of authorized distributors of record. Each manufacturer shall maintain at the corporate offices a current written list of all authorized distributors of record.

(1) Each manufacturer's list of authorized distributors of record shall specify whether each distributor listed thereon is authorized to distribute the manufacturer's full product line or only particular, specified products.

(2) Each manufacturer shall update its list of authorized distributors of record on a continuing basis.

(3) Each manufacturer shall make its list of authorized distributors of record available on request to the public for inspection or copying. A manufacturer may impose reasonable copying charges for such requests from members of the public.

Shipment from manufacturer to wholesaler: The wholesaler receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt.

- The wholesaler should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution that could result in products being exposed to extreme temperatures
- The vehicles used for shipping of Pharmacopeial articles to the wholesaler, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt.
- The receiving wholesaler staff should be informed that the articles are transferred to appropriate storage locations without delays.
- The vehicles used for shipping of Pharmacopeial articles requiring storage at room or controlled room temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures.

Pharmacy to patient or customer: The pharmacy should provide an appropriate label on the package sent through air or surface routes so that the deliverer does not place the package in a mailbox exposed to extremes in temperature.

- For temperature-sensitive articles, it is important that proper arrangements be made to protect the drug from exposure to high temperatures, or in some cases, from freezing conditions.
- The patient or customer should examine the delivery documentation to ensure that the package has not been subjected to any unacceptable delays during shipping and distribution.
- The vehicle used for air or surface shipping and distribution of pharmaceutical packages to the patient or customer, especially those requiring low temperatures, should contain the article suitably packaged in containers that maintain the desired storage conditions until the article reaches the patient or customer.
- If stability studies for the Pharmacopeial preparation indicate that it is particularly sensitive to environmental insults or if appropriate shipping safeguards described in this section are not feasible, then the preparation should be shipped by a different method whereby environmental control can be maintained.

GOOD STORAGE PRACTICE:

Storage statement in monographs

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

Storage in warehouses, pharmacies, trucks, shipping docks: To be stored in locations that adheres to conditions established by the manufacturer. Where the desired conditions are not established, use storage conditions described in the General Notices and Requirements or in the applicable monograph.

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

Storage at "cool," "cold," "refrigerator," and "freezing" conditions: Equipment used for storing Pharmacopeial products at these low temperatures should be qualified according to written procedures provided by the management system. Recording devices can be installed within the equipment and used to enable both air and product temperatures to be recorded at regular intervals. The number and location of monitoring devices should be determined based on the result of the temperature profile. Temperature records should be examined at least once every 24 hours or as provided in the equipment protocol. Cool or cold conditions are moisture-condensing conditions. Humidity-monitoring devices should be used in cases where the repackaged Pharmacopeial article is humidity-sensitive or labelled to avoid moisture. Additionally, there can be installed temperature-monitoring, and where necessary, humidity monitoring alarm devices that have the capability of alerting personnel in the event that control is compromised.

Stability, storage, and labelling:

- The design of stability studies of Pharmacopeial products is based on knowledge of the behaviour, properties, and stability of the drug substance and experience gained from clinical formulation studies.
- The length of the studies and the storage conditions for a Pharmacopeial products should be sufficient to cover storage, shipment, distribution, and subsequent use of a Pharmacopeial products.
- The data gathered from ICH accelerated testing or from testing at an ICH intermediate condition may be used to evaluate the effect of short-term excursions outside the label storage conditions such as those that might occur during shipping.

Climatic Zones:

- The planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in. The United States, Europe, and Japan are characterized by zones I and II.
- The values in are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.

Zones	Type	Temperature (° C)	Humidity (%)
Zone I	Temperate.	21	45
Zone II	Subtropical with Possible High Humidity	25	60
Zone III	Hot and Dry	30	35
Zone IV	Hot and Humid	30	70

Storage statements should be based on the stability evaluations of the Pharmacopeial drug substances and in accordance with national and international requirements. Room Temperature Storage Statements— For products with a storage statement reading, "Store at controlled room temperature," the labeling should read as follows on the package insert: "Store at 20 C to 25 C (68 F to 77 F), excursions permitted between 15 C and 30 C (between 59 F and 86 F).

- Brief exposure to temperatures up to 40 C (104 F) may be tolerated provided the mean kinetic temperature does not exceed 25 C (77 F); however, such exposure should be minimized."

On the immediate container label, the following may read for controlled room temperature (CRT): "Store at 20 C to 25 C (68 F to 77 F), excursions permitted between 15 C and 30 C (between 59 F and 86 F).

CONCLUSION

The storage and distribution are important part of the life-cycle management of drug products. Every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, Good Storage Practice (GSP) and Good Distribution Practice (GDP) as applicable and it is equally important to stay current and be ready to change as new solutions evolve. Thenew technologies should be considered in developing strategies for good distribution practices, controls, and procedures.

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