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Review article

GOOD PRACTICE IN THE COLD DRUG SUPPLY CHAIN

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Abstract

Pharmacy could not function without detailed, efficient, flexible and secure cold distribution chains, so in the future this would mean using more sophisticated delivery techniques and technologies.
The cold chain consists of equipment and rules to ensure a constant temperature for thermo-sensitive products from their production to the time of use.
Aim: The aim of this study is to evaluate data from WHO, EMA and FDA, their guidelines and directions, as well as relevant data from primary, secondary and tertiary literature.
Method: In this paper we will review the regulatory measures and recommendations of the WHO, EU and US regarding the cold chain and will discuss the similarities and differences in their regulation.
We summarized the reviewed literary data and sorted them according to the importance of the treated problem, made a comparison of the regulatory measures in order to ensure a safe cold chain and drew appropriate conclusions.
Result: The reviewed documents do not show large and substantial differences in the approach to the cold chain and its importance for product safety.
Conclusion: Drugs that require storage conditions under controlled temperature must be distributed in a way to ensure that their quality is not diminished.

Keywords: distribution, vaccines, temperature limits

1. Introduction

Good Distribution Practice (GDP) is a quality system that refers to the organization, implementation and supervision of the storage of medicines and medical devices according to a certain order and prescribed storage conditions, before further use or placing on the market and transport from the manufacturer to the end user (Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use).
The term cold chain refers to a series of activities and equipment used to maintain a product in a certain range of low temperatures from production to consumption.
Continuous cold chain is a continuous series of activities for production, storage and distribution in the refrigerator, together with the associated equipment and logistics, which maintain the desired range of low temperatures. It is used to preserve, extend and ensure the shelf life of products such as food, chemicals and pharmaceuticals.

1.1. Aim of the study:

Pharmacy could not function without detailed, efficient, flexible and secure cold distribution chains, so in the future this would mean using more sophisticated delivery techniques and technologies.
The cold chain consists of equipment and rules to ensure a constant temperature for thermo-sensitive products from their production to the time of use.

1.2. Objectives of the study:

The aim of this study is to review the regulatory measures and recommendations of the World Health Organization, the European Union and the United States regarding the cold chain and also to note and discuss the similarities and differences in the regulation of the World Health Organization, EU and USA

2. Materials and Methods

Data from WHO, EMA and FDA, their guidelines and directions, as well as relevant literary data from primary, secondary and tertiary literature were used to achieve the objectives of the study.
We summarized the reviewed literary data and sorted the data according to the topicality of the treated problem, made a comparison of the regulatory measures to ensure a safe cold chain and drew appropriate conclusions.

3. Literature and discussion

3.1. Implementation of the cold chain according to the World Health Organization (WHO)

Cold chain is a process that enables the safe transport of thermolabile products along the supply chain. It relies on science to assess and adjust the relationship between temperature and stability of the product, so temperature monitoring devices are used in international shipments (The Vaccine Cold Chain". www.who.int).
These devices should:
(1) serve as a quick reminder to help recipient countries determine whether the consignment or parts of the consignment have been exposed to temperatures at which vaccines may be damaged; and
2) assist the supplier to determine when, where and to what extent the temperature limits have been exceeded.
The time when the temperature change occurred is important for:
a) the supplier and the manufacturer so they could be able to identify the cause of the change, take corrective action and avoid similar situations in future shipments; and
b) insurance purposes.
Electronic temperature devices provide the most reliable and accurate record of the above information
Each electronic device must be attached to an accompanying card containing the information below, in the appropriate language.
1. Device type:
2. for the person who packs / sends the shipment:
a) instructions for activating the device;
b) a reminder that one device must be placed in each carton delivery;
c) space for entering the following information:
• the name of the supplier;
• date and time of packaging;
• vaccine order number;
• type of vaccine.
3. For the person receiving the shipment:
a) instructions on how to stop the device;
b) illustrations to display information on the LCD screen

3.1.1. Cold chain – Vaccines

The system used to store vaccines in good condition is called a cold chain. It is also called the vaccine supply chain or immunization supply chain. The cold chain consists of a series of links designed to store vaccines

within the WHO recommended temperature ranges, from the point of manufacture to the point of administration.
In order to maintain a secure cold chain of vaccines at the peripheral level, the following key procedures must be followed: store vaccines and diluents in the required temperature range in all locations, pack and transport vaccines to and from places where they are needed according to recommended procedures and store vaccines and diluents within the recommended cold chains during immunization sessions (Lean NG et al., 2020; Bishara NG, 2006).*old chain equipment*

- Refrigerators
- Cold boxes
- Vaccine carriers
- Water packs
- Foam pads

3.1.2. Temperature monitoring devices

- 30-day electronic temperature loggers (30 DTR)
- Electronic freeze indicators
- Stem thermometers

3.2. Implementation of the cold chain according to the rules of the European Union

According to the rules of the European Union, the cold chain is implemented according to the principles of good distribution practice, a quality system is maintained which refers to competent staff, appropriate premises, facilities and equipment. (Quality system, Staff, Documentation and records, Operations, Equipment)

3.3. Cold chain implementation according to FDA

Three regulations from the FDA that refers to cold chain are:

- 21 CFR 203.32 "Prescription Drug Marketing – Drug sample storage and handling requirements."

This subpart (D--Samples) contains two parts that stipulate that (a) "Storage and handling conditions" not adversely affect the drug and (b) manufacturers, distributors of record, and their representatives comply with all compendial and labeling requirements.

- 13 2. 21 CFR 203.36 "Fulfillment houses, shipping and mailing services, co-marketing agreements, and third-party recordkeeping" looks at "co-marketing agreements" with any third party involved in shipping and storing drug samples. This section states that the manufacturer or distributor is responsible for record keeping and documentation and must comply with the Prescription Drug Marketing Act (PDMA) and amendments. The PDMA document contains recommendations relating to 21 CFR Parts 203 and 205 and outlines how to document drug products that pass from manufacturers to Authorized Distributor of Record (ADR) and provisions regarding pedigrees.
- 21 CFR 211.150 of Subpart H: Holding and Distribution - "Distribution procedures" states that these products must be shipped within: "…appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/ National Formulary (USP/NF)."(FDA & ICH (2012): Regulations and Standards for Temperature-Controlled Supply Chains)

3.4. Pharmaceutical cold chain management

Pharmaceutical supply chain members have a variety of global regulatory requirements to meet when handling, storing and distributing environmentally sensitive products. Their focus is to provide a cold chain for the management o. temperature-sensitive pharmaceutical products to ensure that the quality and effectiveness of the product will not be compromised.

This demonstrates the importance of cold chain pharmaceutical management as a result of product portfolio change, requirements for good storage and distribution practices, current regulatory trends, quality management, risk assessment factors, and temperature monitoring.
Trends include:
The responsibility for cold chain management ultimately lies with the manufacturer
Increased supervision, management and control of environmental conditions throughout the supply chain
Increased importance of temperature control and monitoring to mitigate and identify risks

Increased priority of patient safety

Due to the presence of more uncontrolled variables in the distribution process, the development of appropriate temperature and humidity, the monitoring program is essential to protect the quality of the environmentally sensitive pharmaceutical product and to ensure patient safety (Sykes C., 2018).

3.5. Differences between regulatory bodies

The cold chain of drug supply is a process that is controlled and takes place according to precisely defined rules. The differences in its implementation in the WHO, EU and FDA are minimal, because it's main goal is to provide safe drugs and vaccines.
In the European Union, the cold chain is implemented according to the principles of good distribution practice, the quality system is maintained which refers to competent staff, appropriate premises, facilities and equipment.
The Food and Drug Administration for the implementation of the cold chain has three key regulations regarding the monitoring of the temperature during the shipment (Food and Drug Administration: Drug Supply Chain Security Act).
The differences in the implementation of the cold chain are the temperature limits that are declared according to the rules and regulations and they are listed below.
Labels with storage requirements, such as "ambience", "room temperature" and "cold chain", are often found on the outer packaging of pharmaceutical products.

- The European Pharmacopoeia (Pharm. Euro.) Provides some hints in Chapter 1.2 (Other provisions applicable to general chapters and monographs) concerning analytical procedures (Ph. Eur. 6.0, 1742 (01/2008)):

Deep freezing: below -15 ° C;
Refrigerator: 2 ° C to 8 ° C;
Cold: from 8 ° C to 15 ° C;
Room temperature: 15 ° C to 25 ° C.

- There are also several definitions in the WHO Guidelines:

Store frozen: transport refrigerated and stored at -20 ° C (4 ° F).
Store at 2 ° -8 ° C (36 ° -46 ° F): for heat-sensitive products that must not be frozen.
Cold: Store between 8 ° -15 ° C (45 ° -59 ° F).
Room temperature: Store at 15 ° -25 ° C (59 ° -77 ° F).

Ambient temperature: Store at ambient temperature. This is emphasized by the significant variation in ambient temperature. This means "room temperature" or normal storage conditions, which means storage in a dry, clean, well-ventilated area at room temperature from 15 ° to 25 ° C (59 ° -77 ° F) or up to 30 ° C, depending on climatic conditions.

- The US Pharmacopoeia (USP) also has some recommendations. USP <659> Packaging and Storage Requirements provides different examples of different storage conditions, for example (USP 41-NF 36):

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

Medium cold: Any temperature between 8 ° and 15 ° (46 ° and 59 ° F)
Room temperature: The temperature that prevails in the work area.
Controlled room temperature: Temperature is maintained at 20 ° -25 ° (68 ° -77 ° F). Excursions between 15 ° and 30 ° (59 ° and 86 ° F) that are experienced in pharmacies, hospitals and warehouses and during delivery are allowed. Provided that the average kinetic temperature does not exceed 25 °, transient jumps of up to 40 ° are allowed until they exceed 24 hours. Jumps above 40 ° can only be allowed if specified by the manufacturer.
Warm: Any temperature between 30 ° and 40 ° C (86 ° and 104 ° F).
Excessive heat: Any temperature above 40 ° (104 ° F).

4. Conclusion

The world market for biotech pharmaceutical products is growing rapidly. As biopharmaceuticals are temperature sensitive, the cold chain is becoming an increasingly important component of the overall pharmaceutical supply chain.
The WHO has prepared a working document QAS / 04.068QAS / 04.068 recommending the maintenance of the original quality of the medicinal product by applying the principles of good practice (GPP, GDP, GSP) and for medicinal products that require special storage conditions (for example, temperature and relative humidity) and transport they should be secured, checked, monitored and recorded.
In the EU, key concepts are presented in the European Union Good Manufacturing Guidelines, which include: of transport "The quality system operated by the distributors (wholesalers) of medicines should provide storage and the conditions are observed at all times, including during transport "and
"Products requiring controlled temperature storage should also be transported by suitably specialized means."
The FDA cites shortcomings in good distribution practices with a specific focus on temperature control and monitoring during shipment.
The International Conference on Harmonization in ICH Q1A (R2) recommends an assessment of the storage, transport and utilization requirements and the appropriate assurance of their application in order to preserve the original quality of the medicinal product.
The reviewed documents do not show large and substantial differences in the approach to the cold chain and its importance for product safety. Medicines that require storage conditions under controlled temperature must be distributed in such a way as to ensure that their quality is not diminished

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