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General specifications and testing methods for temperature-sensitive medicinal packages in good distribution practice principles

Spécifications générales et méthodes d'essais relatives aux emballages de médicaments thermosensibles selon les principes de bonnes pratiques de distribution

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 122, *Packaging*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Good distribution practice (GDP) is considered as an essential aspect of compliance for all temperature-sensitive medicinal products and to ensure systematic distribution.

Temperature-sensitive medicinal products are susceptible to temperature changes. Those products can become less effective or destroyed when exposed to excessive environments. They need to be kept within a specific range of temperatures from the place of manufacture to the point of administration to the users. Despite increasing awareness and the need of safe handling, transport and storage of temperature-sensitive medicinal products, an international standard of testing methods for their packaging is in great need.

For temperature-sensitive products, qualified equipment like thermal packaging, temperature-controlled containers or temperature-controlled vehicles should be used to ensure correct transport conditions are maintained between the manufacturer, the wholesale distributor and the customer. In case of temperature-controlled vehicles, the temperature monitoring equipment used during transport/storage should be maintained and calibrated at regular intervals. Temperature mapping under representative conditions should be carried out first and should take into consideration seasonal variations if relevant.

Harmonized methods can be a guideline to maintain the recommended temperature range inside an insulated container and physical performance. This document works through enhancing the capacity to distribute and handle the products effectively. This document is intended for anyone involved in transport, storage and handling of them, especially manufacturers, importers, distributor, wholesalers, transporter, etc.

Test methods are based on Australia National Temperature-sensitive Pharmaceutical Storage Guidelines Strive for 5 (2nd Edition), Guidelines on the international packaging and shipping of temperature-sensitive vaccines (WHO/IVB/04.23 Annex 1 and WHO/PQS/E004/CB01-VP.3), ISO 22982-1 and ISO 22982-2.

General specifications and testing methods for temperature-sensitive medicinal packages in good distribution practice principles

1 Scope

This document describes the general specifications of temperature-sensitive medicinal packaging based on the principles of good distribution practice (GDP). It also specifies test methods to validate the package performance for temperature-sensitive medicinal products. This covers the procedures of temperature-recording and testing methods on the performance of insulated containers such as dimensions, weights, storage capacity and robustness in temperature-controlling.

This document does not guarantee the quality and safety of all medicinal products. Under special circumstances where the weight or the characteristics of the products and environment show specific conditions, agreements are followed. This document does not cover the active packaging system, but only covers the passive packaging system able to control the desired temperature without any power sources.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 21067-1, *Packaging — Vocabulary — Part 1: General terms*

ISO 22982-1, *Transport packaging — Temperature-controlled transport packages for parcel shipping — Part 1: General requirements*

ISO 22982-2, *Transport Packaging — Temperature controlled transport packages for parcel shipping — Part 2: General specifications of testing*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 21067-1 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
good distribution practice
GDP
part of quality assurance which ensures that quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorized or entitled to supply medicinal products to the public

[SOURCE: Guidelines of the European Commission, Annex of 2013/C343/01]

3.2
medicinal products
medicine intended for human use or veterinary product administered to any animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by medicinal legislation in both the exporting state and the importing state

[SOURCE: WHO Technical Report Series No.908, Annex 7, modified.]

3.3
temperature-sensitive medicinal product
medicinal product whose quality may be adversely affected by temperature extremes

3.4
temperature-controlled
sequence of transportation events, from the manufacture to the end-user, which maintains temperature-sensitive products within approved temperature specifications

Note 1 to entry: Maintaining temperature control during these transportation events assures that product quality is maintained.

3.5
temperature-recording
continuous measurement to record temperature

3.6
data logger
electronic or mechanical data recorder provided with sensor(s) for measuring the temperature

3.7
coolant
heat-absorbing medium or process

[SOURCE: ISO 15779:2011, 3.11]

3.8
phase changing material
PCM
material with a high heat of fusion that allows it to store or release thermal energy as a form of melting and solidifying at a certain temperature

[SOURCE: ISO 22982-2:2021, 3.2, modified]

3.9
insulated container
thermal container having no devices for cooling and/or heating, either permanently installed or attached

[SOURCE: ISO 830:1999, 4.2.2.1.1, modified — NOTE has been removed.]

3.10
controlled temperature chamber
room or equipment where the temperature uniformity is maintained within a qualified range to ensure product is preserved

EXAMPLE Freezers, refrigerators, cold rooms and stability chamber.

3.11
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 11139:2018, 3.313]

4 General specifications

4.1 General

Temperature-sensitive medicinal packages that require constant temperature during transportation shall be capable of adequately protecting the components of the drug product in the agreed transport environment prior to application.

Temperature-sensitive medicinal packages shall have no adverse effect on the quality of the product, the immediate container and secondary packaging of the medicine and shall offer adequate protection from external environment and contamination. The selection of containers and packaging material shall be based on storage and transportation requirements of the medicinal product. The space required for the amount of medicinal products, the expected external temperature extremes, the estimated maximum transportation time including transit process at customs, etc., are also important elements to consider as well as the qualification and the validation of the shipping containers.

The container shall be labelled appropriately to:

— identify the product accurately;

— ensure the correct and proper handling and storage conditions of the product; and

— provide special precautions or warnings if needed.

If the expiration date is different, depending on the storage conditions of the product, this shall be checked. Special conditions and requirements shall be taken into consideration. Appropriate information shall be added for specific products (e.g. Advanced Therapy Medicinal Products (ATMPs), medicinal products derived from blood, immunological medicinal products, narcotic/psychotropic substances, radio-medicinals, etc.).

The container shall meet the basic requirements of 4.2, 4.3, 4.4 and 4.5 in terms of appearance, performance and stability.

4.2 Physical performance

A package/container shall prove its physical reliability throughout the supply chain. Robustness test of the container shall be performed in accordance with test methods specified in 6.3.

4.3 Dimensional stability

A package/container shall maintain its dimensional stability throughout the supply chain. In principle, the dimensions of the standard module set by ISO 3394 are recommended.

4.4 Safety

A package/container including any component such as a coolant or PCM shall prove its safety to meet the requirements set by ISO 22982-1.

4.5 Thermal performance

A package/container including any component such as a coolant or PCM shall prove its functionality to meet the requirements set by ISO 22982-1 and tested by ISO 22982-2.

5 Preparing a packaging system

5.1 General considerations before packing

To maintain the specific range of temperature in passive temperature-controlled packaging system, the weight and latent heat of PCM (or any coolant) shall be pre-calculated. The calculation shall be based on the experimental results or mutual agreements with users. The inner temperature of the insulated containers shall be measured using a calibrated thermometer. The following procedure is recommended to be followed.

a) The container shall be pre-cooled before use.

b) The temperature shall be checked on an hourly basis.

c) The container shall be kept out of direct sunlight.

d) The number of PCM or coolant should be required depending on ambient temperature, product type, size of the container, number of products, capacity, etc.

5.2 Temperature-recording equipment

For temperature-recording equipment, battery operated thermistor data recorders or thermocouple wire base multi-channel data logger recorders are recommended to be used for the test. The equipment shall have a resolution of 0,1 °C and an accuracy of ±1,0 °C. The equipment is recommended to have the capability to store digital temperature reading at specified time intervals. Throughout the testing series, all components such as thermocouple, wire, data logger connection shall be properly maintained and calibrated.

A controlled temperature chamber shall have enough room to accommodate the packages that can be stabilized at specific temperature profiles. Temperature mapping is recommended to identify the temperature stability within the chamber.

5.3 Packing into the heat insulated containers

There are two options to put PCM (or any coolant) and temperature-sensitive medicinal products into the insulated container.

1) Placing directly into the container.

   a) PCM (or any coolant) shall be placed to cool the inside of the container.

   b) Insulating materials shall be placed at the bottom of the container.

   c) A thermometer shall be placed in the centre of the product.

   d) The product should be surrounded by packaging. Conditioned PCM (or any coolant) shall be placed on top before closing the container.

e) To reduce the risk of unintentional freezing, the product shall not be in direct contact with the PCM (or any coolant).

f) Temperature shall be monitored and recorded prior to departure and upon arrival.

2) Placing the products into a container, then putting into a larger insulated container.

a) PCM (or any coolant) shall be placed to cool the inside of the selected container.

b) A thermometer inside the container shall be placed in the centre of the products and the lid shall be secured.

c) The container shall be packed inside a large insulated container and placed with PCM (or any coolant). After that, the lid shall be secured.

d) Temperature shall be monitored and recorded prior to departure and upon arrival.

Personnel shall be trained in the procedures for assembling the insulated container and using the PCM. There shall be a control system for the reuse of the PCM (or coolant) to ensure that incompletely cooled or contaminated PCMs are not used. There shall be enough physical separation between frozen and refrigerated PCMs. The whole process shall be documented.

6 Test procedure

6.1 Thermal performance

6.1.1 Temperature profiling

Insulation performance of temperature-sensitive medicinal packages shall be determined with temperature-mapping and in accordance with test methods specified in ISO 22982-2.

6.1.2 Location of temperature sensors

Use temperature sensors for measuring temperatures (to an accuracy to be given) and a recorder capable of exchanging data (wireless or using a data-line, e.g. radio frequency identification (RFID), Bluetooth).

The products shall be fully packed in an insulated container. Packaging shall be done as quickly as possible. The time taken to load into each container shall be recorded. Temperatures of the container shall be continuously checked. The sensors shall be capable of accuracy to ±0,5 °C. An insulated container requires a minimum of eight simultaneous temperature measurements. See the example in Figure 1 for the location of the temperature sensors.

The ambient temperatures surrounding an insulated container shall remain within ±3 °C. The internal temperature of an insulated container shall be recorded at a designated point inside the container while the validation is being performed. Be careful not to affect the quality of the seal. Place the data logger/thermocouple outside the products, not inside.