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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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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).

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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

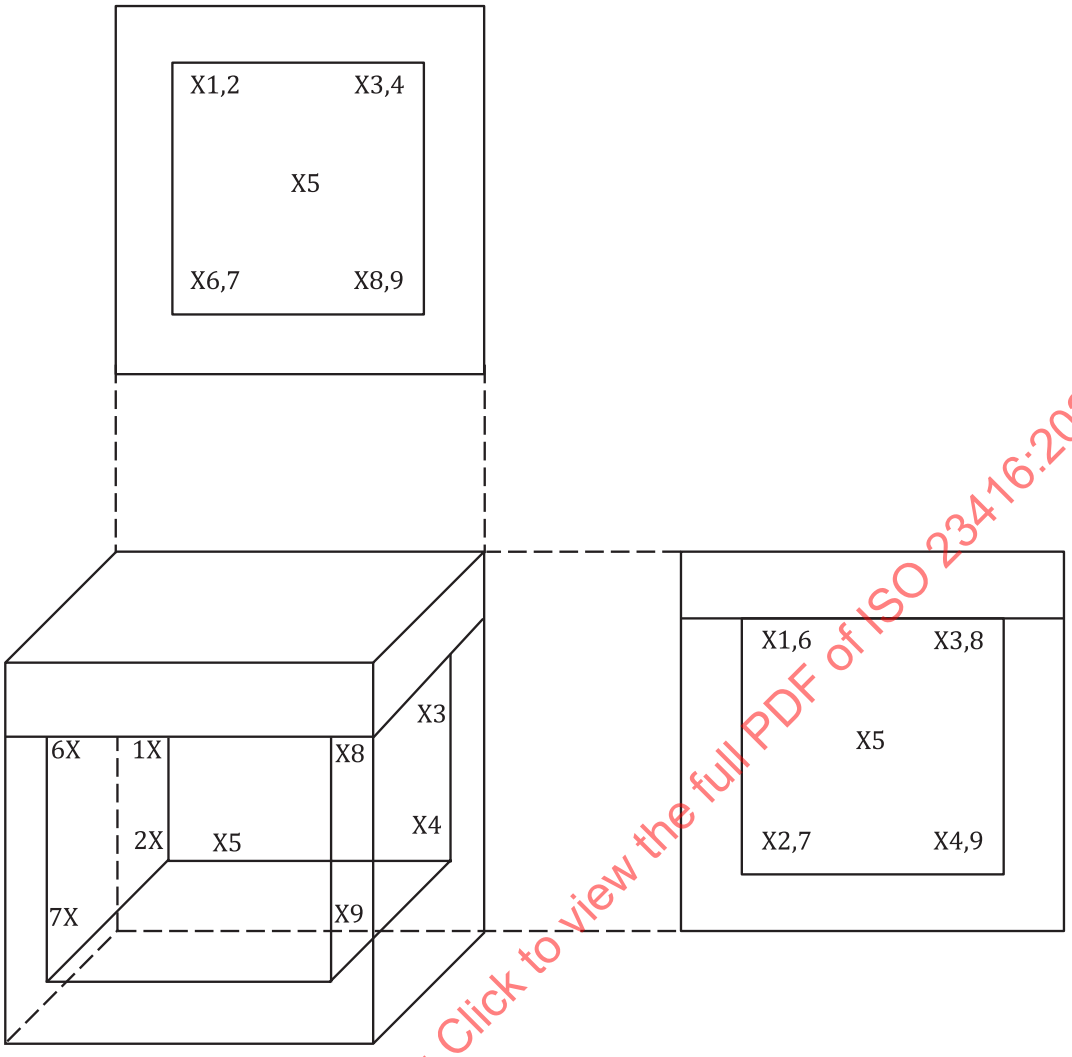
Insulation performance of temperature-sensitive medicinal packages shall be determined with temperature-mapping and in accordance with test methods specified in ISO 22982-2.

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.



Key

1X	upper left back	X1,2	upper left front corner
2X	lower left back	X3,4	upper right front corner
X3	upper right back	X6,7	upper left back corner
X4	lower right back	X8,9	upper right back corner
X5	centre	X1,6	middle left back corner
6X	upper left front	X3,8	middle right back corner
7X	lower left front	X2,7	middle left low corner
X8	upper right front	X4,9	middle right front corner
X9	lower right front		

Figure 1 — Example of location of temperature sensors in an insulated container

6.1.3 Temperature-recording

a) The temperature-recording shall be done at pre-determined interval by parties concerned. Check Figure 2 for the temperature-recording process.

b) The product and PCM (or any coolant) shall be immediately loaded into the package. Insert required wrapping paper or cushioning material and tape or secure the packaging. Each package shall be weighed and recorded.

c) The thermocouple probes or monitors shall be placed on the exterior of the package such as top and/or bottom of the package to record the ambient environment during testing. When packing the product, it is necessary to check the operating state or position of the probe.

d) When thermocouple probes are used for the insulated container, the probe wires shall not cause air leaks or gaps upon closing the lid or top of the package.

e) The package shall be placed in the set environment on a pallet or open platform to permit the ambient temperature to circulate completely around all surfaces of the package during testing.

f) Record all test information. Temperatures shall be recorded at specific time intervals. If equipped, a pre-programmed controller should be used for specific cyclic/soaks or ramp periods based on the exposure profile of the environment according to ISO 22982-2.

g) When the final test period is completed, the package shall be removed from the environment. All observations are recorded such as damage to product, leaking refrigerant packs, any equipment failures, etc.

h) All test data shall be collected from the temperature-recording or monitoring system. This information can be used to prepare a graphic representation of the performance profile of the package under specific condition.

i) Report preconditioning duration and temperature, temperature profile, time, point conditions and results.

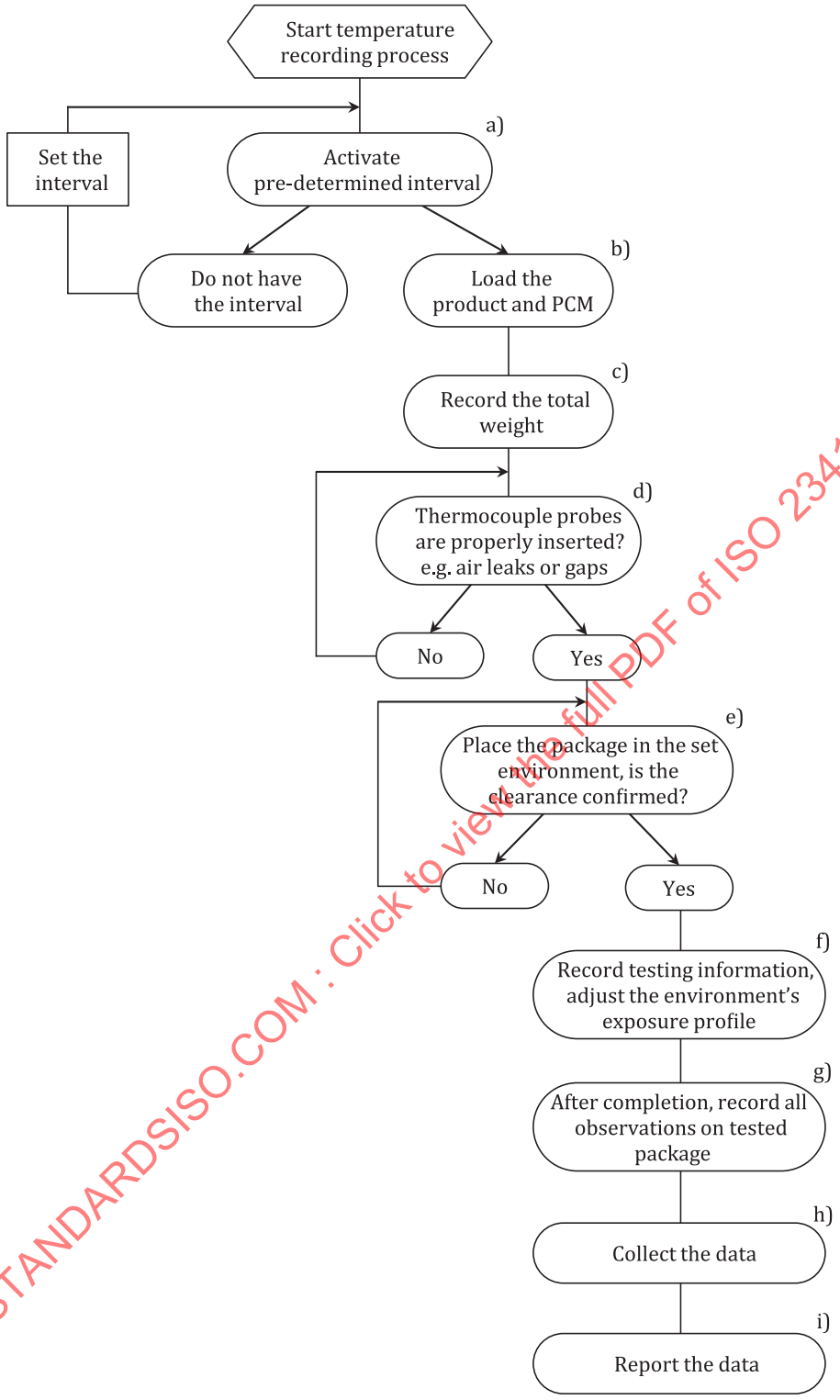


Figure 2 — Flow chart of temperature-recording process

6.2 Storage and weight capacity

6.2.1 Storage capacity measurement

Referring to Figure 3, external dimensions (length, width and height) and internal dimensions (length, width and height) shall be recorded. The number of PCMs (or coolants) designated in accordance with

the experimental results or mutual consultation with users shall be recorded. The total volume of PCM (or any coolant) used shall be recorded. The storage capacity of the container, C, shall be calculated using Formula (1).

$$C = V_{int} - (V_{PCM} \times n_{PCM}) \quad (1)$$

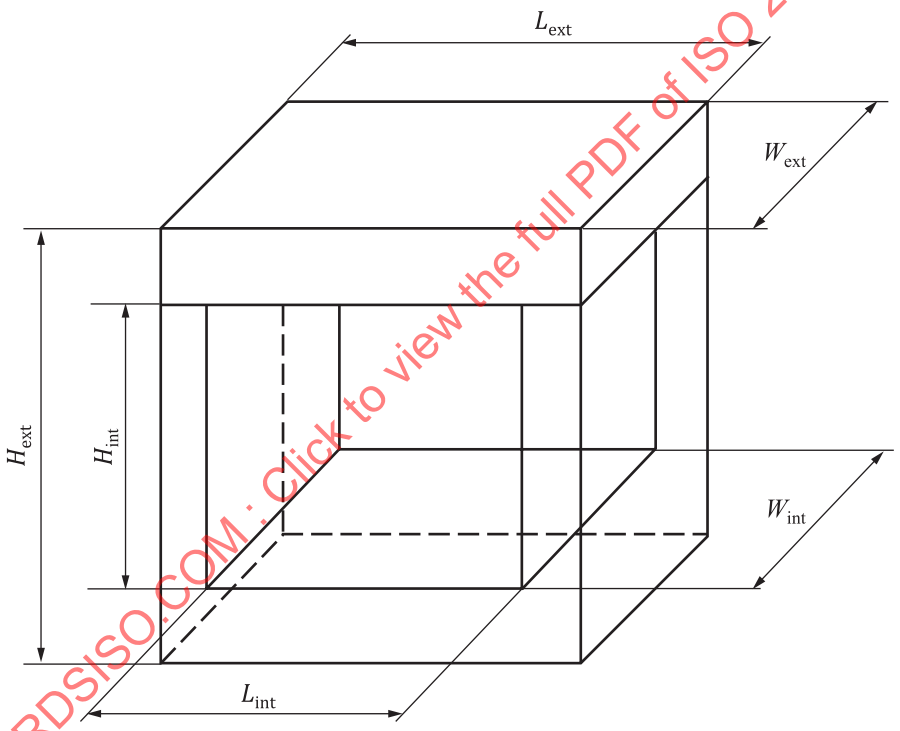
where

C is the storage capacity of the container (±2,0 %);

V_{int} is the internal volume of the container;

V_{PCM} is the volume per each pack of PCM (or coolant);

n_{PCM} is the number of PCM (or coolant) packs.



Key

L_{ext}	external length	L_{int}	internal length
W_{ext}	external width	W_{int}	internal width
H_{ext}	external height	H_{int}	internal height

Figure 3 — Storage dimensions excluding PCM

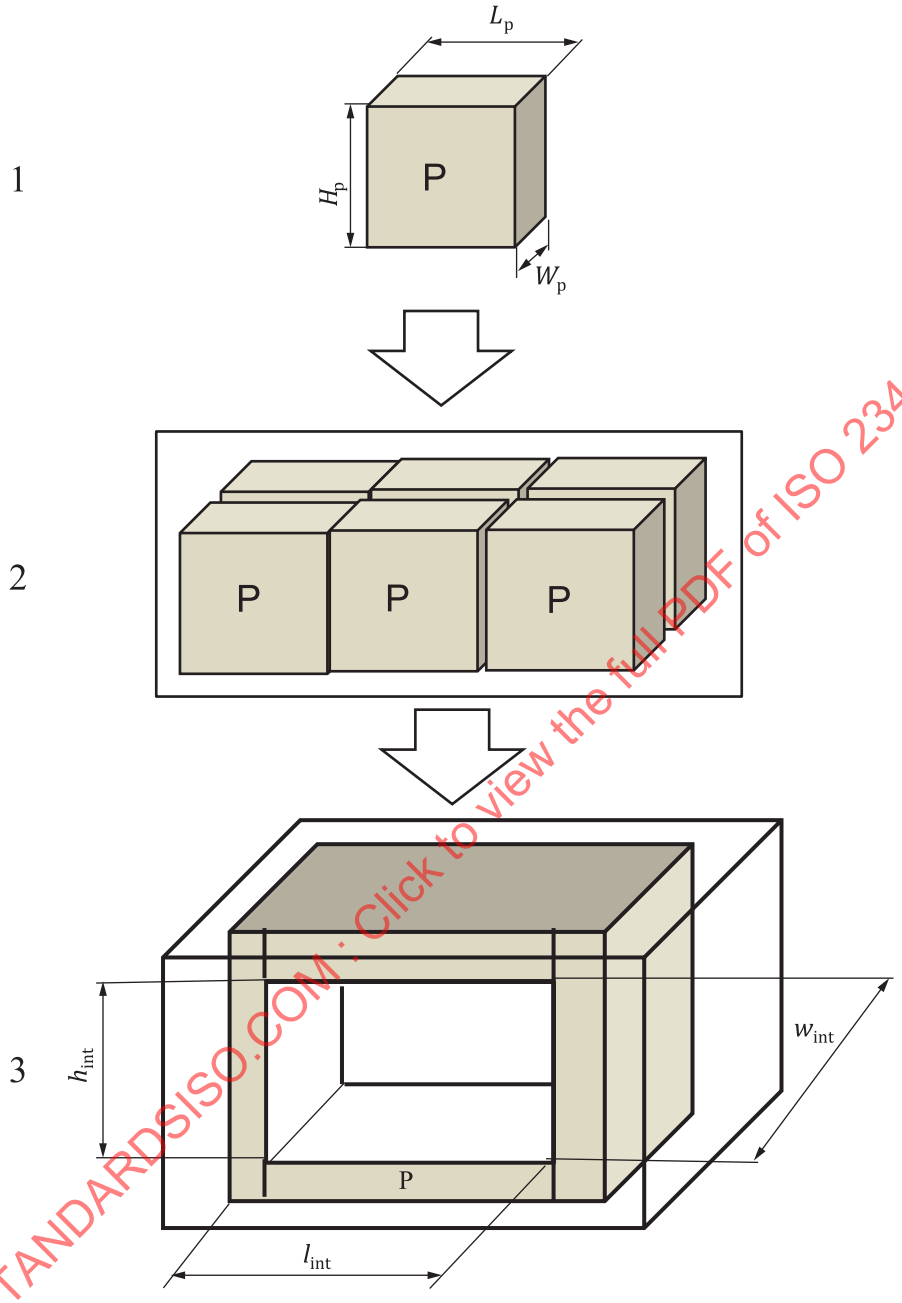
The insulated container shall be lined with PCM (or coolant). The PCM (or coolant) shall be frozen at required condition in accordance with the experimental results or mutual consultation with users.

The minimum overall dimensions of the storage area measured between straight edges placed over the bulging internal faces of the PCMs (or any coolant) shall be recorded (length, width and height).

The storage area shall be packed up to the designated load line specified by the manufacturer.

Measure the total volume of the PCMs (or any coolant).

The lid of an insulated container shall be closed and latched. The total empty volume of the insulated container shall be recorded as the storage capacity. Refer to Figure 4 for storage capacity measurement process including PCM.



Key

1	preparation and measurement of the dimensions of PCM	h_{int}	minimum overall height for storage
2	measurement of the total volume of PCMs to be placed in the insulated container	l_{int}	minimum overall length for storage
3	recording of the total empty volume of the insulated container	L_p	length of a PCM
P	phase changing material (PCM) or coolant	H_p	height of a PCM
w_{int}	maximum overall width for storage	W_p	width of a PCM

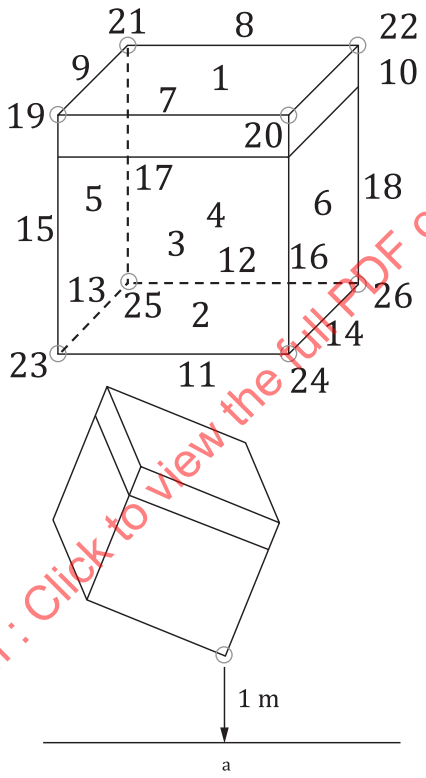
Figure 4 — Storage capacity measurement including PCM

6.2.2 Weight measurement

The weight of the insulated container without PCM (or any coolant) and the total weight of the PCM shall be recorded separately. The insulated container with the PCMs (or any coolant) shall be weighed and the total weight shall be recorded as the maximum loaded weight.

6.3 Robustness test

The controlled temperature chamber shall be pre-conditioned at +18 °C to +24 °C and the conditions shall be recorded. The central void shall be fully filled with a non-breakable dummy load and arranged packaging to prevent the load from shifting. The total weight shall be equal to the maximum loaded weight established in 6.2.2. The faces, edges and corners of the insulated container shall be marked with the test numbers shown in the Figure 5.



Key

1	top	14	right side bottom
2	bottom	15	front left side
3	front	16	front right side
4	back	17	back left side
5	left side	18	back right side
6	right side	19	front top left
7	front top	20	front top right
8	back top	21	back top left
9	left side top	22	back top right
10	right side top	23	front bottom left
11	front bottom	24	front bottom right
12	back bottom	25	back bottom left
13	left side bottom	26	back bottom right
a	Concrete floor.		

Figure 5 — Scheme of robustness test

Using a free fall drop tester, the insulated container shall drop 26 times from 1 m high (measured from the lowest part of the container at the start of each test) onto a concrete floor in the exact order set out in Table 1. One sample is required to perform the robustness test.

Table 1 — Test order of the robustness test

Face	Edges	Corners
1 Top	7 Front top	19 Front top left
2 Bottom	8 Back top	20 Front top right
3 Front	9 Left side top	21 Back top left
4 Back	10 Right side top	22 Back top right
5 Left side	11 Front bottom	23 Front bottom left
6 Right side	12 Back bottom	24 Front bottom right
13 Left side bottom		25 Back bottom left
14 Right side bottom		26 Back bottom right
15 Front left side		
16 Front right side		
17 Back left side		
18 Back right side		

The test shall be stopped after the 26th drop or when part of the load comes off, whichever occurs first. When the load comes off prematurely because the hinges and/or catches fail, the lid shall be re-secured and the test shall be continued. For each drop, any effect on the container such as damages shall be recorded. If the drop height and number of drops differ by agreement of stakeholders, it shall be reported in the report.

Annex A is an example of performance test of insulated container for temperature-sensitive medicinal products.

7 Test Report

The following information shall be included in the test report.

a) the sample information, including the number of samples used, external and internal dimensions of the insulated container, type of container material, and empty weight and fully loaded weight (total weight);

b) the date of the test;

c) the name, position and signature of the person who approved the test report;

d) a reference to this document, i.e. ISO 23416:2023;

e) a detailed temperature history for all tests in tabular format (for all channels) and temperature mapping report if applicable;

f) the result(s), including dimensions, weights and storage capacity measurements, thermal performance test and robustness test.

g) any deviations from the procedure and any unusual features observed.

Annex A
(informative)

Example of performance test of insulated container for a temperature-sensitive medicinal product

A.1 General

This is an actual example of performance test of insulated container for temperature-sensitive medicinal products. This container is designed to maintain the temperature (2 °C ~ 8 °C) for 100 h. See Figures A.1 to A.7.

A.2 Components of a packaging system

Figure A.1 — Insulated container (top) and PCMs (bottom). Five PCMs are designed for this container (four on side, one on top)

Figure A.2 — PCMs assembled in an insulated container