

Supplement 10

Checking the accuracy of temperature control and monitoring devices

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Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

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Abbreviations

DUT	device under test
SOP	standard operating procedure
TTSP	time- and temperature-sensitive pharmaceutical product

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Glossary

Standard operating procedure (SOP): A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Temperature control device: A device which actively controls the operation of cooling plant used to store or transport TTSPPs.

Temperature monitoring device: A device which monitors the temperature of spaces used to store or transport TTSPPs.

Thermal time constant: The most common definitions of the thermal reaction time are the so-called tau (τ , the 19th letter of the Greek alphabet) and "T90". Tau stands for the time a device needs to adapt to 63% of the end value of a temperature change whereas T90 represents the time to adapt to 90% of the change. T90 is approximately equal to 2.5 times Tau. These constants are commonly evaluated by experiment on the test device under well-defined conditions as described in EN 12830.¹

Time and temperature-sensitive pharmaceutical product (TTSP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Triple point: The temperature and pressure at which a substance can exist in equilibrium in the liquid, solid, and gaseous states. The triple point of pure water is at 0.01 degrees Celsius and 4.58 millimetres of mercury and is used to calibrate thermometers.

¹ EN 12830, Temperature recorders for the transport, storage and distribution of chilled, frozen, deep-frozen/quick-frozen food and ice cream – Tests, performance, suitability.

1. Introduction

This technical supplement has been written to amplify the recommendations given in section 4.10 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.² It describes a way to check the accuracy of temperature monitoring and temperature control devices using the “ice-water” procedure, and it outlines the limitations of this approach. This method can be used in situations where it is not possible to carry out a full three-point calibration using the services of a nationally or internationally accredited calibration laboratory.

1.1 Requirements

As a general rule, temperature measurement and control devices must periodically be calibrated to prove their accuracy over the full operating temperature range and according to the device’s data sheet definitions. Proven accuracy is mandatory because inaccurate readings can lead to a false sense of security and place time- and temperature-sensitive pharmaceutical products (TTSPPs) at risk.

Some devices are covered by calibration certificates from the device manufacturer. These certificates are valid for a defined period and the associated devices may be used throughout this period without additional calibration. An example of this is a single-use temperature monitoring device, which is designed to be discarded at the end of a journey, or when the battery powering the device expires. To ensure conformity, the manufacturer of such products must supply a calibration certificate with the device.

However, there are circumstances under which proper device calibration or recalibration is needed. The list below is not comprehensive but illustrates some of these circumstances:

- A calibration certificate is not available because it has been lost.
- The device is used for longer than the period covered by the calibration certificate, either at the user’s risk or with the approval of the manufacturer.
- The device was used or treated beyond the manufacturer’s data sheet limitations (e.g. it was subjected to excessive temperature or shock).
- The battery powering the device was replaced.
- The device’s measurements are suspect.
- The device manufacturer specifies that a calibration procedure should be carried out at regular intervals.

² <http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf>

- Regulatory bodies require regular proof of calibration, e.g. at 12-month intervals, and proof of calibration cannot be provided by the manufacturer's certificate.

1.2 Objectives

Wherever possible, calibration should be carried out in accordance with the device manufacturer's instructions, or by following a device-specific standard operating procedure (SOP). Ideally, a full three-point calibration should be carried out by a nationally or internationally accredited calibration laboratory with proven accuracy standards and appropriate equipment. However, there are many circumstances where accredited calibration is not possible because no suitable laboratory is available. The simple and accurate method described in this Technical Supplement can be used to prove the device's functionality and accuracy at one single point of temperature using the so-called ice-water procedure.

1.3 Target readership

This document is intended to be read by managers and technical staff who are responsible for the monitoring, installation and maintenance of temperature measurement and control equipment throughout the cold chain. Responsible managers must understand the necessity for calibration; in the absence of a suitable calibration laboratory, technical personnel must be able to carry out and/or supervise the accuracy checking procedure described below.

2. Guidance

The method described below is relatively simple to carry out but requires close attention to detail. The accuracy of the results is also dependent upon the use of a high-quality reference thermometer with a valid calibration certificate.

2.1 Associated materials and equipment

Reliable results will be achieved if the following equipment and materials are used.

- a. Wherever possible, use reference temperature measurement equipment regularly calibrated by an accredited laboratory, e.g. Fluke Hart Scientific precision equipment.³ Figure 1 shows an example of this type of instrument.

Figure 1
Example of a reference thermometer



Source: Fluke Hart

- b. Always use a temperature measurement reference instrument which is of higher accuracy than the device to be checked – for example, a thermometer with a rated accuracy of $\pm 0.2\text{ }^{\circ}\text{C}$ should be used to check a device with a rated accuracy of $\pm 0.3\text{ }^{\circ}\text{C}$.

³ <http://us.flukecal.com/products/temperature-calibration>

Note that mention of this company does not imply any endorsement or recommendation by the World Health Organization.

- c. A thermally insulated container, tub open to the atmosphere, and sufficiently large to contain enough melting ice-water to provide stable temperature conditions and allow full immersion of the device under test (DUT) as described in section 3. In the cold chain operating environment, a vaccine carrier or small cold box with a hinged or separate lid would be a suitable choice. The size required depends on the dimensions of the DUT.
- d. Disposable latex gloves.
- e. Enough clean distilled water must be available to make ice cubes and to set up a proper and stable ice-water triple-point mixture. The DUT should be sealed inside a transparent waterproof pouch before immersing it in the liquid in order to avoid water ingress and resulting damage. As much air as possible should be extracted to ensure that the DUT is in good contact with the ice-water mixture. Sealing is always recommended, even for DUTs with a high international protection rating (IEC 60529 IP protection class rating), because the protection might have been damaged – for example by dropping the device or during battery replacement. Where the DUT has an external sensor, the sensor may be immersed directly in the bath, provided it has an IP7 or IP8 protection class rating. Otherwise it should be sealed in a pouch as described above, with the pouch tied tightly around the lead above the level of the ice-water.

2.2 Procedure

The ice-water bath provides an accurate reference temperature at 0.0°C if the melting ice-water mixture is properly set up, handled and maintained. An accurate temperature is achieved by this method because an ice-water mixture in a container which is open to the atmosphere will stabilize at its own “triple point”. At this point all three aggregate states of water coexist: liquid, solid and gaseous. For more physical details refer to ASTM E563-11.

2.2.1 Prerequisites

- a. Only place clean equipment and distilled water inside the container. Use clean latex gloves to handle ice and equipment.
- b. Although the temperature of the ice-water mixture stabilizes itself, its temperature must still be monitored before and during the procedure using the calibrated reference thermometer. This is a mandatory requirement in order to prove the functionality and stability of the ice-water bath.

- c. During extended testing periods enough ice must be added to the bath to maintain the water-ice equilibrium temperature and to prevent a possible temperature rise caused by excessive melting of the ice.
- d. Note that only DUTs which display a temperature reading can be checked by this method because the temperature indicated by the DUT must be compared to the ice-water bath temperature. Devices without a display need additional equipment to capture an immediate measurement read-out so that this can be compared with the reference temperature reading. This additional equipment is manufacturer-specific.

2.2.2 Establishing the ice-point bath (excerpt from ASTM E563-11⁴)

- a. Before using the bath, chill the required amount of distilled water close to 0.0 °C.
- b. Freeze a suitable amount of the same water to produce ice-cubes, making sure that there is a sufficient quantity for the complete test run.
- c. Prepare shaved or fine crushed ice with a maximum 2 mm to 3 mm particle diameter; the finer the ice particles, the more accurate the ice-water temperature.
- d. Prepare the bath in the clean thermally insulated container. The container should be large enough not to affect the water-ice equilibrium temperature. The width, length or diameter and the overall depth must ensure that, when the thermal equilibrium state is reached, the test objects will not significantly modify the temperature of the bath over the region to which the ice point is to be applied. For normal applications, a width, length or diameter at least 100 mm larger than the maximum DUT dimension size, and a depth of at least 300 mm should be sufficient.
- e. Alternately add shaved ice and chilled water to the vessel, using just enough water to saturate the ice but not enough to float it. As the vessel fills, compress the ice-water mixture to force out excess water. The objective is to surround each particle of ice with water, filling all voids, but to keep the ice particles as close together as possible.

⁴ ASTM E563-11 Standard practice for preparation and use of an ice-point bath as a reference temperature. West Conshohocken, PA: ASTM.

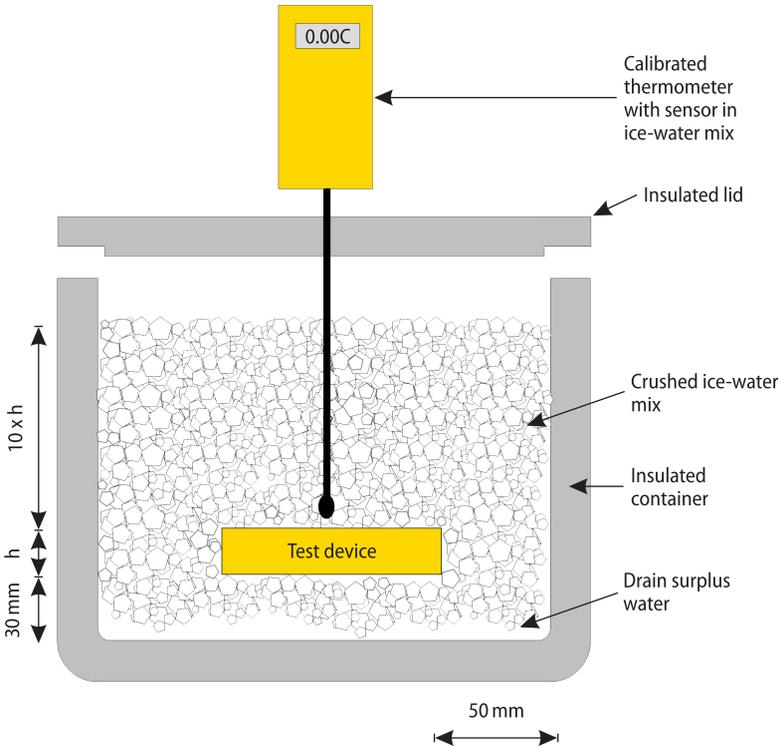
Continue adding ice and water and compressing until the vessel is filled to the required level. Decant or siphon off excess water.

- f. Use the reference thermometer throughout the entire test period to confirm that a stable temperature is maintained.
- g. Cover the ice-point bath to protect it during the test period. Use an opaque and thermally insulating cover or stopper that is suitable for the application. This reduces heat transfer to the ambient environment through the surface of the bath. Allow the bath and vessel to equilibrate for at least 30 minutes before using.

2.2.3 Placing the device in the bath

- a. Seal the DUT in a clean plastic bag. Make sure that as little air as possible is trapped inside the bag in order to avoid false results caused by floating and/or lack of contact between the DUT and the ice-water.
- b. Pre-cool the DUT in water at less than +3.0 °C before immersing it in the bath. Pre-cooling the DUT reduces the time taken to reach equilibrium at the ice point; it also helps to preserve the bath at the ice point for a prolonged time. Furthermore, it ensures that the water-ice interface will be in close contact with the DUT; negligible melting is important, otherwise the water film thickness between the DUT and the ice-water will increase and distort the test results.
- c. Form a well in the ice-water bath that has the dimensions and intended immersion depth of the DUT.
- d. Insert the sealed DUT to a depth of at least ten object diameters or heights respectively below the surface. Keep the DUT a minimum of 30 mm above the bottom of the container to avoid the zone at the bottom where denser meltwater tends to accumulate (Figure 2).
- e. Replace the lid. For devices with an external sensor, make sure that the lid seals well around the sensor lead.
- f. Allow the bath and DUT to come to thermal equilibrium. Allow for the thermal time constant of the DUT.

Figure 2
Ice-water bath arrangement



2.2.4 Carrying out the accuracy check, step-by-step

- Establish and maintain the ice-water bath, prove its temperature with the reference thermometer.
- Ensure that the DUT remains immersed in the ice-water bath as described in point 3.3d above.
- Directly read the DUT temperature display while it is still immersed in the bath. If this is not possible, remove the DUT and immediately read its temperature indicator; prompt action avoids false readings resulting from exposure to the ambient temperature.
- Record the readings on an accuracy check reference data chart as per sample taken from EVM-SOP-E2-2. Store the chart at least until the next accuracy check takes place, and preferably for a minimum of three years.

2.2.5 Maintaining the bath temperature

- a. As ice particles in the bath melt, excess water begins to accumulate. This melt water has a temperature slightly above 0.0 °C. Since the density of water is at its maximum at +4.0 °C, the slightly warm meltwater will collect at the bottom of the bath and, hence, around the DUT. Under these conditions, the bath will no longer be at 0.0 °C and cannot serve as an ice-point bath. For this reason surplus water should be removed, as it accumulates, from the bottom of the bath by decanting or siphoning. The presence of excess water can be detected if water overspill occurs when the ice is depressed. Add ice particles, and chilled water, as necessary so that the ice slush column always extends to at least 30 mm below the lowest point of the test object.
- b. In order to sustain the ice-point over prolonged periods, the ice-point bath can be immersed in another larger insulated bath that is kept near to 0.0 °C.

2.2.6 Actions to take following the test

There are two possible test outcomes: pass or fail.

1. The DUT passes the test

A pass is achieved if the DUT temperature indication deviates from the reference thermometer reading⁵ by less than the tolerance allowed in the data sheet. In this case the DUT should be physically labelled as follows:

Accuracy valid until: <enter the date one year after the accuracy check>.

Note: If the manufacturer or the regulatory authority stipulates a shorter or longer period of validity, enter the appropriate date to take account of this.

After this period expires the accuracy check must be repeated, as described in this document.

⁵ For example, if the reference instrument has an accuracy of ± 0.5 °C and the DUT deviates 0.3 °C from the reference instrument reading, this is a pass.

2. The DUT fails the test

If the DUT temperature indication deviates from the reference thermometer reading⁶ by more than the tolerance allowed in the data sheet the DUT fails the test. In this case, take one of the following actions:

- a. If the sensor can be adjusted, carry out the adjustment according to the manufacturer's instructions. Then repeat the accuracy check according to the procedure described above.
- b. If the sensor can be replaced, but the accuracy of the device is not solely dependent on the performance of the sensor head, replace the sensor according to the manufacturer's instructions. Then repeat the accuracy check.
- c. If the sensor can be replaced, and the accuracy of the device depends entirely on the performance of the sensor head, the sensor can simply be replaced with a new factory-calibrated sensor in accordance with the manufacturer's instructions. No further check is then required until the next accuracy/calibration date falls due.
- d. If the sensor can neither be replaced nor adjusted, the whole DUT must be replaced and a *non-conformity report* must be issued to the relevant decision-makers to ensure that the DUT is removed from service and replaced.

⁶ For example, if the reference instrument has an accuracy of ± 0.5 °C and the DUT deviates 0.6 °C from the reference instrument reading, this is a failure.

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Revision history

Date	Change summary	Reason for change	Approved

