PQS Independent type-testing protocol

WHO/PQS/E003//E006/IN07-VP.1
Original: English
Distribution: General

TITLE: Chemical Freeze Indicator

Product verification protocol:	E006/IN07.VP.1
Applies to specification ref(s):	E006/IN07.1
Date of this revision:	13 June 2019
Date of previous version:	New specification

Contents

1. Scope

This document describes the procedure for verifying the performance of freeze indicators. The testing of passive products only is covered by this protocol.

2. Terms and definitions

Acceptance Quality Limit (AQL): The "quality level that is the worst tolerable" according to ISO 2859-1. It represents the worst tolerable process average (mean) in percentage that is still considered acceptable; that is, it is at an acceptable quality level.
Backing card: Card to which the indicator is permanently attached containing information to activate (if necessary) and to interpret the appearance of the indicator. The card may be made from water resistant material.
In writing: Communication by letter, fax or email.
Legal manufacturer: The natural or legal person with responsibility for the design, manufacture, packaging and labelling of a product or indicator before it is placed on the market under the person's own name, regardless of whether these operations are carried out by that person or on that person's behalf by a third party.
Reseller: A commercial entity, licensed to act on behalf of a legal manufacturer, and which carries product liability and warranty responsibilities no less onerous than those carried by the legal manufacturer.

3. Normative references (use most current version)

EMAS: European Union Eco-Management and Audit Scheme.
ISO 2859-1 : 2014: Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection.
ISO 3951-1 : 2013 Sampling procedures for inspection by variables - Part 1: Specification for single sampling plans indexed by acceptance quality limit (AQL) for lot-by-lot inspection for a single quality characteristic and a single AQL
ISO 3951-2 : 2013 Sampling procedures for inspection by variables - Part 2: General specification for single sampling plans indexed by acceptance quality limit (AQL) for lot-by-lot inspection of independent quality characteristics
ISO 9001: 2015: Quality Management Systems – Requirements.
ISO 14001: 2015: Environmental management systems - Requirements with guidance for use.
ISO/IEC 17025: 2005: General requirements for the competence of testing and calibration laboratories.

The following informative reference is also recommended:

US Pharmacopeia 37 - NF 32: <1118> Monitoring Devices: Time, Temperature and Humidity

4. Applicability

Type-testing to be carried out by an independent ISO/IEC 17025 testing laboratory, accredited by

WHO.

5. Type-testing procedure

5.1 Sample control

Test samples should be stored in accordance with manufacturer's instructions. At least 500 test samples should be provided to enable the test laboratory to select random sets for testing. For example, if a test requires 30 samples, three different sets of 10 samples each could be selected. Where the design of the indicator requires that it should be activated by the user, indicators must be supplied in the inactivated state.

5.2 Test procedure

Note: Clause references in parenthesis refer to WHO/PQS/E006/IN07.1: *WHO Performance Specification for freeze indicators*.

5.2.1 Test 1: Type examination

- **Step 1:** Check all samples for similarities between different models[1], dissimilarities between samples of one model and any defects or damage.
- **Step 2:** Record any differences between the samples received.
- **Step 3:** Take a digital photograph of each type of indicator.
- **Step 4:** Tabulate the following information for each model submitted for examination. Obtain any additional supporting information required in writing from the legal manufacturer or reseller and attach this information to the report:

Identification
- Select a sample of 10 indicators.
- Code each test sample (a unique identifier to be assigned by the testing laboratory).
- State indicator model and type.
- Record if sample was provided by a legal manufacturer or reseller
- Record country of origin.
- Record conformity assessment markings, if present.
- Measure dimensions with and without backing card if supplied (Clause 4.4.1 *Dimensions*).

Indicator characteristics
- Method for activating indicator (if applicable) and record how the indicator demonstrates whether the indicator is in the active or inactive state (Clause 4.2.1).
- Mode of operation in compliance with Clause 4.2.2.

1 The purpose of this inspection is to establish whether products offered by competing companies are re-badged versions of an otherwise identical indicator.

- End point temperature (Clause 4.2.3).
- Manufacturer's stated operating temperature range when activated (Clause 4.2.5).
- Manufacturer's stated process for quality control (Clause 4.2.6).
- Manufacturer's stated shelf life (Clause 4.2.8).
- Ambient temperature range during transport and storage when not activated (Clause 4.3.1).
- Ambient humidity range during transport and storage (Clause 4.3.2).
- Declaration from the manufacturer that the indicator is adequately robust (Clause 4.3.3 Durability).
- Declaration from the manufacturer to attest that the materials used are non-toxic and non-irritant to the end user and substantially harmless to the environment (Clause 4.6).
- Record the manufacturer's warranty (Clause 4.7).

Human factors

- Visual change when the end point has been reached (Clause 4.2.2 and Clause 4.5.1).
- The backing card, if supplied (Clause 4.5.2).
- Visual change legible for a person with normal visual acuity (Clause 4.5.3).
- Means for attaching indicator to vaccine packaging (Clause 4.5.4).
- Instructions (Clause 4.8).
- Procedure to provide training for the vaccine manufacturer or any downstream user for correct handling, correct application and checking of the indicator (Clause 4.9).

Acceptance criteria: Type examination indicates full conformity with all specification requirements.

5.2.2 Test 2: Stability during storage

- **Sample size:** 30 indicators.

- **Step 1:** Store 15 test samples at an ambient temperature equal to the upper limit of the operating conditions as specified by the manufacturer, 95% RH for a period of 48 hours.

- **Step 2:** Examine test samples for visual change.

- **Step 3:** Store same 15 test samples at an ambient temperature equal to the lower limit (without triggering indicator) of the operating conditions as specified by the manufacturer 5% RH for a period of 48 hours).

- **Step 4:** Examine test samples for visual change.

- **Step 5:** Repeat Steps 1 to 4 with a new set of 15 test samples but with the lower limit of the operating conditions (without triggering indicator) and 5% RH conditions first and subsequently the upper limit of the operating conditions and 95% RH conditions.

- **Step 6:** Activate test samples if necessary. Stabilize test samples in a water bath or air incubator for at least one hour at 2°C ± 0.2°C warmer than the end point temperature for

the indicator. Test samples in a water bath to be in sealed pouches. Temperature of water bath or air incubator to be accurate to ± 0.2°C [2].

- **Step 7:** Decrease temperature of water bath or air incubator to 1°C lower than the end point temperature (i.e. -1.5°C) for 60 minutes.

Acceptance criteria: No visual change in any test sample at the end of Step 5. All samples to show no change after Step 6 and show appropriate visual change at the end of Step 7.

Rejection criteria: If test samples do not comply with acceptance criteria, stop testing and report results of Tests 1 and 2 only.

5.2.3 Test 3: Temperature accuracy test

- **Sample size:** 30 indicators.

Note: If using pouches to perform test, use transparent pouches and ensure there is minimal air trapped in the pouch. It is recommended to use a vacuum sealer.

- **Step 1:** Activate 30 previously untested samples in accordance with manufacturer's instructions if this action is required. Otherwise proceed to Step 2.

- **Step 2:** Stabilize 30 test samples in a water bath or air incubator for at least one hour at 2°C ± 0.2°C warmer than the end point temperature for the indicator. Test samples in a water bath to be in sealed pouches. Temperature of water bath or air incubator to be accurate to ± 0.2°C[3].

- **Step 3:** Starting at +1.5°C, once the bath has reached the set point temperature, allow samples to equilibrate for 60 minutes. Record which test samples exhibit a visual change. Note: When evaluating the samples, the time out of the bath should be minimized.

- **Step 4:** Decrease the temperature in 0.5°C increments allowing the bath to stabilize each time. Allow samples to equilibrate for 60 minutes. Record which test samples exhibit a visual change. Continue Step 4 until all test samples have completely changed appearance or until after testing at -2.0°C.

- **Step 5:** Increase temperature up to +5°C and hold for 60 minutes for 15 test samples only (Set A) for comparison with remaining 15 test samples (Set B) kept at the final test temperature in Step 4.

- **Step 6:** Set B test samples to be set aside for Test 4.

---

2 Test samples in a water bath or air incubator to be surrounded by an array of temperature sensors. The average of which to be accurate to ± 0.2°C.

3 Test samples in a water bath or air incubator to be surrounded by an array of temperature sensors. The average of which to be accurate to ± 0.2°C.

Acceptance criteria: Indicators must show a complete visual change within the temperatures and time limit required by specification Clauses 4.2.3 and 4.2.4. Visual appearance to be maintained throughout Step 5.

5.2.4 Test 4: Low ambient temperature test

- **Sample size:** The 15 Set B test samples from Test 3 (those which have *not* been subjected to a temperature of +5°C).
- **Step 1:** Expose test samples to a temperature of -20°C ± 1°C for six hours.
- **Step 2:** Remove test samples from the test chamber to room temperature.
- **Step 3:** Record whether each test sample continues to display end point visual change.

Acceptance criterion: All test samples to continue to display the end point visual change.

5.2.5 Test 5: High ambient temperature test

- **Sample size:** The 15 Set A test samples from Test 3 and 15 Set B test samples from Test 4.
- **Step 1:** Condition all test samples to a temperature of 43°C ± 0.5°C for at least six hours.
- **Step 2:** Remove test samples from the test chamber and record whether test sample displays end point visual change at time of removal or soon afterwards recording the time it takes to show end point.

Acceptance criterion: All test samples to display the end point visual change within a maximum of five minutes following removal from test chamber.

5.2.6 Test 6: Soak test

- **Sample size:** 30 indicators.
- **Step 1:** Prepare previously untested samples. Those test samples only designed to be affixed to vials must be affixed to vials. Those test samples with backing cards must be on backing cards.
- **Step 2:** Submerge test samples in a water bath with no waterproof pouches at +5 ± 0.2°C for eight hours.
- **Step 3:** At the end of the eight-hour period, remove the labels from the water bath and carefully dry the soaked labels with absorbent towels.

- **Step 4:** Place samples in a desiccant chamber at +5 ± 0.2°C for 16 hours.

- **Step 5:** Test in accordance with Test 3: Steps 2 to 6.

Acceptance criterion: No water damage observed. No change in appearance after completion of Test 3: Step 3. Samples to meet the acceptance criteria from Test 3.

5.2.7 Test 7: Observer perception test

- **Sample size:** Activate (if necessary) 30 previously untested samples. Prepare 15 test samples which have not reached their end point and condition 15 test samples to show a visual change having reached their end point.

- **Step 1:** Five naive[4] observers must read the instructions as provided by the manufacturer.

- **Step 2:** Place the 30 test samples hidden in a box in random order.

- **Step 3:** Working independently, the five observers, under tungsten or florescent light at 100 lux on the working plane, must sort the test samples into two groups. Repeat the test using the same five observers working independently under bright sunlight or equivalent. Record the light levels used in both tests. Record the time taken by each observer to complete the test.

Acceptance criteria: All five observers are able to sort the two groups of test samples with 100% accuracy under both lighting regimes. The mean time taken to complete the task should not exceed two minutes.

5.3 Test criteria for qualification

A final report to be issued after testing is complete. The report of the tests must contain the following data and analyses:

- **Summary:** Conclusions and recommendations.

- **Test 1:** Results of type examination, tabulated data and photographs of samples.

- **Test 2:** Results of storage stability test.

- **Test 3:** Results of temperature accuracy test.

- **Test 4:** Results of low temperature test.

- **Test 5:** Results of high temperature test.

4 I.e. those who are previously unfamiliar with this type of indicator.

- **Test 6:** Results of water-resistance test.

- **Test 7:** Results of observer perception test.

- **Annexes:** Information from manufacturer as examined in Test 1. Additional supporting documentation requested and received from the legal manufacturer or reseller during the course of the type-testing. Test chamber temperature records and laboratory instrumentation calibration records to be kept on file for later scrutiny.

6. Quality control checklist

6.1 Quality control standards

All testing and reporting must be carried out in accordance with the requirements of ISO 17025:2005 (or equivalent) or a later edition.

6.2 Quality audit

An on-site inspection of the manufacturing plant is not required by the test laboratory.

7. Prequalification evaluation

A product may qualify to be included on the register of PQS approved products when the dossier indicates full conformity with the requirements of specification **E006/IN07.1**. (The PQS Secretariat reserves the option to apply other requirements.)

8. Modified products

The legal manufacturer or reseller must notify WHO in writing of any changes which affect the performance of the product. WHO will carry out a desk evaluation of the reported change(s). If any change is deemed adversely to affect the performance of the product, WHO may request full or partial re-verification based on the test procedures described in this document.

Revision history			
Date	Change summary	Reason for change	Approved
		.	