PQS Independent type-testing protocol

TITLE: Threshold Indicator

Product verification protocol:	E006/IN04.VP.1
Applies to specification ref(s):	E006/IN04.1
Issue date:	09 July 2018
Date of last revision:	New protocol

Contents

1. Scope

This document describes the procedure for verifying the performance of threshold indicators. This protocol covers the testing of passive products only.

2. Normative references

ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories.
WHO/PQS/E006/TI0x.1: WHO Performance Specification for Threshold Indicators

3. Terms and definitions

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 his own name, regardless of whether these operations are carried out by that person himself or on his 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.

4. Applicability

Type-testing to be carried out by an independent ISO/IEC 17025 testing laboratory that has been accredited by WHO.

5. Type-testing procedure

5.1 Sample control

Manufacturers must provide at least 500 test samples so that the test laboratory can select random sample sets for testing. For each test, the testing laboratory should select sample sets equally from at least three different locations within the full sample provided by the manufacturer.

Where design of the threshold indicator requires that it should be activated by the user, manufacturers must supply indicators in the inactivated state. Laboratories should store active indicators as defined by the manufacturer's instructions until the time of testing.

5.2 Test procedure

5.2.1 Test 1: Type examination

- **Step 1:** Take a digital photograph of a sample indicator.
- **Step 2:** Tabulate the following information according to the type of indicator submitted for examination and 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 from the batch provided; note the batch number in the records,
- Code each test sample (a unique identifier must be assigned by the testing laboratory),
- State the indicator type,
- Record if sample was provided by a legal manufacturer or reseller,
- Record country of origin,
- Record conformity-assessment markings,
- Measure dimensions with and without backing card if supplied (Clause 4.4: *Dimensions*).

Indicator characteristics

Verify and record that the following requirements are met:

- (If applicable) method for activating indicator and note how the indicator demonstrates whether it is in the inactive/active state, as per Clause 4.2.1.
- Mode of operation complies with Clause 4.2.2.
- Manufacturer's specifications define the Threshold temperature, as per Clause 4.2.3.
- Manufacturer's specifications define the manufacturer's stated operating temperature range (when activated), as per Clause 4.2.5.
- Manufacturer's specifications define the manufacturer's stated process for quality control, as per Clause 4.2.6.
- Manufacturer's stated shelf life complies with Clause 4.2.8.
- Manufacturer's specifications define the ambient temperature range during transport and storage (not activated), as per Clause 4.3.1.
- Manufacturer's specifications define the ambient humidity range during transport and storage complies, as per Clause 4.3.2.
- Declaration has been provided by the manufacturer to attest to the indicator's compliance with Clause 4.3.3: *Durability*.
- Declaration has been provided by the manufacturer to attest that the materials used are non-toxic and non-irritant to the end user and substantially harmless to the environment, as per Clause 4.6.
- Manufacturer's warranty is included; record type, as per Clause 4.7.

Human factors

Perform the following verifications:

- Does the visual change comply with Clause 4.2.2 and Clause 4.5.1 when the threshold temperature has been reached?
- Is the visual change legible for a person with normal (corrected to 20/20) visual acuity, as per Clause 4.5.3?
- Does the indicator have a means for attaching it to vaccine packaging, as per Clause 4.5.4?
- Do the instructions comply with Clause 4.8?

– Does the manufacturer have a procedure in place to provide training for the vaccine manufacturer or any downstream user for correct handling, correct application and checking of the indicator, as per 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.

Steps 1 through 5 apply only to indicators that can be activated; Step 6 applies only to always-active indicators. Steps 7 and 8 apply to all samples.

- **Step 1:** Store 15 test samples at -30°C ambient temperature for a period of 48 hours. Indicators which require physical activation before placement with the vaccine load are to be stored in the inactivated state.
- **Step 2:** Examine test samples for visual change.
- **Step 3:** Store the same 15 test samples at +70°C ambient temperature for a period of 48 hours. Only those indicators which require physical activation before placement with the vaccine load are to be tested, and that test should be performed on the indicator in its inactivated state).
- **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 +70°C conditions first for test samples that are not activated, followed by the -30°C conditions.
- **Step 6:** Store 15 test samples of always-active indicators at -30°C ambient temperature for a period of 48 hours. Store a second set of always active indicators at +70°C ambient temperature for a period of 48 hours.
- **Step 7:** Activate test samples if necessary. Stabilize test samples in a water bath for at least one hour at 2°C ± 0.1°C colder than the threshold temperature for the indicator. Samples tested in a water bath must be in sealed pouches. Temperature of water bath to be accurate to ± 0.1°C.
- **Step 8**: Increase temperature of water bath to [threshold temperature] +1°C (e.g. 41°C) for 15 minutes; the time from when the bath reaches the test temperature to the time the samples are assessed.

Acceptance criterion: No visual change in any test sample at the end of Step 4 or Step 7 with the exception of the always-active samples exposed to +70°. All samples to show visual change at the end of Step 8.

Rejection criterion: 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.

- **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 test samples in a water bath for at least 1 hour at 2°C ± 0.1°C colder than the threshold temperature for the indicator. Samples tested in a water bath must be in sealed pouches. Temperature of water bath to be accurate to ± 0.1°C.[1]
- **Step 3:** Increase the temperature in increments of 0.5°C at 15-minute intervals towards the threshold temperature; the time from when the bath reaches the test temperature to the time the samples are assessed. Record which test samples exhibit a visual change. Continue this procedure to where all test samples have completely changed appearance.
- **Step 4:** Decrease temperature to 5°C below the threshold temperature and hold for 60 minutes for 15 test samples only (Set A). Remaining 15 samples (Set B) to be kept at the final test temperature in Step 3 for comparison.
- **Step 5:** Set B test samples to be set aside for Test 4.

Acceptance criteria: Visual change after completion of Step 3 to be complete within ± 1 . 0 °C of the threshold temperature within the time limit required by specification Clause 4.2.5. Visual change to be maintained throughout Step 4.

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 +35°C).

- **Step 1:** Expose test samples to a temperature of -20°C ± 5.0°C for 6 hours.
- **Step 2:** Remove test samples from the test chamber to room temperature.
- **Step 3:** Record whether each test sample continues to display visual change.

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

5.2.5 Test 5: High ambient temperature test

1 Test samples in a water bath to be surrounded by an array of temperature sensors or previously qualified to be homogeneous. The average of which to be accurate to ± 0.1°C.

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 visual change at time of removal or soon afterwards.

Acceptance criterion: All test samples to maintain the visual change following removal from test chamber.

5.2.6 Test 6: Soak test

Sample size: 30 indicators.

- **Step 1:** Prepare test samples. Only those test samples that are designed to be affixed to vials must be affixed to vials. Only 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 ± 3.0°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 both groups in a desiccant chamber at +5 ± 3.0°C for 16 hours.
- **Step 5:** Test in accordance with Test 3: Steps 2 to 4.

Acceptance criterion: No water damage observed. All samples to meet the criteria of Test 3: Step 3. Visual appearance to be maintained throughout Test 3: Step 4.

5.2.7 Test 7: Observer perception test

Sample size: Activate (if necessary) 30 new test samples. Prepare 15 test samples which have not reached their visual change and condition 15 test samples to show a visual change having reached their threshold temperature.

- **Step 1:** Five naive observers to read the instructions as provided by the manufacturer.[2]
- **Step 2:** Place the 30 test samples hidden in a box in random order. Since some threshold indicators are small and difficult to handle (if not already on a backing card), threshold indicators should be attached to a substrate for ease of handling.
- **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

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

used in both tests. Record the time taken by each observer to complete the test.

Acceptance criterion: 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.
- **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 for evaluation to be included on the register of PQS prequalified products if the dossier indicates full conformity with the requirements of specification **E06/IN03.1**. (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.

9. Revision history (New protocol)

Date	Change summary	Reason	Approved