PQS Independent type-testing protocol

TITLE: Combined Vaccine Vial Monitor and Threshold Indicator

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Contents:

1. Scope

This specification describes general performance requirements for non-electronic *Combined Vaccine Vial Monitor (VVM) and Threshold Indicator (TI).* This is a chemical indicator designed to warn health workers when either the cumulative time-temperature exposure or the peak temperature threshold of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used.

Before the end point is reached, gradual monotonic shade changes in the VVM active surface can alert health workers that particular vials have been partially exposed which then can be used in preference to those that have not been exposed.

VVMs and threshold indicators can be supplied in an active state or be made active by manufacturer's own designed method. Each individual indicator must

comply with and be tested in accordance with their own appropriate specification and protocol.

Each indicator technology must comply with the current version of their own appropriate specification: *PQS Performance Specifications: Vaccine Vial Monitor* WHO/PQS/E006/IN05.3 and *PQS Performance Specifications: Threshold Indicators* WHO/PQS/E006/IN04.1

Each indicator technology must be tested in accordance with the current version of their own appropriate protocol: *PQS Independent type-testing protocol: Vaccine Vial Monitor* WHO/PQS/E006/IN05.VP.3 and *PQS Independent type-testing protocol: Threshold Indicators* WHO/PQS/E006/IN04.VP.1

It is important that the performance of the VVM which undergoes a gradual change, does not affect the Threshold Indicator which exhibits a rapid change when the threshold temperature is exceeded.

The tests in this verification protocol are only for those indicators where one indicator is overlaid by another indicator.

2. Normative references

References to be made to the latest published versions of the following. Dates are given for versions current at the time of publishing this specification.

EMAS: *European Union Eco-Management and Audit Scheme.*

ISO 9001 : 2015: *Quality Management Systems – Requirements*.

ISO 14001 : 2015: *Environmental management systems - Requirements with guidance for use.*

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 5-3 : 2015 *Photography-Density measurements-Part 3: Spectral Conditions*.

3. Terms and definitions

AQL: Acceptance Quality Limit. The acceptable quality limit prescribes an industry standard for the allowed number of defective samples that are considered acceptable when testing random samples within a batch according to the required level of confidence in a product. (See ISO 2859-1 : 2014.)

Active surface: A time-temperature sensitive indicator which changes shade and whose reaction rate closely matches the stability profile of the vaccine[1].

End point: The point at which time-temperature exposure has altered the shade of the active surface so that it exactly matches or is darker than the reference surface. At this point, and thereafter, the vaccine should no longer be used.

In writing: means communication by letter, fax or email.

Legal Manufacturer: The natural or legal person with responsibility for the design, manufacture, packaging and labeling of a product or device 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.

Montreal Protocol: Montreal Protocol on Substances that Deplete the Ozone Layer.

OD: Optical Density – reflected OD in the case of this specification. The logarithmic measure of light reflected from the surfaces of the VVM are measured by an appropriate instrument such as a spectrodensitometer or a densitometer. $OD = - \log_{10} R$, R reported in decimal format.

R – I: The reference surface value OD minus the active surface value OD.

Reference surface: A patch surrounding the active surface against which the shade of the active surface can be directly compared.

Reaction rate: The rate at which the active surface responds to time-temperature exposure.

Re-seller: 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.

Spectrodensitometer: Instrument to measure reflected optical density. Note that not all spectrodensitometers have the ability to measure spectral data or display colorimetric information. Owing to the small size of the VVM's reference ring and indicator area, it is necessary to ensure the target and aperture centering of the spectrodensitometer is suitable for measuring the active surface and the reference surface. Conversion of spectral data to optical density is defined within ISO 5-3:2009 *Photography-Density measurements-Part 3: Spectral Conditions*. All such instruments must be calibrated before use each day according to the instrument manufacturer's instructions.

Start point: The optical density of the active surface of the VVM at the time when the VVM is received by the vaccine manufacturer[2].

Vial: In the case of this specification, a "vial" also refers to other primary containers containing vaccine (onto which a VVM may be applied), for example, droppers, ampules or pre-filled syringes.

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[1] In consultation with the WHO, the vaccine manufacturer should match the stability profile of their vaccine to the time-temperature profile of one of the VVM types described in the PQS Catalogue.

[2] It is the vaccine manufacturer's responsibility to store the VVMs correctly to prevent any change in the start OD during the period elapsing between the time of receipt of the VVM to the time of its application to the filled vaccine vial.

VVM: Vaccine Vial Monitor comprising, as a minimum, an active surface, a reference surface and the substrate to which these surfaces are applied by the VVM manufacturer.

4. Applicability

Type testing must be carried out by an independent ISO/IEC 17025 accredited testing laboratory, accredited by WHO. On-site inspection of the legal manufacturer's production facilities may be carried out by WHO or by a consultant appointed by WHO for this purpose.

5. Type-testing procedure

The following tests to be carried out for "overlaid" combined indicators only where the VVM is normally tested at temperatures colder than the TI threshold temperature. If the VVM has to be tested at temperatures higher than the TI threshold temperature, the manufacturer to supply separated versions for testing according to appropriate VPs.

5.1. Sample control

500 combined indicators to be supplied, so that the test laboratory can select random samples from those provided.

5.2 General test procedure

5.2.1 VVM transit, storage and handling

Transit: Samples supplied in an active state must be packed in an insulated container with dry ice or frozen gel packs and there must be ***residual*** dry ice or partially frozen gel packs in the container when it arrives at the laboratory.

Storage: Before testing, active indicators must be stored in temperatures at or below –24°C in a freezer whose temperature is recorded frequently. Indicators in cold storage should be packaged to avoid condensation and moisture contamination. Testing should commence within two weeks of the arrival of the samples at the laboratory[3].

Active indicators should be stored in no-light conditions as appropriate.

Handling: When active samples are handled in preparation for the tests they must be removed from the freezer, in small batches for the briefest period possible, before being returned again to storage at or below –24°C. For indicators which are supplied initially inactive, follow the manufacturer's instructions for storage and handling.

5.2.2 Test conditions

Conditioning test samples: Activated test samples should be conditioned in a water bath to age the VVM component for Test 2.

Temperature stability: The threshold indicator component must be tested for accuracy in a water bath which must be maintained within a tolerance of ±0.1°C[4].

[3] This is to help track shipment or storage issues if early results show non-compliance.

[4] 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.

The temperature of the water bath should be monitored at least every 5 minutes.

A summary of the water bath data should be included in the final report.

Light sensitivity: The active surface of some VVM models is sensitive to light. The laboratory should store and test these under "no-light" conditions.

5.2.3 OD measurements

For Test 2, OD measurements can be made using a spectrodensitometer with a 2 mm diameter measurement aperture with traceable calibration using BCRA[5] Series II tiles. Conversion of spectral data to optical density is defined within ISO 5-3 : 2009 Photography-Density measurements-Part 3: Spectral Conditions.

5.2.4 Test 1: Type examination

Step 1: Check all samples for similarities between different models[6], dissimilarities between samples of one model, and any defects or damage.
Step 2: Record any differences between the samples ordered and those 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 Re-seller and attach this information to the report:

Identification

- Code each test sample or batch (a unique identifier to be assigned by the testing laboratory)
- State model
- Legal Manufacturer or Re-seller
- Record country of origin
- Record conformity assessment markings.
- Measure dimensions (Clause 4.4.1 Dimensions).

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

5.2.5 Test 2: Effect of VVM transition on TI performance

Sample size: 150 combined indicators.
Step 1: Activate 150 previously untested samples in accordance with manufacturer's instructions if this action is required. Otherwise proceed to Step 2.
Step 2: Divide samples into five batches of 30 each. Condition all samples at +37 ± 0.2°C in a water bath, without light. Remove appropriate batch as indicated below and measure the active surface OD.
Step 3: At the beginning of the test period (0%), remove the Batch I and measure the OD of the active surface on the 30 samples.

[5] BCRA = British Ceramic Research Association

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

Step 4: Seal test samples in a pouch and immerse samples in a water bath for at least 1 hour at 2°C ± 0.1°C colder than the threshold temperature for the indicator. Temperature of water bath to be accurate to ± 0.1°C[7]. Increase the temperature by 0.5°C increments at 15 minute intervals towards the end point temperature; the time from when the bath reaches the test temperature to the time the samples are assessed. Record the temperature when test samples exhibit a visual change.
Continue this procedure to where all test samples have completely changed appearance. Then decrease temperature to 35°C and hold for 60 minutes. Store this batch at or below –24°C for Test 3.
Step 5: After 25% of the OD change towards the reference surface OD (±0.03 OD on average for the set), remove Batch II and measure the OD of the active surface on the 30 samples.
Step 6: Repeat Step 4. Store this batch at or below –24°C for Test 3.
Step 7: After 50% of the OD change towards the reference surface OD (±0.03 on average for the set OD), remove Batch III and measure the active surface OD on the 30 samples.
Step 8: Repeat Step 4. Store this batch at or below –24°C for Test 3.
Step 9: After 75% of the OD change towards the reference surface OD (±0.03 on average for the set OD), remove Batch IV and measure the active surface OD on the 30 samples.
Step 10: Repeat Step 4. Store this batch at or below –24°C for Test 3.
Step 11: After completion of the agreed test period, remove the Batch V and measure the active surface OD on the 30 samples. Store this batch at or below –24°C for Test 3.
Acceptance criteria: Visual change after completion of Step 4, 6, 8 and 10 to be complete within ±1.0°C of end point within the time limit required by Clause 5.2.3 of *PQS Independent type-testing protocol: Threshold Indicators* WHO/PQS/E006/IN04.VP.1.Visual change to be maintained throughout Step 4, 6, 8 and 10.

5.2.6 Test 3: Water resistance test

Sample size: A total of at least 30 combined indicators selected equally from each of the 5 batches.
Step 1: Prepare test samples. Those test samples only designed to be affixed to vials must be affixed to vials (when samples are to be applied to vials in Test 3, the samples must remain on the release liner throughout Test 2).
Step 2: Submerge test samples in a water bath with no waterproof pouches at +5 ± 3°C for 8 hours.
Step 3: At the end of the 8 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°C for 16 hours.

Acceptance criterion: Text and/or diagrams must still be clear and legible. No change in appearance after completion of Test 3. Step 4 to be completed for all test samples. Visual appearance to be maintained throughout Step 4.

[7] 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.

6. 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 temperature accuracy test.
- **Test 3:** Results of water-resistance test.
- **Annexes:** Information from manufacturer as examined in Test 1. Additional supporting documentation requested and received from the Legal Manufacturer or Re-seller during the course of the type-testing. Test chamber temperature records and laboratory instrumentation calibration records to be kept on file for later scrutiny.

7. Quality control checklist

7.1 *Quality standards:* Verification testing must be carried out in accordance with the requirements of ISO 17025:2005 (or equivalent).
7.2 *Quality audit:* An on-site inspection of the manufacturing plant is not required by the test laboratory.

8. Pre-qualification evaluation

A product may qualify for evaluation to be included on the register of PQS approved products in when the dossier indicates full conformity with the requirements of specification **E06/IN06.1**. (The PQS secretariat reserves the option to apply other requirements.)

9. Modified products

The legal manufacturer or re-seller 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.

10. Revision history

Revision history			
Date	Change summary	Reason for change	Approved
March 2019	Various changes	To comply with the specification	IG