PQS performance specification

WHO/PQS/E006/IN06.1
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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.

There are two main types of combined indicator. One where the two indicators are together on the same label, another where one indicator is overlaid onto another indicator. 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 is breached.

The *Combined Vaccine Vial Monitor (VVM) and Threshold Indicator (TI)* must meet the requirements of the current version of *PQS Performance Specifications: Vaccine Vial Monitor* WHO/PQS/E006/IN05.3 and *Threshold Indicators* WHO/PQS/E006/IN04.1

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

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..

measured by an appropriate instrument such as a spectro-densitometer 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.
spectro-densitometer: Instrument to measure reflected optical density. Note that not all Spectro-densitometers 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.
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. Requirements

Each indicator's own specification applies except for the following.

4.1 *General:* The indicators cannot be attached to a backing card because the VVM must be on a vial or other primary vaccine container.

4.2 *Performance:*

4.2.1 *Mode of operation:* The threshold component of the combined indicator must conform to Clause 4.2.2 of WHO/PQS/E006/IN04.1 and the cumulative component must conform to section 4.1.1 of WHO/PQS/E006/IN05.3

4.3 *Instructions:* Illustrated instruction sheets in English, to be supplied in every carton. Instructions printed in other languages to be supplied on client's request. Illustrated instructions for the combined VVM and TI must be provided. These should show:

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.

(a) Storage instructions for active and non-active indicators.
(b) How to activate each indicator or a clear instruction that the indicator is always active.
(c) Visual state of the combined indicator before the end point has been reached.
(d) Visual state of the combined indicator when the end point has been reached.

4.4 *Training:* The product manufacturer to provide training for the vaccine manufacturer so that the manufacturer can correctly handle, apply and test the combined indicator.

4.5 *Verification:* 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/IN05.3-VP.3 and *PQS Independent type-testing protocol: Threshold Indicators* WHO/PQS/E006/IN04-VP.1

A combined indicator where one indicator overlays another should be verified in accordance with PQS VP E006/IN06-VP.1.

5. Product dossier

The legal manufacturer or re-seller is to provide WHO with a pre-qualification dossier containing the following:

- Dossier examination fee in US dollars.
- General information about the legal manufacturer, including name and address.
- Unique identification reference for the product type.
- Full specifications of the product being offered, covering all the requirements set out in this document, including details of product marking and traceability.
- Certified copies of all type-approvals obtained for the product, including CE marking.
- Certified photocopies of the legal manufacturer's ISO 9001 2015 quality system certification.
- Details of the legal manufacturer's internal AQL sampling procedures in accordance with ISO 3951 and ISO 2859
- Where available, certified photocopies of the legal manufacturer's ISO 14001 certification, EMAS registration or registration with an equivalent environmental audit scheme. (Conformity with an environmental audit scheme is not mandatory; however preference will be given to manufacturers who are able to demonstrate compliance with good environmental practice.)
- Test report(s) from a PQS approved laboratory proving conformity with the product specifications.
- A minimum of 10 samples of the product shipped in accordance with the manufacturer's instructions together with product instruction insert – both in English language.
- Indicative cost of the product per 100 units, per 1,000 units and per 10,000 units EXW (Incoterms 2015).

6. Change notification

The legal manufacturer or re-seller is to advise WHO in writing of any changes which adversely affect the performance of the product after PQS pre-qualification has taken place.

7. Defect reporting:

The legal manufacturer or re-seller must advise WHO and the UN purchasing agencies in writing in the event of all product recalls, component defects and other similar events.

8. Revision history

Revision history			
Date	Change summary	Reason for change	Approved