PQS performance specification

WHO/PQS/E006/IN05.4
Original: English
Distribution: General

TITLE: Vaccine Vial Monitor

Specification reference:	E006/IN05.4
Product verification:	E006/IN05/VP.4
Issue date:	19 October 2020
Date of last revision:	15 May 2018

Contents:

1. Scope:

This specification describes general performance requirements for *Vaccine Vial Monitor (VVM).* This is a chemical indicator designed to warn health workers when the cumulative time-temperature exposure 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 shade and monotonic 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 can be supplied in an active state or be made active by manufacturer's own design method. VVMs may also be supplied together on the same label with other indicators. Each indicator technology must comply with and be tested in accordance with their own appropriate specification and verification protocol.

Note the specifications given in this document include examples of currently approved VVM types– more types may be added on application to the WHO PQS. The detailed specifications of each new VVM type will be defined in the PQS Catalogue.

2. Normative references:

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].

[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.

End point: The point at which time-temperature exposure has altered the shade of the active surface so that it exactly matches 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.
Mean Kinetic Temperature (MKT): A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.
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 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.
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 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.

[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.

4. Requirements:

4.1.1 General:

The VVM comprises an outer reference surface and an inner active surface. The change of the active surface is limited to a change of shade, from light to dark. Any colour is permitted for the VVM design, but changes in hue when activated are not permitted.

4.1.2 Format and dimensions:

Please see Annex 1 the VVM design specification.

4.1.3 Activation:

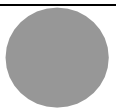
The VVM may be continuously active or made into an activated state e.g. by means of a physical removal of a "trigger strip" or other positive user intervention. Manufacturer must provide instructions and controls to ensure that it is visibly obvious whether the VVM is in an activated or inactivated state. Only activatable VVMs require visibly obvious cues.

4.2 Performance

4.2.1 Optical density change:

The optical density change of the indicator is illustrated in the Figure 1 below. At the start point the shade of the active surface is lighter than the reference surface. The end point is indicated when the shade of the active surface matches the shade of the reference surface. The end point is exceeded when the shade of the active surface is darker than the reference surface. Clauses 4.2.2 to 4.2.5 describe allowed parameters for the shade change.

Figure 1. The shade change of the indicator

Start point		Square lighter than circle
End point		Square matches the circle
End point exceeded		Square darker than the circle

Note: the central surface is the active surface.

4.2.2 Optical density at start point and end point:

- At the start point, the optical density of the active surface must be lower than the optical density of the reference surface by a difference of at least 0.23.
- The end point is reached when the difference in the average optical density obtained from readings at two different points on the reference surface and the optical density of two different points of the active surface is 0.00. The end point is exceeded when the OD of the active surface is higher than OD of the reference surface.

- The specifications for the Start OD of both the reference and active surfaces and the OD difference between the two surfaces (R-I) with their permitted tolerances must be specified by the manufacturer of the VVMs. Tolerances should include any effect from the liner.

4.2.3 Homogeneity of the reference surface: The optical density of one 2 mm diameter portion of the reference surface must be within 0.03 of the optical density at any other two 2 mm diameter portions of the reference surface, when measured with a densitometer (with a 2 mm diameter aperture).

4.2.4 Variation of the reference surface within the lot: The average optical density of at least two measurements in different positions on the reference surface of one sample must be within 0.03 of a similar average optical density of the reference surface of any other sample within the same lot.

4.2.5 VVM reaction rates: Reaction rates specific to different *example* types of VVM, relating to groups of vaccines according to their stability at two specific temperature points in Table 1a and Table 1b below. Note that VVM0.5 and VVM½ may be used interchangeably.

Table 1a: VVM reaction rates by type

Type (Vaccines)	**Maximum time to end point at +37°C**	**Maximum time to end point at +25°C**	**Maximum time to end point at +5°C**	**Time to end point at +5°C**
VVM30: High Stability	30 days	193 days	NA*	≥4 years
VVM14: Medium Stability	14 days	90 days	NA*	≥ 3 years
VVM11: Intermediate Stability	11 days	71 days	NA*	≥2.5 years
VVM7: Moderate Stability	7 days	45 days	NA*	≥2 years
VVM2: Low Stability	2 days	NA*	225 days	NA*
VVM1: Very Low Stability	1 day	NA*	100 days	NA*
VVM0.5: Extremely Low Stability	0.5 days	2 days	28 days	NA*

**VVM (Arrhenius) reaction rates determined at two temperature points only*

*** VVM (Arrhenius) reaction rates determined at 25°C and 5°C, the 37°C value is approximate*

Table 1a specifications:

- ***(Applies to all except VVM0.5)* At +37°C, RH 33% ± 5% and RH 75% ± 5%**, the primary limits are set such that at the specified time no more than 5% of VVMs shall reach end point at the lower temperature limit of 35°C and no less than 95% shall

reach end point at the upper temperature limit of 37°C. Further, secondary limits are applied to restrict how far beyond the primary specification the end points are allowed to be. At the specified time no more than 0.1% of VVMs shall reach end point at the lower secondary temperature limit of 34.5°C and no less than 99.9% shall reach end point at the upper secondary temperature limit of 37.5°C.

- ***(Applies to VVM0.5 only)* At +25°C, RH 33% ± 5% and RH 75% ± 5%**, the primary limits are set such that at the specified time no more than 5% of VVMs shall reach end point at the lower temperature limit of 23°C and no less than 95% shall reach end point at the upper temperature limit of 25°C. Further, secondary limits are applied to restrict how far beyond the primary specification the end points are allowed to be. At the specified time no more than 0.1% of VVMs shall reach end point at the lower secondary temperature limit of 22.5°C and no less than 99.9% shall reach end point at the upper secondary temperature limit of 25.5°C.
- **At +5°C (applies to VVM2, VVM1 and VVM0.5) and +25°C (applies to VVM7, VVM11, VVM14 and VVM30) specifications (ambient humidity in submerged foil/polythene pouch**): Limits are set such that at the specified time no more than 5% of VVMs shall reach end point at the lower temperature limit (2°C or 22°C, respectively) and no less than 95% shall reach end point at the upper temperature limit (5°C or 25°C, respectively).

Table 1b: VVM reaction rates by type

Type (Vaccines)	Maximum time to end point at +55°C	Maximum time to end point at +45°C	Approx-imate Maximum time to endpoint at +37°C	Time to end point at +25°C
VVM250: Very High Stability	17 days	73 days	250 days*	≥900 days

**VVM (Arrhenius) reaction rates determined at 55°C and 45°C, the 37°C values are approximate*

Table 1b specifications:

- **At +55°C, RH 33% ± 5% and RH 75% ± 5%**, the primary limits are set such that at the specified time no more than 5% of VVMs shall reach end point at the lower temperature limit of 53°C and no less than 95% shall reach end point at the upper temperature limit of 55°C. Further, secondary limits are applied to restrict how far beyond the primary specification the end points are allowed to be. At the specified time no more than 0.1% of VVMs shall reach end point at the lower secondary temperature limit of 52.5°C and no less than 99.9% shall reach end point at the upper secondary temperature limit of 55.5°C.
- **At +45°C specifications (ambient humidity in submerged foil/polythene pouch**): Limits are set such that at the specified time no more than 5% of VVMs shall reach end point at the lower temperature limit (42°C) and no less than 95% shall reach end point at the upper temperature limit (45°C).

Please see Table 2 next page.

Table 2: Allowable ranges of R – I at the specified time to end point (Cyan mode measured with Spectrodensitometer)

VVM Type	Primary limits: ±1°C measured at 25°C/37°C/55°C (including Overall uncertainty)		Secondary limits: ±1.5°C measured at 25°C/37°C/55°C (including Overall uncertainty)	
	Lower limit AQL = 5%	Upper limit AQL = 5%	Lower limit AQL = 0.1%	Upper limit AQL = 0.1%
VVM30	-0.19	0.03	-0.23	0.06
VVM14	-0.15	0.03	-0.18	0.06
VVM11	-0.13	0.03	-0.16	0.05
VVM7	-0.11	0.03	-0.13	0.05
VVM2	-0.09	0.03	-0.10	0.04
VVM1	-0.08	0.03	-0.09	0.04
VVM0.5*	-0.10	0.03	-0.12	0.05
VVM250**	-0.10	0.03	-0.12	0.05

**25°C **55°C*

Table 2 defines the allowable range of R-I at the specified time and specified temperature consistent with the VVM reaction rate specifications.

4.2.6 Overall uncertainty: The expected total uncertainty for measuring the difference between the optical density of the reference surface and active surface is ± 0.03. The measurement uncertainty for a single measurement is ± 0.02. Major sources of uncertainty are instrument error both for the reference surface and the active surface, repeatability, and variation in end point caused by an allowed temperature tolerance of ± 0.2°C in the temperature bath. (The VVMs should be tested in water baths or incubators whose mean kinetic temperature is controlled to within ± 0.2°C.)

4.2.7 Reversion: The indicator must not revert to a lighter shade at any point in its life when exposed to conditions likely to be found during normal use. After the endpoint is reached, the active surface must remain the same shade or darker than the reference surface.

4.2.8 Integrity and location of VVMs:

Before a vial or ampule is opened, the VVM should not be removable; it should resist removal from the vaccine vial as much as a label meeting current vaccine labeling requirements. In addition, the performance of the VVM should not be changed by soaking in water for 8 hours. The optical density of water-exposed samples should conform to within ± 0.04 or ± 10% of initial (R – I) whichever is the greater.

The location of the VVM on the vial depends upon whether the vaccine must be discarded at the end of the immunization session in which it is opened, or whether any remaining contents in an opened vial can be retained for use in subsequent sessions. The following cases apply:

- **For multi-dose vials containing a vaccine that can be used in subsequent sessions:** Regardless of the vaccine presentation (liquid, freeze-dried or two vial combinations of liquid and freeze-dried), the VVM must be permanently attached to the label of the vaccine vial and must remain readily observable before, during, and after use, until the entire contents of the vial have been used.
- **For vaccines that must be discarded at the end of the session or within 6 hours, whichever comes first:** The VVM must be attached to the vaccine vial or ampule and must remain readily observable until the vial or ampule is opened, but not observable after opening. In order to achieve this requirement, the VVM must be located on the flip-off top of a vial or on the neck of an ampule.
- **On a product by product basis, WHO will advise both the vaccine and the VVM manufacturer where the VVM is to be located.** Locating the VVM on the bottom of a vial or ampule is never acceptable – it must always be in a visible location.

4.2.9 Application Surfaces: VVMs should be designed to be applied to the following substrates: Vaccine manufacturers must ensure permanent adhesion to the vaccine container. Note: Users should check there is adequate adhesion of the VVM to the vaccine container.

- Glass (e.g. tops of ampules).
- Vial labels.
- Plastic containers of a composition for which permeation of adhesive components is not a risk.
- Foil pouches.
- For vial cap applications, VVMs should be designed to be applied to smooth, flat plastic surfaces with no embossed areas, recessed areas, or ridges. The use of excessive release agents in the manufacture of the vial caps should be avoided.

4.3 Traceability: Each roll of VVMs must be labeled with its product identity (part number) together with its lot number[3].

4.4 Interface requirements:

None.

4.5 Human factors: The shade change must be monochromatic in its response to cumulative time-temperature exposure within the limits of the allowed shade variation. The observer must be able to distinguish between an unchanged indicator, an intermediate shade change and the end point of the indicator. There must be a gradual change in the shade of the active surface.

4.6 Materials: Materials used must be non-toxic and non-irritant to the end user and substantially harmless to the environment. The VVM must meet any requirements in force concerning toxicity of labels or packaging in the country of manufacture.

4.7 Servicing & warranty: The product is to be maintenance-free and all batches of the product must be warranted to conform to the requirements of this specification for the specified shelf life of the product when stored in accordance with the manufacturer's instructions.

[3]Vaccine manufacturers must keep records of the lot number of the VVMs affixed to each individual batch of vaccine.

4.8 Disposal and recycling: The product will be disposed of in conjunction with the vial to which it is attached.

4.9 Instructions: An instruction insert, providing vaccine manufacturers with all necessary storage, handling and application directions and Traceability directions (with reference to clause 4.3) is to be supplied with every carton containing rolls of VVMs. The insert is to be printed in English. If any vaccine manufacturer requires an instruction insert in an additional language, this will be a matter for independent negotiation between the VVM manufacturer and the vaccine manufacturer.

4.10 Training: The VVM manufacturer must provide training for the vaccine manufacturer in order that the manufacturer can correctly handle, apply and test VVMs.

4.11 Verification: In accordance with PQS Verification Protocol **E006/IN05.VP.4**.

5. Packaging:

Materials used for packaging the finished product are to be free of CFC compounds as defined in the Montreal Protocol.

6. On-site installation:

VVMs will be applied to vaccine vials by vaccine manufacturers.

7. 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
- Details of the legal manufacturer's internal AQL sampling procedures in respect of ISO 3951 and ISO 2859
- Certified photocopies of the legal manufacturer's ISO 9001 quality system certification.
- Certified photocopies of the legal manufacturer's ISO 14001certification, 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.)
- Laboratory test report(s) proving conformity with the product specifications.
- A minimum of five samples of each of the types of VVM shipped in accordance with manufacturer's instructions, together with product instruction insert in English language.
- Indicative cost of the product per 10 000 units, per 100 000 units and per 1 000 000 units EXW (Incoterms 2015).

8. Maintenance:

Product to be maintenance free.

9. 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, in relation to any of the requirements set out in this specification, after PQS pre-qualification has taken place.

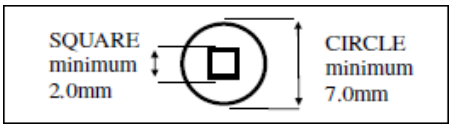
10. Defect reporting:

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

Annex 1: Format and dimensions of VVMs

The VVM must take the form of an inner active surface at the centre of an outer reference surface:

Figure 2



The ratio of the area of the inner active area to the area to the outer reference area (including the inner active area) is to be no smaller than 1:10. This ratio is satisfied by the above example.

The VVM must be large enough for the shade change to be readily apparent but small enough to fit onto the vial label or vial cap etc. It is recommended that the outer reference surface be no larger than 11 mm across.

Revision History			
Date	Change summary	Reason for change	Approved
14 Mar 2006	Test procedure redrafted with general amendments to the form of wording but not to the content. Normative references, definitions and additional clauses added.	To achieve conformity with PQS documentation standards.	UK
29 Nov 2006	General revisions	Following consultation with industry.	UK (30 Nov 2006 – PQS secretariat)
7 Apr 2011	2: ISO 3951 and 5-3 added. 3: Spectrodensitometer definition added. 4.2.4: Spectrodensitometer specification changed. VVM2 brown liner OD exception added. 4.2.4: Table 1 changed. 4.2.7: Table 2 changed. 4.2.9: Spectrodensitometer change. 4.2.12: Clause renamed. Text amended. 4.2.13: New clause added. 4.12: Training requirement added. 7. ISO 9001 date removed. 7. Incoterms date amended.	Consultation with industry. Consultation with industry. Previous model no longer manufactured. Plus manufacturer's suggestion. Spectrodensitometer model change. Spectrodensitometer model change. Spectrodensitometer model change. To accommodate reconstituted vaccines that can be kept for subsequent immunization sessions. Consultation with industry. Consultation with industry. Consistency with other PQS documents. Current edition.	
18 July 2011	4.2.12: Text amended	Consistency with suggested VVM location	UK 18 July 2011
19 Jan 2012	4.2.12: Text amended	Change back to previous version Change E06 to E006	DM Jan 2012
22 May 2018	All sections of this specification have been completely revised	Consultation with industry and PQS team.	IG May 2018
October 2020	Added VVM1 and VVM0.5, and associated information to Table 1a and the following section respectively	To accommodate potential new vaccine types	IG October 2020