PQS performance specification

WHO/PQS/E06/IN05.2
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TITLE: Vaccine Vial Monitor

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Contents:

1. Scope:

This specification describes the performance requirements for a *Vaccine Vial Monitor (VVM)* suitable for application to a vaccine vial by a vaccine manufacturer. The product is used to indicate the cumulative heat exposure of a vial of vaccine so that health workers know whether the cumulative heat history of the product has exceeded a pre-set limit.

2. Normative references:

EMAS: *European Union Eco-Management and Audit Scheme.*
ISO 9001: 2000: *Quality Management Systems – Requirements.*
ISO 14001: 2004: *Environmental management systems - Requirements with guidance for use.*
ISO 2859-1: 1999: *Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection.*
ISO 3951:1989 Sampling procedures for inspection by variables of percent nonconforming.
ISO 5-3:1995 Photography-Density measurements-Part 3: Spectral Conditions.

3. Terms and definitions:

AQL: Acceptance Quality Limit
Active surface: A time-temperature sensitive colour patch whose reaction rate closely matches the stability profile of the vaccine to which the VVM is attached[1].
Spectrodensitometer: The specification for the Start R-I, Indicator OD values, Reference Ring, and OD limits found in **E06/IN05.2** are based on measurements with an X-Rite Model 500 series spectrodensitometer. Measurements taken with other instrumentation will require a conversion factor. Due to the small size of the VVM's reference ring and indicator area, it is necessary to modify the target and aperture centring of the spectrodensitometer (as sold by the instrument supplier). The VVM manufacturer will be responsible for providing the service to install the target and centre the aperture. Conversion of spectral data to optical density is defined within ISO 5-3:1995 Photography-Density measurements-Part 3: Spectral Conditions.
End point: The point at which time-temperature exposure has altered the colour 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 labelling 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.

[1] It is the vaccine manufacturer's responsibility to match the stability profile of their vaccine to the time-temperature profile of one of the four VVM types described in clause 4.2.8 of this specification.

OD: Optical Density.
Reference surface: A colour patch against which the colour of the active surface can be directly compared.
Reaction rate: The rate at which the active surface responds to time-temperature exposure.
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.
Start point: The colour of the active surface of the VVM at the time when the VVM is received by the vaccine manufacturer[2].
VVM: Vaccine Vial Monitor comprising, as a minimum, an active surface, a reference surface and the substrate to which these are applied by the VVM manufacturer.

4. Requirements:

4.1 *General:* Vaccine Vial Monitor suitable for application to a vaccine vial by a vaccine manufacturer.

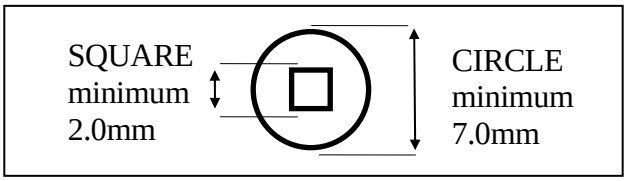
The principal purpose of this product is to warn health workers when the cumulative heat exposure of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used. This is defined as the end point.

Before the end point is reached, changes in the appearance of the VVM are used to alert health workers to the fact that heat exposure has occurred. Heat-exposed vials can then be used in preference to those that have not been exposed.

4.2 *Performance:*

4.2.1 *Format and dimensions:* The VVM is a circle of colour, minimum diameter 7.0mm with a square of colour, minimum dimensions 2.0 x 2.0mm positioned in the centre of the circle (See Figure 1). Whatever dimensions are chosen, the ratio of the area of the square to the area of the circle (including the square) is to be at least 0.1:1. `

Figure 1. Format and dimensions of VVM

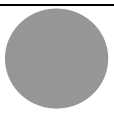


4.2.2 *Design:* The circle of the VVM comprises a static, reference surface and the square comprises the active surface. The colour change of the active surface is limited to a change of shade, from light to dark. Any colour is permitted for the VVM design, but changes in hue are not permitted.

[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.

4.2.3 *Colour density change:* The colour density change of the indicator is illustrated in the Figure 2 below. At the start point the colour of the square is lighter than the circle. The end point is indicated when the colour of the square matches the circle. The end point is exceeded when the colour of the square is darker than the circle. The following clauses describe the colour change in more detail.

Figure 2. The colour density 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 square is the active surface.

4.2.4 *Colour at start point and end point:*

- At the start point, the colour density of the square as measured by an X-rite Model 500 series spectrodensitometer, must be lighter than the colour shade of the circle by a difference of at least 0.25 OD densitometer units for all VVM except for the VVM2 Dots on Brown Liner where the minimum difference will be 0.23 OD.
- The end point is reached when the difference in the average colour density obtained from readings at least two different points on the circle and the colour density of the square is 0.00 OD, as measured by the densitometer. The end point is exceeded when the colour of the square is darker than the colour of the circle.
- The specifications for the Start R-I and the Indicator OD are shown in Table 1.

Table 1: Start R-I and Indicator OD

Category, Liner	Start R-I	Active Surface Start OD (I)
VVM30, White and Clear Liner	0.52 ± 0.11	0.09 ± 0.04
VVM30, Brown Liner	0.49 ± 0.11	0.12 ± 0.04
VVM14, White and Clear Liner	0.41 ± 0.09	0.10 ± 0.04
VVM14, Brown Liner	0.38 ± 0.09	0.13 ± 0.04
VVM7, White Liner	0.41 ± 0.09	0.11 ± 0.04
VVM7, Brown Liner	0.38 ± 0.09	0.13 ± 0.04
VVM2, White Liner	0.32 ± 0.07	0.13 ± 0.05
VVM2, Brown Liner	0.29 ± 0.06	0.16 ± 0.05

4.2.5 *Homogeneity of the reference surface:* The colour density of one 2mm diameter portion of the circle must be within 0.03 OD of the colour density at any other two 2mm diameter portions of the circle, when measured with a colour densitometer.

4.2.6 *Variation of the reference surface within the lot:* The colour density of one 2mm diameter portion of the reference circle of one sample must be within 0.03 OD of the colour density of the reference circle of any other sample within the same lot.

4.2.7 *Reference surface colours:* The colour of the reference area is specified in Table 2.

Table 2: Reference surface colours

Category, Liner	Reference Surface OD (R)
VVM30, White and Clear Liner	0.61 ± 0.15
VVM30, Brown Liner	0.61 ± 0.15
VVM14, White and Clear Liner	0.51 ± 0.13
VVM14, Brown Liner	0.51 ± 0.13
VVM7, White Liner	0.52 ± 0.13
VVM7, Brown Liner	0.51 ± 0.13
VVM2, White Liner	0.45 ± 0.12
VVM2, Brown Liner	0.45 ± 0.11

4.2.8 *VVM reaction rates:* Reaction rates are specific to four different models of VVM, relating to four groups of vaccines according to their heat stability at two specific temperature points (See Table 3).

Table 3: VVM reaction rates by category of heat stability

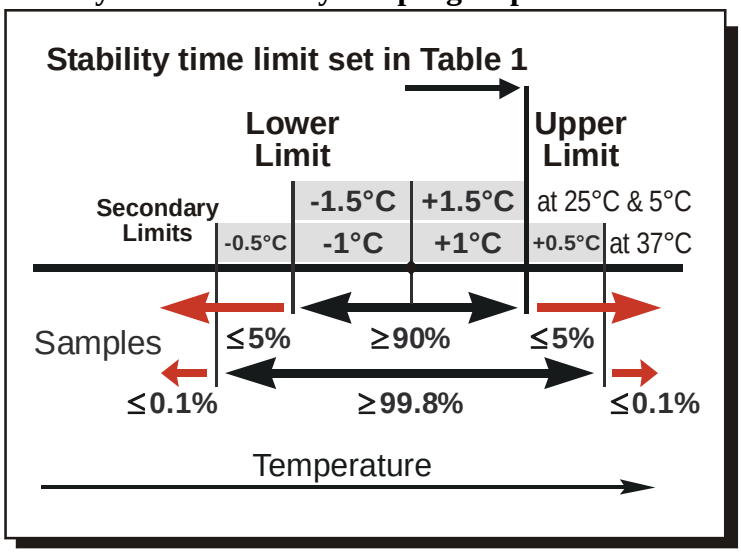
Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
VVM 30: High Stability	30	193	> 4 years
VVM 14: Medium Stability	14	90	> 3 years
VVM 7: Moderate Stability	7	45	> 2 years
VVM 2: Least Stable	2	N/A*	225 days

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

- **At the +37°C specifications, RH 33% +/-5% and RH 75% +/-5%:** At least 90% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1°C. Further, secondary limits are applied to restrict how far beyond the primary specification the TTIs are allowed to be. At least 99.8% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1.5°C.

- **At the 5°C and +25°C specifications (ambient humidity in submerged foil/polythene pouch)**: At least 90% of VVMs tested should reach the end point at the maximum time in the range of the specified temperature ±1.5°C.
- **Tolerance:** A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point at a temperature above the upper limit and 5% at a temperature below the lower limit (See Figure 3).

Figure 3. Stability limit criteria by sample group



- **Allowable range of end points:** Table 4 defines the allowable range of end points such that 90% of a production lot must reach the end point at the specified time within a range of ±1°C and that 99.8% of the lot must reach end point within a range of ±1.5°C.

Table 4: Allowable range of end points

VVM Type	Primary Limits: ±1°C measured at upper limit (including OD tolerance)		Secondary Limits: ±1.5°C measured at upper limit (including OD tolerance)	
	Lower Limit	Upper Limit	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
VVM7	-0.11	0.03	-0.13	0.05
VVM2	-0.09	0.03	-0.10	0.04

4.2.9 *Global Measurement Accuracy:* The allowable total error for measuring the difference between the colours of the circle and square is ± 0.03 OD when using an X-Rite 500 series spectrodensitometer or later qualified model. The measurement error for a single measurement is ± 0.02 OD. Major sources of error are instrument error, both for the circle and the square, repeatability, and variation in end point caused by an allowed temperature variation of ± 0.2°C.

500 series spectrodensitometers require a smaller target than what is provided by the manufacturer (X-Rite). Installation of the smaller target and centering of the aperture must be performed by the VVM manufacturer.

4.2.10 Water Bath Precision and Control: The VVMs should be tested in water baths controlled to within ± 0.2°C. (Any additional 0.1°C variation in temperature control requires an allowance for additional measurement error.)

4.2.11 Reversion: The indicator must not revert to a lighter colour at any point in its life when exposed to conditions likely to be found during normal use. After the endpoint is reached, the square must remain the same colour as the circle or become darker than the circle.

4.2.12 Integrity and location of VVMs:

Before a vial or ampoule 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. Water-exposed samples should conform to within +/-0.04 OD units.

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 ampoule and must remain readily observable until the vial or ampoule 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 ampoule.
- **For monodose vials:** The VVM must be attached either to the label on the vaccine vial or on the flip-off top of a vial, or on the neck of an ampoule.

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 ampoule is never acceptable – it must always be in a visible location.

4.2.13 Application Surfaces: VVMs must be designed to be applied to the following substrates:

- Glass (e.g., glass vials).
- Paperboard (e.g., primary or secondary packaging).
- Plastic containers of a composition for which permeation of adhesive components is not a risk.

For vial cap applications, VVM dots are designed to be applied to smooth, flat 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.

Note: Each user should ensure there is adequate adhesion of the VVM to the vaccine container. Permanent adhesion may not be guaranteed when the VVM is applied to some plastic materials.

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

4.4 *Physical characteristics:* Overall dimensions: As clause 4.2.1, Figure 1.

4.5 *Interface requirements:*
None.

4.6 *Human factors:* The colour change must be monotonic in its response to cumulative heat exposure within the limits of the allowed variation. The observer must be able to distinguish between an unchanged indicator, a 50% colour change and the end point of the indicator.

4.7 *Materials:* The exposed surface of the VVM must not endanger human health. The materials of the VVM must be non-toxic and non-irritant. The VVM must meet any requirements in force concerning toxicity of labels or packaging in the country of manufacture.

4.8 *Reliability:* All batches of the product must be warranted to conform to the requirements of this specification.

4.9 *Servicing provision:* The product is to be maintenance-free.

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

4.11 *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. 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.

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

4.13 *Verification:* In accordance with PQS Verification Protocol **E06/IN05.VP.2.**

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

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 reseller 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 3951:1989.
- Certified photocopies of the legal manufacturer's ISO 9001 quality system certification.
- Where relevant, 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.
- Where available, laboratory test report(s) proving conformity with the product specifications.
- A minimum of five samples of each of the four types of VVM shipped with frozen icepacks, together with instruction insert in English language.
- Indicative cost of the product per 10,000, per 100,000 units and per 1,000,000 units EXW (Incoterms 2010).

8. On-site maintenance:

Not applicable.

9. Change notification:

The legal manufacturer or reseller 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 reseller 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.

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 November 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.	UK (9 May 2011)