



TITLE: Vaccine Vial Monitor

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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*.

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 attached¹.

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 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.

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 manufacturer².

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.

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 4.2.6 of this specification.

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

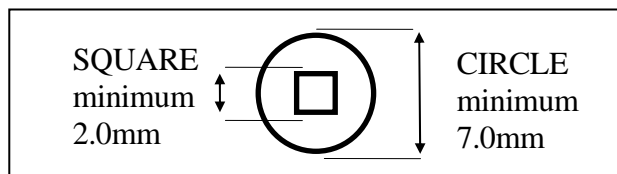
The principal purpose of this product is to warn health workers when the cumulative heat exposure of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used. This is defined as the **end point**.

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.
- 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 Xrite Model 404 GS or GSX colour reflection densitometer, or later qualified model, must be lighter than the colour shade of the circle by a difference of at least 0.25 OD densitometer units³.
- 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

VVM Category	Start R-I	Indicator OD
VVM30: White or Clear Liner	0.54 ± 0.11	0.11 ± 0.04
VVM30: Brown Liner	0.51 ± 0.11	0.14 ± 0.04
VVM14: White or Clear Liner	0.44 ± 0.09	0.12 ± 0.04
VVM14: Brown Liner	0.41 ± 0.09	0.15 ± 0.04
VVM7: White or Clear Liner	0.44 ± 0.09	0.12 ± 0.04
VVM7: Brown Liner	0.41 ± 0.09	0.15 ± 0.04
VVM2: White or Clear Liner	0.34 ± 0.07	0.15 ± 0.05
VVM2: Brown Liner	0.31 ± 0.06	0.18 ± 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

³ Note: The specification for the Start R-I and the Indicator OD values, the Reference Ring Specification and OD limits found in this document are based on measurements with a X-rite Model 404 GS or GSX colour reflection densitometer calibrated to the standard TEMPTIME colour reflection reference card or to a secondary card calibrated to the TEMPTIME card. Measurements taken with other instrumentation or an X-Rite Model 404 GS or GSX colour reference densitometer calibrated to an X-Rite colour reflection reference card will require a conversion factor.

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

VVM Category	Reference Ring Specification
VVM30: White or Clear Liner	0.65 ± 0.12
VVM30: Brown Liner	
VVM14: White or Clear Liner	0.56 ± 0.10
VVM14: Brown Liner	
VVM7: White or Clear Liner	
VVM7: Brown Liner	
VVM2: White or Clear Liner	0.49 ± 0.09
VVM2: Brown Liner	

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).

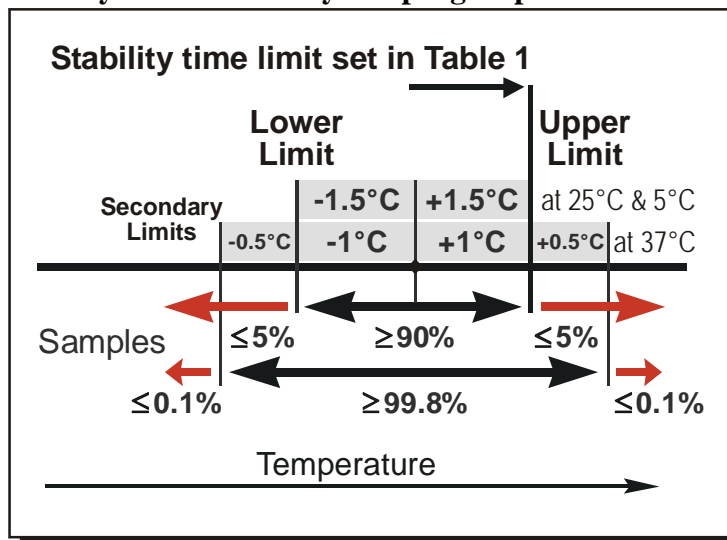
Table 3: VVM reaction rates by category of heat stability

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 $\pm 1^\circ\text{C}$ and that 99.8% of the lot must reach end point within a range of $\pm 1.5^\circ\text{C}$.

Table 4: Allowable range of end points

VVM Type	Primary Limits: $\pm 1^\circ\text{C}$ measured at upper limit (including OD tolerance)		Secondary Limits: $\pm 1.5^\circ\text{C}$ 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	-0.24	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 404 GS(X) colour reflectance densitometer, 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 $\pm 0.2^\circ\text{C}$.
- 4.2.10 *Water Bath Precision and Control:* The VVMs should be tested in water baths controlled to within $\pm 0.2^\circ\text{C}$. (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 of VVMs:*

The integrity of VVMs depends on the presentation of the vaccine:

- **For liquid vaccines:** The VVM will be permanently attached to the vaccine vial, even after the vial has been opened and must remain readily observable before, after and during use. Prior to opening, the VVM should not be removable: it should resist removal from the vaccine vial as much as a label meeting current requirements.
- **For freeze dried vaccines:** The VVM will 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. Prior to opening, the VVM should not be removable: it should resist removal from the vaccine vial as much as a label meeting current requirements.

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.

4.3 *Traceability:* Each roll of VVMs must be labeled with its product identity (part number) together with its lot number⁴.

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

4.12 Training: No requirement.

4.13 Verification: In accordance with PQS Verification Protocol **E06/IN05.VP.1**.

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 2859-1: 1999.
- Certified photocopies of the legal manufacturer's ISO 9001 2000 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 2000).

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 06	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 06	General revisions	Following consultation with industry	UK (30 November 2006 - PQS secretariat)