SPECIFICATIONS FOR VACCINE VIAL MONITORS (VVM)

Specification reference	***:***	***E6/IN5***
Applies to test procedures	***:***	***E6/PROC/5***
Date of issue	***:***	***25 March 2002[1]***

Purpose

Vaccine vial monitors serve primarily 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. In addition, changes in the appearance of the VVM before this limit is reached will serve to guide health workers to first use more exposed vials of vaccine.

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). The ratio of the area of the square to the area of the circle (including the square) is at least 0.1, whatever dimensions are chosen.

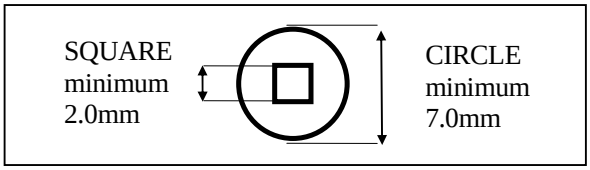


Figure 1. Format and dimensions of VVM

Design:

The circle of the VVM acts as a static, reference colour and the square is a changing, active colour change device. The colour change 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.

Colour:

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 paragraphs describe the colour change in more detail.

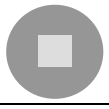
• ***Start point***		• ***Square lighter than circle***
• ***End point***		• ***Square matches the circle***
• ***End point exceeded***		• ***Square darker than the circle***

Figure 2. The colour density change of the indicator (The central square is the active surface)

[1] *Replaces the previous version of 13 August 1999*

Definition of the start-point

The colour of the active surface of the VVM at the time of labelling of the vaccine vial is called the 'start point'.

At the start point, the colour density of the square as measured by a colour densitometer[2], must be lighter than the colour shade of the circle by a difference of at least 0.25 OD densitometer units.

Definition of the end-point

The colour of the active surface of the VVM at the limit of use of the vaccine vial is called the 'end point'.

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.

Homogeneity of the reference colour

The colour density of one 2mm diameter portion of the circle must be within 0.01 OD of the colour density at any other two 2mm diameter portions of the circle, when measured with a colour densitometer.

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 1).

Table 1: VVM reaction rates by category of heat stability

Category: (Vaccines)	**No. days to end point at +37°C**	**No. days to end point at +25°C**	**Time to end point at +5°C**
VVM30 HIGH STABILITY	30	193	> 4 years
VVM14 MEDIUM STABILITY	14	90	> 3 years
VVM7 MODERATE STABILITY	7	45	> 2 years
VVM2 LEAST STABLE	2	NA*	225 days

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

At +37°C, RH 33% +/-5% and RH 75% +/-5%, at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 25% below the upper limit (See Figure 3).

At +25°C (ambient humidity in submerged plastic/foil pouch) at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 for VVM30, VVM14 and VVM7 categories, or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 40% below the upper limit (See Figure 3).

[2] *Colour reflection densitometer Xrite Model 404 GS or GSX*

At 5°C (ambient humidity in submerged plastic/foil pouch), all VVM30, VVM14, and VVM7 samples should reach the end point after the lower time limit specified in Table 1. Conformance can be determined by extrapolation from high temperature (25 and 37°C) data. At 5°C (ambient humidity in submerged plastic/foil pouch), at least 90% of VVM2 samples tested should reach the end point within a range of time whose upper limit is 225 days and whose lower limit is 40% below the upper limit (See Figure 3).

A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit (See Figure 3).

The colour change shall be monotonic in its response to cumulative heat exposure within the limits of the allowed variation. The observer shall be able to distinguish between unchanged, 50% and the end point of the indicator.

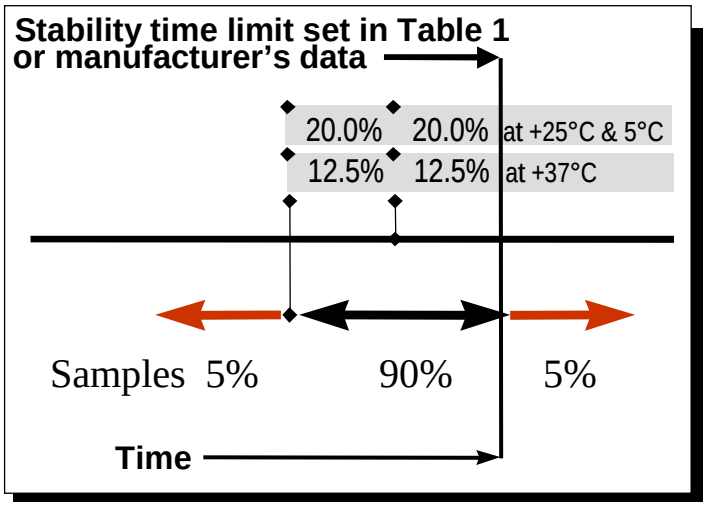


Figure 3. Stability limit criteria by sample group

Global Measurement Accuracy:

The allowable total error for measuring the difference between the colours of the circle and square is ± 0.04 OD when using an X-Rite 404 GS(X) colour reflectance densitometer. Major sources of error are instrument error for both the circle and square, repeatability, and variation in end point caused by an allowed temperature variation of ± 0.2°C.

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.)

Reversion

The indicator shall 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 shall remain the same colour as the circle or become darker than the circle.

Integrity of VVMs

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

For liquid vaccines:

The VVM shall be permanently attached to the vaccine vial, even after the vial has been opened and 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 shall be attached to the vaccine vial or ampoule, remaining 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. They should conform to within +/-0.04 OD units.

Safety

The exposed surface of the VVM shall not be able to endanger human health. The materials of the VVM shall be non-toxic and non-irritant. The VVM should meet any requirements in force concerning toxicity of labels or packaging in the country of manufacture.