PQS performance specification

WHO/PQS/E006/IN04.1
Original: English
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TITLE: Threshold Indicators

Specification reference:	E006/IN04.1
Product verification protocol:	E006/IN04-VP.1
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Contents:

1. Scope:

This specification describes the performance requirements for non-electronic *threshold indicators* which give a visual warning when a certain temperature has been exceeded during transport and storage of vaccines. They can be used to monitor temperature in vaccine carriers in the context of Controlled Temperature Chain (CTC) immunization campaigns, where vaccines are placed outside of the cold chain. Threshold indicators can also be used in conjunction with Vaccine Vial Monitors (VVMs) to give a more rapid indication when vaccine has been exposed to high temperatures during storage and transit.

Two main types of threshold indicators are covered: those which are always active and those which can be made into an activated state by means of a removable strip or similar means.

For the combined VVM & threshold indicator, the threshold indicator must comply with this specification and the VVM part of the combined indicator must comply with PQS specification E006/IN05. Electronic indicators are not covered by this specification.

2. References:

2.1 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 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 9001: 2015: *Quality Management Systems – Requirements.*

ISO 14001: 2015: *Environmental management systems - Requirements with guidance for use.*

ISO/IEC 17025: 2005: *General requirements for the competence of testing and calibration laboratories.*

2.2 Informative references

US Pharmacopeia 37 - NF 32: <1118> *Monitoring Devices: Time, Temperature and Humidity*

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.)

Backing card: In some cases it is recommended that the indicator is permanently attached to a "card" containing information to activate (if necessary) and interpret the visual appearance of the indicator. The card may be made from any water resistant material and need not be rigid in construction.
Insert: General information necessary for correct use and interpretation of the indicator.
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.
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.

4. Requirements

4.1 *General:* Threshold indicators take the form of a visual indicator which may be attached to a backing card.

4.2 *Performance:*

4.2.1 *Activation:* The indicator may be activated by means of a physical removal of an "activation strip" or other positive user intervention. Activatable indicator must visibly demonstrate when the indicator is in an activated or inactivated state. No visual change must occur unless the indicator is activated.

4.2.2 *Mode of operation:* The indicator must exhibit an irreversible rapid visual change when the temperature has exceeded the threshold temperature within 15 minutes as specified in Clause 4.2.3 and Clause 4.2.4. The visual change can take the form of any of the following:

– change in shade
– change in colour
– reveal or obscure text or symbols

4.2.3 *Threshold temperatures:*
+XY°C indicator: Full visual change must take place when the temperature reaches XY°C, where XY = [threshold temperature].

4.2.4 *Tolerance:* ±1.0°C. The tolerance is set such that no more than 1% of indicators shall show visual change at the specified temperature minus 1.0°C, and no less than 99% shall show visual change at the specified temperature plus 1.0°C (e.g. for a 40°C indicator, ≤1% shall reach endpoint at 39°C and ≥99% shall show visual change at 41°C).

4.2.5 *Operating (activated) temperature range:*
Upper limit (without indicator reversion): 70°C.

Lower limit (without product failure): – 30°C.

4.2.6 *Quality control:* Indicator production must follow Good Manufacturing Practices with appropriate testing controls. Manufacturers and supply chain

users can verify indicator performance by sampling and testing of multiple production lots in accordance with AQL standards. .

4.2.7 *Power source:* None.

4.2.8 *Shelf life:* Minimum 3 years from date of manufacture, including operational life, when stored under recommended conditions.

4.3 *Environmental requirements*

4.3.1 *Ambient temperature range during transport and storage* ***(not activated)****:* -30°C to +70°C.

4.3.2 *Ambient humidity range during transport and storage* ***(not activated)****:* *5*%RH to 95% RH.

4.3.3 *Durability:* The product is to be constructed of materials that are adequately robust and durable for the intended use. The indicator should be unaffected by anticipated impact, pressure or bending e.g. caused by coolant packs or the weight of vaccine vials. This includes indicators affixed to a vaccine vial.

4.3.4 *Moisture:* The indicator and backing card (if supplied) to be water resistant.

4.4 *Physical characteristics*

4.4.1 *Overall dimensions:* to be defined with and without backing card if supplied.

4.4.2 *Weight:* Not critical.

4.5 *Human factors:*

4.5.1 *Appearance:* When the threshold temperature is exceeded, there must be an irreversible visual change which must take the form of a complete, rapid and permanent transformation. Products that retain an intermediate state will not be acceptable. The visual change must be of high contrast so that it is readily distinguishable by users with colour blindness.
Examples of visual changes are specified in Clause 4.2.2.
Care should be exercised if pictogram symbols are used. The visual change must avoid possibilities for ambiguities and confusion in the culture and region of use. For example, if a ‘Tick’ or ‘OK’ symbol is obscured when Clause 4.2.3 conditions are met, the absence alone of a symbol may not be clearly understood as “do not use”. Alternatively, an indicator could reveal a “do not use” pictogram when Clause 4.2.3 conditions are met.

4.5.2 *Backing card:* If supplied, the backing card material should be water resistant and contain appropriate instructions as stated in Clause 4.9.

4.5.3 *Legibility:* It must be possible for a person with normal visual acuity (20/20 with or without corrective lenses) to interpret the visual change of the indicator both in bright sunlight and in tungsten/fluorescent lighting at 100 lux on the working plane, before and after activating and after reaching the end point.

4.5.4 *Mounting:*
The product should have a means of attachment, for example, a self-adhesive strip. The indicator response should not be affected by orientation.

4.6 *Materials and disposal:*
Materials used must be non-toxic and non-irritant to the end user and harmless to the environment. The product must meet all requirements concerning toxicity of materials and packaging in force in the country of manufacture.

4.7 *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 at least three years for the product when stored in accordance with the manufacturer's instructions.

4.8 *Instructions:* Illustrated instruction sheets in English, to be supplied in every carton. Instructions printed in other languages to be supplied on client's request.
- Storage instructions for active and non-active indicators.
- How to activate the indicator or a clear instruction that the indicator is always active.
- Visual state of the indicator when the temperature has not exceeded manufacturer's specified threshold temperature.
- Visual state of the indicator when the temperature has exceeded manufacturer's specified threshold temperature.

If supplied, *backing cards* to have the above instructions which can be diagrammatic.

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

4.10 *Verification:* In accordance with PQS Verification Protocol **E006/INXY.VP.1**

5. Packaging:

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

6. On-site installation

Not applicable.

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.
- 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.
- Where relevant, certified photocopies of the legal manufacturer’s ISO 14001 2015 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.

- One sample 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).

8. On-site maintenance:

Not applicable.

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 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.

Revision history			
Date	Change summary	Reason for change	Approved
14 Mar 06	Specification redrafted. Normative references, definitions and additional clauses added.	To achieve conformity with PQS documentation standards	UK
22 Sep 06	4.10: minor change. 5: 'CFC' changed to 'ozone-depleting'.	In response to final review comments.	UK
29 Nov 06	4.2.5: Interpretation guide and supplier information has been changed	New assignments for vaccines were done based on the new temperature sensitivity information	30 Nov 2006 UK - PQS secretariat
04 Sep 16	This draft has been completely revised – particularly Section 4 Requirements.	To show parity with similar PQS specifications e.g. for the VVM.	IG
04 Feb 18	Complete review of all sections	To show parity with similar PQS specifications e.g. for the freeze indicator	IG