	PQS performance specification	WHO/PQS/ E006/IN07.1 Original: English Distribution: General

TITLE: Chemical Freeze indicator	
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Product verification protocol:	E006/IN07.VP.1
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Contents

1. Scope

This specification describes the performance requirements for passive freeze indicators. These devices give an irreversible visual warning when freeze-sensitive vaccines have been exposed to freezing temperatures during transit or storage. Electronic indicators are not covered by this specification.

2. Terms and definitions

Acceptance Quality Limit (AQL): The "quality level that is the worst tolerable" according to **ISO 2859-1**. It represents the worst tolerable process average (mean) in percentage that is still considered acceptable; that is, it is at an acceptable quality level.

Backing card: Card to which the indicator is permanently attached containing information to activate (if necessary) and to interpret the appearance of the indicator. The card may be made from water resistant material.

Insert: General information card or sheet providing all the information necessary for correct use and interpretation of the indicator.

In writing: 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 the person's own name, regardless of whether these operations are carried out by that person or on that person's behalf by a third party.

Montreal Protocol: The Montreal Protocol, finalized in 1987, is a global agreement to protect the stratospheric ozone layer by phasing out the production and consumption of ozone-depleting substances (ODS).

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.

3. Normative references (use most current version)

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.

The following informative reference is also recommended:

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

4. Requirements

4.1 General

Freeze indicators take the form of a self-adhesive visual indicator. This indicator may be attached to a syringe pack, backing card, secondary packaging, an individual vial or other substrate as specified by the immunization programme.

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. It must be visibly obvious 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 visual change when the temperature is colder than the freeze temperature 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 symbol (See *Clause 4.5.1*).

4.2.3 Indicator temperature

The indicator must reach its endpoint by exposure to a temperature colder than –0.5°C within 60 minutes.

4.2.4 Tolerance

±1.0°C or better.

98.0% of indicators must reach their endpoint between and including + 0.5°C and – 1.5°C with 1% potentially too high and 1% potentially too low.

4.2.5 Operating (activated) temperature range

Upper limit: According to manufacturer's instructions.
Lower limit (without triggering indicator): +1.0°C.
Lower limit (without product failure): –30°C.

4.2.6 Quality control

Indicator production must follow Good Manufacturing Practices (GMP) with appropriate testing controls. Details of the internal AQL sampling procedures with reference to ISO 3951 and ISO 2859 should be made available on request. Manufacturers and supply chain users can verify indicator performance by sampling and testing of multiple production lots. All tests should be carried out in laboratories which meet the requirements of IEC 17025 or equivalent, e.g. ISO 9001.

4.2.7 Power source

None.

4.2.8 Shelf life

Minimum 3 years from date of manufacture, inclusive of operational life, when stored and used in accordance with manufacturer's instructions.

4.3 Environmental requirements

4.3.1 Ambient temperature range during transport and storage (not active)

-30°C to +70°C.

4.3.2 Ambient humidity range during transport and storage

5 to 95% RH, when stored in accordance with the manufacturer's instructions.

4.3.3 Durability

The product 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 Dimensions

*T*o be defined with and without backing card if supplied.

4.4.2 Weight

Not critical.

4.5 Human factors

4.5.1 Visual indication

When the end point has been reached, this must be indicated by an irreversible visual change which must take the form of a complete 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 normal visual acuity (with or without glasses) and colour vision though manufacturers should avoid the most commonly confused colours. 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; this can be avoided by including a reference pictogram that illustrates the indicator before and after the symbol is obscured. Alternatively, an indicator can reveal a "do not use" pictogram when Clause 4.2.3 conditions are met.

4.5.2 Backing card

A backing card should be water resistant and contain all instructions as stated in *Clause 4.8.*

4.5.3 Legibility

It must be possible for a person with normal visual acuity (with or without glasses) 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 for attaching it to the vaccine packaging – 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.

4.8 Instructions

Illustrated instruction sheets in the form of an insert, in English, to be supplied in every carton. Instructions printed in other languages to be supplied on client's request.

- How to activate the indicator or a clear instruction that the indicator is always active.
- Visual state of the indicator when temperatures are warmer than -0.5°C.
- Visual state of the indicator when temperatures are colder than -0.5°C for up to 60 minutes.

Backing cards (if supplied) must have the above instructions, which may be diagrammatic.

4.9 Training

The product manufacturer must provide training for the vaccine manufacturer and other downstream users so that the indicator will be correctly handled, applied correctly and checked.

4.10 Verification

In accordance with PQS Verification Protocol **E006/IN07.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 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.

- Certified copies of all type-approvals (if present) 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.
- Laboratory test report(s) proving conformity with the product specifications.
- One sample of the product and of the instruction leaflet 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 reseller is required to advise WHO in writing of all changes which may affect the performance of the product after PQS prequalification has taken place.

10. Defect reporting

The legal manufacturer or reseller is required to advise WHO and the UN purchasing agencies in writing in the event of safety-related product recalls, component defects and other similar events. If requested to do so by WHO/UNICEF, the manufacturer is to submit a report to WHO/UNICEF stating the number of affected systems and the number of components repairs/replacements provided, together with copies of any associated field reports.

Revision history			
Date	Change summary	Reason for change	Approved