

LABELLING GUIDANCE FOR CONTROLLED TEMPERATURE CHAIN (CTC) QUALIFICATION FOR VACCINE MANUFACTURERS

20 OCTOBER 2020



BACKGROUND INFORMATION ON STABILITY TESTING AND CTC QUALIFICATION:

Experience thus far with use of Controlled Temperature Chain (CTC) vaccines indicates that a longer CTC duration may be more important than CTC qualification at a high temperature (e.g., above 40°C). Therefore, WHO currently recommends that vaccine manufacturers conduct CTC stability tests at both 37°C and 40°C and seek to extend the CTC duration for as many days as data supports beyond the current minimum of 3 days. Manufacturers should also engage in dialogue with WHO before stability testing for CTC qualification to discuss the programmatic need for CTC use of the particular vaccine, suitability of the test protocol, and minimum acceptable potency level for regulatory and WHO prequalification approvals. Manufacturers should also contact WHO after stability testing for CTC qualification to discuss the results and confirm labelling plans for the product insert prior to regulatory and WHO prequalification approvals. The appropriate contacts at WHO are:

- Anna-Lea Kahn (kahna@who.int) for programmatic and strategy guidance
- Carmen Rodriguez Hernandez (rodriguezhernandezc@who.int) for CTC qualification and regulatory guidance

CTC PRODUCT INSERT TEXT GUIDANCE:

It is important that product insert text regarding CTC instructions is consistent and fits the programmatic use cases for the particular vaccine. WHO therefore requests that vaccine manufacturers provide draft text to WHO for review prior to submission for national regulatory approval. The text will vary depending upon characteristics of the vaccine, but should address, at minimum:

1. Normal storage temperatures and conditions, including any risk of freezing, when appropriate.
2. CTC storage temperatures and conditions, with specific reference to the term "Controlled Temperature Chain"ⁱ as a policy that must be adopted well in advance of any vaccination planning and not implemented following accidental excursions.
 - Duration of CTC use at one or more **temperatures** (for a clearly stated consecutive **number of days**).
 - **Example:** "This vaccine may be kept for a single period of time of up to 5 days at temperatures not exceeding 40°C, just prior to use."
 - Statement that CTC use is **immediately prior to administration**.
 - **Example:** "Once removed from the cold chain for use in a CTC, this vaccine must be used within the allowed number of CTC days and should not be returned to refrigeration."
 - Recommendation to **monitoring the upper threshold temperature** with either a Peak Temperature Threshold Indicator or through a VVM with an integrated upper temperature indicator (VVM-TI)ⁱⁱ. This is needed because a VVM changes colour in response to cumulative heat exposure, which may not be rapid enough at higher temperatures. A threshold indicator (TI) is therefore also needed when

- vaccines are kept in a CTC as they react rapidly if exposed at or above a defined threshold temperature.
- Example: “In addition to monitoring accumulated heat exposure through the Vaccine Vial Monitor (VVM), the upper CTC threshold temperature limits should be monitored with an appropriate additional tool, such as a peak temperature threshold indicator (PTTI).”
 - When appropriate, clear storage conditions for **diluents**
 - Example: “When implementing a CTC approach, the diluent for this vaccine must be stored and transported in the same manner and at the same temperature as the vaccine.”
3. Handling instructions after container **opening or reconstitution**. Kindly note that CTC is not compatible with a multi-dose vial policy. Therefore, when implementing delivery with a CTC, vaccinators must consume the vaccine within 6 hours or the end of the immunization session (whichever is soonest.) Any remaining doses in a multi-dose vial must be discarded at the end of the day.
 4. Reminders about checking the expiration date and vaccine vial monitor.

The information above is informal and just meant to provide some early context. As above, please direct questions regarding draft product insert text to both Anna-Lea Kahn (kahna@who.int) and Carmen Rodriguez Hernandez (rodriguezhernandezc@who.int).

CTC RESOURCES:

- General: https://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/
- Stability testing guidance (see the Annex 5 document): <https://www.who.int/biologicals/areas/vaccines/ectc/en/> Note that this document is not meant to suggest testing temperatures. These guidelines themselves are not sufficient, consultation with WHO is essential.

ⁱ WHO defines the Controlled Temperature Chain (CTC) as a specific approach to vaccine management allowing vaccines to be kept at temperatures above the long-term storage condition for a limited period of time, under monitored and controlled conditions appropriate to the stability of the antigen.

ⁱⁱ WHO encourages manufacturers of CTC-qualified vaccines to consider applying a VVM with an integrated peak temperature threshold indicator (VVM-TI), which greatly facilitates CTC implementation for national immunization programmes.