

## Immunization Practices Advisory Committee (IPAC) Statement

### Out of cold chain (OCC) and Controlled Temperature Chain (CTC) use of vaccines:

*The following statement has been prepared by the CTC working group, which has been established under the authority of IPAC. The mission of this working group is to convene key stakeholders to define a shared vision and strategy for CTC. Members of the group include subject matter experts from IPAC member institutions or from their affiliates (WHO, UNICEF, Gavi, IFPMA, DCVMN, MSF, PATH). The working group provides manufacturers with the possibility of bilateral, confidential discussions regarding vaccine labelling consistent with CTC usage.*

*Please find additional background and links to further information in the two pages following the statement, or contact the CTC working group secretariat, Anna-Lea Kahn: [kahna@who.int](mailto:kahna@who.int)*

### Statement on Controlled Temperature Chain (CTC) and Out of Cold Chain (OCC) vaccine usage

The WHO Immunization Practices Advisory Committee (IPAC) recommends that countries store, transport and distribute vaccines at temperatures above 8°C only if these products have been licensed for use in a Controlled Temperature Chain (CTC). IPAC further calls for acceleration of vaccine licensing and labelling consistent with CTC usage. The committee recognises that manufacturers, regulators, national programs and immunization partners consider that on-label indication of temperature storage conditions will enhance communication of correct handling and maintenance of the quality of vaccines above 8°C.

Nevertheless, IPAC recognizes that under special circumstances such as emergency situations, countries may consider delivering certain vaccines out of the cold chain (OCC) for public health benefit especially for otherwise unreachable populations. Should a country choose to use a vaccine OCC, this should only be an interim short-term step while licensure and labelling consistent with CTC is sought for the vaccine. Further, IPAC recommends that countries observe the following five conditions:

1. Understand that any associated liability with OCC off-label use must be accepted by the country, irrespective of WHO guidance;
2. Apply the OCC strategy **only** to:
  - a. a specific vaccine product, not to a class of vaccine products, where stability data suggest thermostability appropriate to the country's climate. Due caution is necessary with live attenuated vaccines in particular and adequate provision of cold chain management of reconstituted vaccines at the vaccination sites is essential.
  - b. a vaccine product fitted with a vaccine vial monitor (VVM);
3. Set and monitor explicit time and temperature limitations on the use of the specific product OCC;
4. Ensure adequate vaccine handling training of health workers; and
5. Use appropriate temperature monitoring tools in addition to VVM, such as peak temperature threshold indicators.

## Background

All vaccines currently recommended by the World Health Organization (WHO) Expanded Programme on Immunization (EPI) and delivered through WHO/UNICEF require storage and transportation below 8°C. Presently, the only permitted deviation from this policy is in the context of a Controlled Temperature Chain (CTC), for which WHO has established the following programmatic criteria:

1. The vaccine should be used in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery.
2. The vaccine must be able to tolerate ambient temperatures of at least +40°C for a minimum of 3 days and should be accompanied by:
  - a. A vaccine vial monitor (VVM) on each vial, and
  - b. A peak threshold indicator in each vaccine carrier.
3. The vaccine must be licensed for use in a CTC by the relevant regulatory authorities and prequalified by WHO, with a label that specifies the conditions.

All other use of EPI vaccines out of the cold chain (OCC) implies a departure from established and approved EPI policies and vaccine manufacturer product handling recommendations and is thereby considered “off-label” vaccine use. Unlike CTC, OCC does not have a clear definition or monitoring regulations. OCC is understood as any practice involving the removal of a given vaccine from the cold chain based on indications that this vaccine is thermostable, but without the regulatory approval of storage under these conditions by national regulatory authorities and without subsequent prequalification by WHO of an on-label indication for such storage. When a vaccine is used OCC, the extent of temperature exposure to temperatures beyond 8°C can be indicated by the VVM.

The strategy of using a vaccine outside of the traditional cold chain has the potential to extend their reach and to render immunization programmes more efficient, particularly in the last mile of outreach efforts, where logistics are complex and time consuming. While OCC use of vaccines may also have the advantage of bypassing the potentially long regulatory process required for labelling consistent with CTC usage, a number of risks are associated with OCC: many countries are not comfortable with applying off-label implementation for vaccines because of perceptions that this might decrease vaccine potency and increase adverse events following immunization (AEFIs). Further, there may be vaccines against the same disease that have different thermostability profiles; this makes a universal OCC recommendation for vaccine type difficult. The CTC indication evolved out of the recognized benefits of cold chain flexibility but with the acknowledgment that countries are generally reluctant to use vaccines off-label, preferring proper regulatory approvals to be associated with all adopted practices.

The initial vaccine targeted for licensing and labelling consistent with CTC usage was the Hepatitis B vaccine, noting the usefulness of CTC for enabling timely birth-dose vaccination and a number of documented OCC experiences. However, despite widespread recognition of their generally high thermostability, standard recommendations for stability testing and the regulatory pathway to qualify Hepatitis B vaccines for CTC use became challenging, due to the variability across products and manufacturers. Focus therefore was shifted to the new Meningitis A vaccine (MenAfriVac®), which became the first vaccine to be licensed and pre-qualified for use in a CTC in 2012, paving the way for additional candidate vaccines.

However, with further experience of licensure and prequalification efforts, it also became clear that the methodology for demonstrating thermostability is not a “one-size fits all approach”. Some vaccines, which had received National Regulatory Authority (NRA) approval for a label variation compatible with CTC, have been held up in the prequalification stage as the data that suggested thermostability proved insufficient subsequent to more in-depth inspection and analysis. Such

confusion further articulated the need for additional scientific and regulatory guidance on demonstrating thermostability, while emphasizing the critical role of regulatory approvals.

In the interest of clarifying the required regulatory pathways for CTC, the WHO Department for Essential Medicines and Health Products – responsible for vaccine regulation matters - developed the guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions, commonly referred to as the ECTC Guidelines and approved by the Expert Committee on Biological Standardization (ECBS) in 2015. That guidance document includes the possibility of indicated storage at different specified temperatures above 8°C for any specified duration. However, from the programmatic perspective, for vaccines delivered through WHO/UNICEF, manufacturers have been informed that for programmed delivery under CTC, a label claim for stability of at least three days at a minimum of 40°C is preferred. Any such claim should be included in the package insert after approval of the responsible NRA and prequalification from WHO and thus is considered “on-label” vaccine use.

Thermostability data exist for multiple vaccines, leading to some calls for interim “off-label” use outside of the traditional cold chain. It is in this context that IPAC has been asked to deliver a clear position on OCC-use of vaccines, as presented above. This is especially important to avoid the potential for off-label OCC usages to lead to confusion with the CTC initiative and/or to discourage manufacturers and other partners from pursuing licensing and labelling consistent with CTC usage for appropriate vaccines. IPAC acknowledges that WHO and partners are investing energy in promoting CTC as a long term evolution for vaccine storage outside of the traditional cold chain, and encourage acceleration of these efforts. The CTC working group has a continuing brief to support further development of the CTC strategy.

You will find more information about CTC here:

[http://www.who.int/immunization/programmes\\_systems/supply\\_chain/ctc/en/](http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/)

CTC publications and guidance:

[http://www.who.int/immunization/programmes\\_systems/supply\\_chain/ctc/en/index1.html](http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/index1.html)

Background material on CTC:

[http://www.who.int/immunization/programmes\\_systems/supply\\_chain/ctc/en/index2.html](http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/index2.html)

CTC infographic:

[http://www.who.int/immunization/programmes\\_systems/supply\\_chain/resources/WHO\\_CTC\\_Infographic.pdf?ua=1](http://www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf?ua=1)

CTC FAQ:

[http://www.who.int/immunization/programmes\\_systems/supply\\_chain/resources/Controlled-Temperature-Chain-FAQ.pdf?ua=1](http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf?ua=1)

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