WHO Guidance Note: Vaccine Diluents

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THE PROPER HANDLING AND USE OF VACCINE DILUENTS

World Health Organization

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SUMMARY OF WHO GUIDANCE ON THE PROPER HANDLING AND USE OF VACCINE DILUENTS

A vaccine diluent is the liquid mixed with a lyophilized (freeze-dried) vaccine in order to reconstitute the lyophilized vaccine and provide the final vaccine for administration. A vaccine diluent may be sensitive to heat or freezing, and may require transportation and storage in the cold chain. This guidance note outlines the proper handling and use of vaccine diluent, including, but not limited to, critical steps for reconstituting vaccines safely.

Diluent handling

Diluents vary widely in composition, and therefore only the diluent assigned by the manufacturer for the specific vaccine and presentation should be used.* Never replace a vaccine diluent with water for injection, and never inject an oral vaccine or a diluent used to reconstitute an oral vaccine.

Diluent storage

- Unless otherwise specified by the manufacturer, the correct temperature for long-term storage of diluents is +2°C to +8°C.
  - Diluent packaged with or attached to the vaccine should always be stored with the corresponding vaccine at +2°C to +8°C.
  - Diluent not packaged with the vaccine can be stored at room temperature ONLY if the manufacturer's instructions allow it. In this case, the manufacturer's instructions regarding cooling prior to reconstitution should be followed.
  - Diluents should NEVER be frozen.
- Wherever possible, vaccines and diluents should be stored in a refrigerator that is reserved for this purpose.
- The vaccine vial monitor (VVM) that is attached to the vaccine vial can serve as a visual trigger to assist a health worker in properly applying the multi-dose vial policy, especially in knowing when the reconstituted product must be discarded.
- All diluents should be managed according to standard storage and warehousing practices for vaccines.

Diluent use

- The reconstituted product should be discarded at the end of the immunization session, or within six hours of opening, whichever comes first, UNLESS the reconstituted vaccine meets the criteria for keeping the vaccine for up to 28 days, as indicated in the WHO Policy Statement: Multi-dose Vial Policy (WHO/IVB/14.07).
- Vaccinators should be adequately trained to ensure that the diluent used to reconstitute a vaccine is the correct one assigned by the manufacturer.
  - Appropriate job aids, such as posters, should be provided.
  - Training on the proper handling of diluents should be combined with training on handling multi-dose vials after opening, as specified in the revised WHO Multi-dose Vial Policy. †

* To ensure that a specific vaccine and diluent are approved for use together, refer to the relevant vaccine product sheet on the WHO prequalified vaccines website (http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html, accessed 11 July 2015).

† WHO Policy Statement: Multi-dose Vial Policy (MDVP). Revision 2014. Geneva: World Health Organization; 2014 (WHO/IVB/14.07; http://apps.who.int/iris/handle/10665/135972, accessed 11 July 2015). Individual instructions on handling opened multi-dose vaccine vials can also be found on the WHO Performance, Quality and Safety (PQS) website (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/, accessed 11 July 2015).

Intended audience

This WHO Guidance Note is designed to provide guidance to national and senior-level programme managers on the proper handling of vaccine diluents and their use in reconstitution. Based on this guidance, aide memoires, training guides and other job aids including supervisory tools should be developed for use at district and facility level to provide more practical guidance on how to safely store, handle and use vaccine diluents.

How to use this document

This Guidance Note explains how to correctly handle and use vaccine diluents. The purpose is to enable vaccinators, logisticians and programme managers to understand how diluents should be used with vaccines and the proper conditions for their appropriate storage and stock management.

This document revises and replaces the WHO Vaccines and Biologicals Update, Volume 34, *Proper handling and reconstitution of vaccines avoids programme errors, issued in December 2000 (1).*

This document is designed to be used in conjunction with *WHO Policy Statement: Multi-dose Vial Policy (MDVP). Revision 2014. Geneva: World Health Organization; 2014 (WHO/IVB/14.07).*

Use of the word diluent in this document

In this document, the term diluent means: a liquid mixed with a lyophilized (freeze-dried) vaccine in order to reconstitute the lyophilized vaccine and provide the final vaccine for administration. In strict pharmaceutical terms, a diluent is an inactive substance such as water for injection *(2)*. In the immunization context, the diluent (liquid used for reconstitution) may also be a liquid containing an adjuvant to enhance immune response or be a vaccine used to reconstitute another vaccine to provide a final combination vaccine. For this reason, a diluent must be strictly used in the recommended quantities, may also be heat or freeze sensitive, and may require transportation and storage in the cold chain *(3)*.

Context

Since 2000, many new vaccines have been included in the Expanded Programme on Immunization (EPI) and many more have been developed. Some of these vaccines are manufactured in lyophilized (freeze-dried) form and must be combined with a diluent before injection. This process is called reconstitution. In certain circumstances, some liquid vaccines may also be available in concentrated formulations and must be diluted with a diluent before administration.

Lyophilization is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapour without passing through a liquid phase. Lyophilization of certain vaccines offers a number of advantages in terms of vaccine production, storage and distribution. This is because vaccines are biological products which are generally heat sensitive, so increased heat stability in a dry state can help to better meet the ambient temperature vaccine transport and storage needs of countries and communities with limited reliable power for refrigeration *(4)*.

Reconstitution must be performed in strict accordance with the manufacturer's instructions. Each diluent is specially formulated for each vaccine, and therefore diluent products are NOT interchangeable. For example, some diluents contain an aluminium adjuvant that is essential to the effectiveness of the vaccine, some contain a preservative, and some are actually a liquid vaccine used to reconstitute a lyophilized vaccine. Examples of different diluents and their composition are given in the Annex.

This Guidance Note takes into account the different requirements of new vaccines introduced since 2000, providing updated guidance on WHO's recommendations for the safe handling of vaccine diluents and their use in reconstitution.

Diluent composition

Because of the variety of diluents available, a vaccinator must be meticulous in verifying that each vaccine is reconstituted ONLY with its assigned diluent in order to ensure that the vaccine is effective. Diluents are formulated specifically for their corresponding vaccine and may contain any or all of the following:

- stabilizers that affect heat sensitivity;
- preservatives to maintain the integrity of the vaccine during storage and distribution;
- bactericides to maintain the sterility of the reconstituted vaccine;
- chemicals to assist in dissolving the vaccine into a liquid;
- buffers to ensure the correct pH balance (level of acidity or alkalinity);
- adjuvants to enhance immune response; and
- a separate and different vaccine.

I. WHO RECOMMENDATIONS ON HANDLING VACCINE DILUENTS

When using vaccine diluents, always bear in mind the following important guidance.

- Never reconstitute a vaccine with a different diluent to the one specified by the manufacturer.
  - Never replace a vaccine diluent with water for injection (see 'Water for injection', below).
  - Never inject an oral vaccine or a diluent used to reconstitute an oral vaccine (see 'Diluents for oral vaccine', below).
- Never freeze a vaccine diluent containing an active substance (see 'Diluents with active substances', below).
- Never use a reconstituted vaccine if foreign particulate matter is observed (see 'Volume of diluents', below).

A. Water for injection

Water for injection should NEVER be used to replace the diluent assigned by the manufacturer. Doing so is a very dangerous practice in terms of both the efficacy and safety of the vaccine, and must be discontinued if practiced.

B. Diluents for oral vaccine

Diluents for oral vaccines tend to be of significantly large volumes per dose, and are not formulated for injection. These diluents may not have sterility characteristics and constituents appropriate for a sterile injection. To avoid serious injury to the recipient, neither oral vaccines nor their assigned diluents should ever be injected.

C. Diluents with active substances

When a vaccine or adjuvanted diluent is used to reconstitute a vaccine, the utmost care must be taken to ensure that the correct diluents are used. Some of these diluents are also freeze sensitive and should therefore be stored and transported in the cold chain with the same care as any other freeze-sensitive vaccine. An example of this is liquid DTP-HepB (do not freeze), which is combined with lyophilized Hib vaccine. To avoid losing the potency of a vaccine, NEVER freeze a diluent containing an active substance.

D. Volume of diluents

Diluents are prepared by the manufacturer specifically for each vaccine and the quantity of diluent is exactly matched to the required volume to arrive at the proper concentration of the product after reconstitution. Therefore, the total contents of the diluent vial must be withdrawn with the reconstitution syringe and added to the vaccine for reconstitution. This may occasionally provide one or two extra doses in the vaccine vial for potential withdrawal excesses, and this is entirely acceptable. These extra doses, if they can be drawn to measure a full dose, may be administered. Note that following reconstitution, the vaccine should be inspected visually for any foreign particulate matter prior to administration. Never use a reconstituted vaccine if foreign particulate matter is observed. In such cases, the vaccine must be discarded and an official report lodged with the supervisor for follow-up investigation.

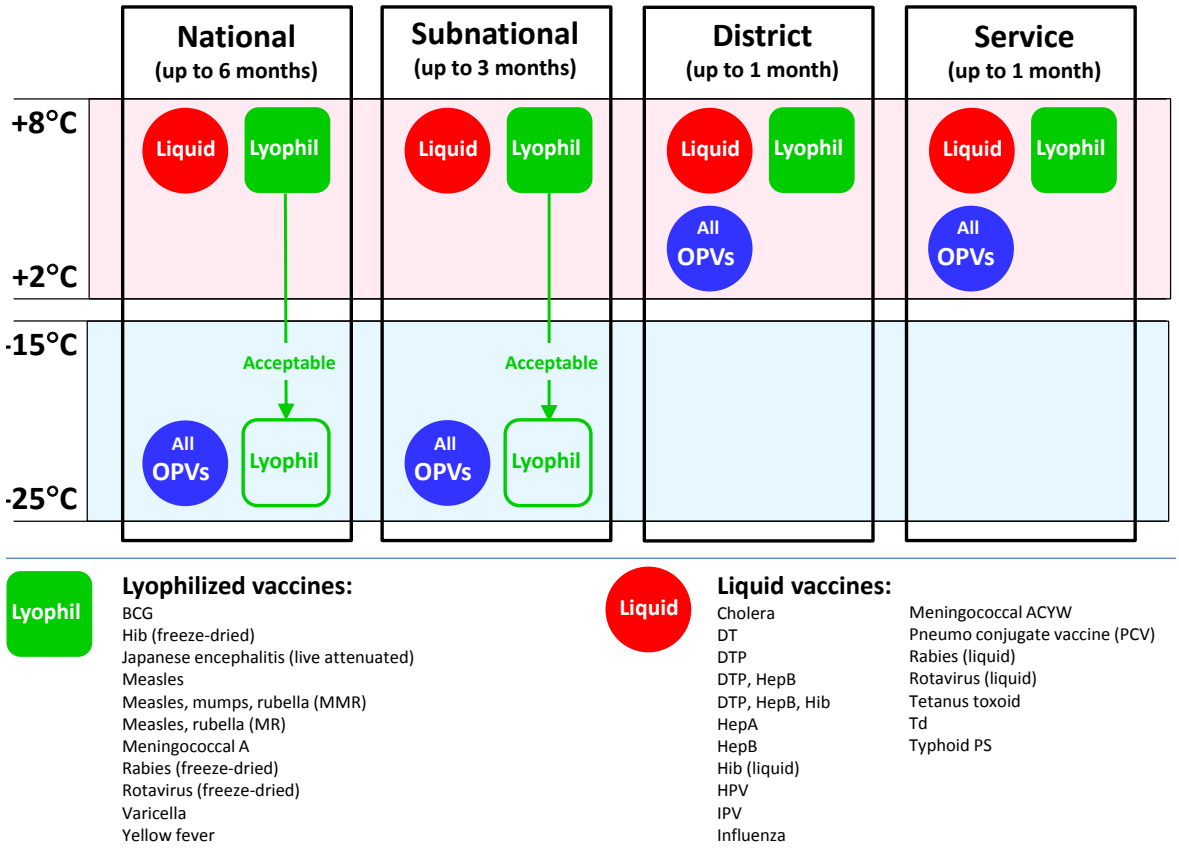
II. PROPERLY STORING AND TRACKING VACCINE DILUENT STOCK

A. Storage of diluents

Unless otherwise specified by the manufacturer, the correct temperature for long-term storage of diluents is +2°C to +8°C. This however is not always practical or cost effective because some diluents can be stored outside the cold chain. In the event that cold chain storage capacity is limited, diluents which are not packaged with the vaccine can be stored at room temperature ONLY if the manufacturer's instructions allow it. In this case, the health worker must take special care to assure that the correct diluent is always used with its designated vaccine, and that the manufacturer's instructions regarding cooling prior to reconstitution are followed. The health worker must also ensure that an adequate number of needles and syringes for reconstitution are available for all the vaccines and diluents.

Diluents should never be frozen. If diluents are packaged with a vaccine, the product should be stored at +2°C to +8°C. Bundled liquid-lyophilized combination vaccines should never be frozen and should also be stored at +2°C to +8°C.

Figure 1. Recommended vaccine storage temperatures and maximum storage periods. *(5)*



1. **Impact of freezing on diluents.** Diluents should never be frozen and should be protected from freezing during transport and storage. There are two main reasons for this. Firstly, the contents of some diluents are sensitive to freezing. For example, diluents that are DTP-containing vaccines are adsorbed onto an aluminium matrix which acts as an adjuvant. Freezing destroys this matrix and thus can lower the efficacy of the product. Such diluents, if suspected of having been frozen, can be tested using the shake test *(6)*. Secondly, the glass vials or glass ampoules in which many diluents are filled are not resistant to freezing and could crack, thereby contaminating the contents and causing unnecessary waste.

2. **Impact of heat on diluents.** If the manufacturer's instructions state that the diluent may be stored outside of the +2°C to +8°C range, the diluent should be cooled to +2°C to +8°C prior to use. The diluent should be cooled to this temperature for at least several hours (and preferably for 24 hours) prior to use for reconstitution. Current formulations of heat sensitive vaccines, but not all, are more stable than in previous years *(5,7,8,9)* and do not require cooling of the diluent. Many vaccines to be reconstituted, especially live attenuated virus vaccines, have only a limited stability when reconstituted, even when kept at +2°C to +8°C *(5,7,10)* and therefore require the diluent to be cooled prior to reconstitution.

Controlled Temperature Chain (CTC)

WHO has defined a Controlled Temperature Chain (11) as a specific set of conditions allowing the transport and storage of a WHO-prequalified vaccine outside the traditional +2°C to +8°C cold chain, for a single excursion at ambient temperatures up to 40°C, for a limited period of time just prior to administration. The vaccine must be licensed and pre-qualified by the appropriate regulatory authorities for use in a CTC, with a label that specifies the conditions. CTC use does not change the use of diluents, except as specified in respective guidance documents, and in accordance with manufacturers' product inserts.

B. Storage of diluents with other medicinal products

Wherever possible, vaccines and diluents should be stored in a refrigerator that is reserved for this purpose *(3)*. If other heat-sensitive supplies, such as drugs, ointments, sera and samples, have to be stored in the same refrigerator, they should be placed in a separate storage container or box in the refrigerator, labelled clearly, and kept completely separate from the vaccines and diluents. Good storage practices indicate that a special area of the refrigerator be reserved for these other products such as the bottom shelf. Note that the fridge should be monitored carefully for acceptable temperature readings according to WHO recommended temperature monitoring principles and appropriate action taken when the acceptable temperature range has