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Guidelines on the international packaging and shipping of vaccines

Immunization, Vaccines and Biologicals

World Health Organization

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Acronyms

The following acronyms are used in this document.

°C	degree Celsius
°F	degree Fahrenheit
AWB	airway bill
BCG	bacille Calmette–Guérin (tuberculosis vaccine)
CCM	(vaccine) cold chain monitor
cm^3	cubic centimetres
DT	diphtheria–tetanus vaccine
DTP	diphtheria–tetanus –pertussis vaccine
ETA	estimated time of arrival
HepB	hepatitis B (vaccine)
Hib	*Haemophilus influenzae* type b (vaccine)
IPV	inactivated polio vaccine
IVB	(Department of) Immunization, Vaccines and Biologicals (WHO)
kg	kilogram
LCD	liquid crystal display
LRC	lot release certificate
MMR	mumps–measles–rubella (vaccine)
MR	measles–rubella (vaccine)
NRA	national regulatory authority
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PQS	performance, quality and safety
SD	Supply Division (UNICEF)
SLP	summary lot protocols
Td	tetanus toxoid and diphtheria (reduced component) vaccine
TT	tetanus toxoid (vaccine)
UN	United Nations
UNICEF	United Nations Children's Fund
VAR	vaccine arrival report
VVM	vaccine vial monitor
WHO	World Health Organization
YF	yellow fever (vaccine)

Preface

The World Health Organization (WHO) document, *Guidelines on the international packaging and shipping of vaccines,* has been one of the most widely used manuals in the field of immunization. It is referenced by UNICEF and PAHO in all their invitations to bid for vaccine supplies and also by countries that directly procure their vaccines.

This 2005 edition* takes into account new developments in the field of vaccine stability, temperature monitoring and information on recently prequalified vaccines. In addition to the updated volume per dose of vaccine, it provides data on the packed volume of diluents and droppers and includes transport-box bulking factors for countries where insulated packages are used for the storage of vaccines. A special section on temperature monitoring has been added to describe the temperature limits for international shipments.

WHO recommends that all United Nations (UN) procurement agencies include the *Guidelines on the international packaging and shipping of vaccines* as part of the technical specifications and requirements in invitations to bid.

This document has been reviewed and commented upon by personnel in the vaccine industry.

* Printed in November 2005, this document revises and replaces all previous versions, including the 2001 version (WHO/V&B/01.05).

1. Insulated packaging standards

On the basis of their thermostability and presentation, vaccines are classified into three categories *(see Table 1)* for packaging of international shipments. WHO specifies the minimum and maximum acceptable temperatures to which vaccines in each category can be exposed during international transport, for a period of at least 48 hours.

As part of the WHO prequalification scheme, vaccine manufacturers are expected to ensure that their packaging complies with the criteria specified below. Validation data should be produced in three consecutively successful runs. Any changes introduced in the packaging must be validated again. The validation test protocol is provided in Annex 1.

1.1. Class A packaging

Prior to – and at the time of packing – the vaccines must be kept within the storage temperature limits recommended by the manufacturer.

The vaccine must be packed to ensure that the warmest temperature inside the insulated package does not rise above **+8°C** in continuous outside ambient temperatures of +43°C for a period of at least 48 hours.

1.2. Class B packaging

Prior to – and at the time of packing – the vaccines must be kept within the storage temperature limits recommended by the manufacturer.

The vaccines must be packed to ensure that the warmest temperature inside the insulated package does not rise above **+30°C** in continuous outside ambient temperatures of +43°C for a period of at least 48 hours.

Diluents for freeze-dried vaccines must always be included with the vaccine shipment in a quantity that matches the quantity of vaccine; diluents, however, do not require temperature-controlled packaging.

1.3. Class C packaging

Prior to – and at the time of packing – the vaccines must be kept within the storage temperature limits recommended by the manufacturer.

The vaccines must be packed to ensure that:

- the warmest temperature inside the insulated package does not rise above **+30°C** in continuous outside ambient temperatures of +43°C for a period of at least 48 hours; and
- the coolest storage temperature of the vaccine does not fall below +2°C in continuous external temperatures of -5°C for a period of at least 48 hours.

Table 1: WHO classification and temperature criteria for international shipment of vaccines (for at least 48 hours)

Class	Type of vaccine	Ambient temperature	Minimum temperature allowed	Maximum temperature allowed
A	OPV	+43°C	no limit	+8°C
B	BCG Hib (freeze-dried) measles MR MMR meningococcal A&C yellow fever	+43°C	no limit	+30°C
C	DTP DTP–HepB DTP–Hib (liquid) DT	+43°C	+2°C	+30°C
	IPV HepB Hib (liquid) Td TT	-5°C	+2°C	+30°C

2. Temperature monitoring devices to be included in international shipments

Temperature monitoring devices should be included in all vaccine shipments to document whether temperature limits have been exceeded. These devices should:

1) serve as a quick reference to help recipient countries determine whether the shipment – or parts of the shipment – have been exposed to temperatures at which vaccines could have been damaged; and

2) help the procurement agency determine when, where, and to what extent temperature limits have been exceeded.

Before accepting a shipment, the recipient should make sure that temperature limits have not been exceeded.

The point in time when a temperature change has occurred is not of immediate concern to the recipient. This information is important a) for the purchasing agency and the manufacturer so they can identify the cause of the change, take corrective measures, and avoid similar situations in future shipments; and b) for insurance purposes.

Electronic temperature devices provide the most reliable and accurate record of the above information. WHO recommends that one electronic temperature device is included in each and every international vaccine shipping carton. Furthermore, WHO no longer recommends the use of the vaccine cold chain monitor card (CCM)[1] and/or freeze indicators in international shipments.

[1] Except under exceptional circumstances where dry ice continues to be used.

Table 2: Specifications of the electronic devices for international shipments[a]

Storage temperature	Range: -20°C to +70°C
Operating temperature	Range: -20°C to +55°C
Display visibility range	Range: -10°C to +55°C
Temperature measuring accuracy	± 0.5°C or better
Time measuring accuracy	± 10 seconds per day, or better
Initial delay (see point 2 below)	1 hour
Recording period	10 days
Storage before START	minimum of 18 months
Data retention after STOP	minimum of 6 months

[a] For specific devices with these features, refer to the WHO web site: *http://www.who.int/vaccines-access/vacman/pis/pqs.htm*

The electronic devices should, at a minimum, meet the specifications outlined in Table 2 (above) and have the functions outlined below.

1) A "start" function to activate the device at the time the carton is being loaded with vaccine.

2) A "stop" function to allow the recipient to stop the recording when the vaccine arrives at its destination.

3) A one hour "initial delay" function so the device can acclimatize to the temperature inside the shipping carton before it starts recording.

4) A "history" function to provide details of violations of the temperature limit in terms of time, range and duration. This function is primarily to provide information for the use of the procurement agency.

5) A liquid crystal display (LCD) screen[2] to provide a visual display of the information and also to show the symbol that indicates whether the device is functional or not. This symbol, and also the alarm indicator, should be static (i.e. should not flash or blink) so as to be visible when the screen is scanned or photocopied for documentation purposes.

6) An alarm set according to WHO's recommended settings *(see Tables 3 and 4 below).*

Table 3: WHO-recommended alarm settings for international shipments of DTP, DT, TT, Td, HepB, IPV, liquid Hib and combination vaccines

Temperature	Alarm type	Period for triggering the alarm
45°C	single event	1 hour
30°C	cumulative	10 hours
-0.5°C	single event	1 hour

[2] In addition to the LCD screen feature on which all history can be read, the data can be downloaded. However, devices with a download option but without an LCD screen are not recommended.

Table 4: WHO-recommended alarm settings for international shipments of OPV and freeze-dried BCG, measles, MR, MMR, lyophilized Hib, yellow fever and meningitis vaccines

Temperature	Alarm type	Period for triggering the alarm
45°C	single event	1 hour
30°C	cumulative	10 hours
10°C	cumulative	20 hours

Vaccine manufacturers are required to validate their packaging twice for a period of 48 hours: i) at ambient temperatures under +43°C and ii) at ambient temperatures under -5°C. This validation is critical to ensure that the packaging complies with the above requirements and will not set off an alarm.

Batteries for electronic devices do not perform under extremely cold temperatures, such as when vaccines are being transported with dry ice. All vaccine manufacturers are encouraged to validate their Class A and B packaging with frozen icepacks in order to phase out the use of dry ice. In exceptional cases – where dry ice continues to be used – WHO recommends the inclusion of one cold chain monitor card per shipping carton instead of an electronic device.

Each electronic device should be attached to a backing card that includes the information outlined below, in the appropriate language.

1. The type of device:

   Type 1: for DTP, DT, TT, Td, HepB, IPV, liquid Hib and combination vaccines

   Type 2: for OPV and freeze-dried BCG, measles, MR, MMR, lyophilized Hib, yellow fever and meningitis vaccines

2. For the person packing/sending the shipment:
   a) instructions on how to activate the device;
   b) a reminder that one device must be placed in each shipping carton;
   c) space for the following information to be entered:
      - the supplier's name;
      - date and time of the packing;
      - vaccine purchase order number;
      - vaccine type.

3. For the person receiving the shipment:
   a) instructions on how to stop the device;
   b) illustrations to show information on the LCD screen – how it will indicate problems/no problems and the alarm-status display;
   c) Tables 5 and 6 *(below)* showing what to do.

Table 5: Information to be displayed on the backing card of electronic device – Type 1 (for DTP, DT, TT, Td, HepB, IPV, liquid Hib and combination vaccines)

Alarm temperature	What to do with vaccines
45°C	Contact UNICEF
30°C	Contact UNICEF
-0.5°C	Conduct shake test[a]. USE vaccine if passes. Inform UNICEF of test result.

[a] Shake test guidelines are given in Annex 2.

Table 6: Information to be displayed on the backing card of electronic device – Type 2 (for OPV and freeze-dried BCG, measles, MR, MMR, lyophilized Hib, yellow fever and meningitis vaccines)

Alarm temperature	What to do with	
	OPV	Other vaccines
45°C	Contact UNICEF	Contact UNICEF
30°C	Contact UNICEF	Contact UNICEF
10°C	Contact UNICEF	Accept

3. Storage volume standards

The storage volume per dose of vaccine varies according to the type of vaccine, the number of doses per vial or ampoule, the dimensions of a) the vial or ampoule and b) the secondary packaging[3]. Countries that receive their vaccines through UN agencies and do not know in advance which vaccines they will receive, should estimate their cold-chain requirements on the basis of the figures for maximum volume per dose provided in Table 7 below.

Vaccine manufacturers should ensure that the storage volume per dose of the vaccines they supply to UN agencies remains below the maximum figures listed in Table 7. If, however, this proves impossible, WHO should be notified.

[3] Secondary packaging includes the primary packaging (i.e. the vaccine vial), the packet containing the vaccine vial and any intermediate packaging.

Table 7: Maximum recommended packed volume per vaccine dose[a]

Vaccine type	Dose per vial	cm^3 per dose
BCG (freeze-dried)	20	1.2
DTP, DT, Td, TT	10	3.0
	20	2.0
DTP–HepB	2	6.0
	10	3.0
DTP–Hib	10	2.5
DTP + Hib (freeze-dried)	1	45.0
	10	12.0
DTP-HepB + Hib (freeze dried)	1	22.0
	2	11.0
HepB	1	18.0
	1 in UNIJECT	30.0
	2	13.0
	6	4.5
	10	4.0
	20	3.0
Hib (liquid)	1	15.0
	10	2.5
Hib (freeze-dried)	1	13.0
	2	6.0
	10	2.5
Measles (freeze-dried)	10	3.5
MMR (freeze-dried)	1	16.0
	10	3.0
MR (freeze-dried)	10	2.5
Meningitis A&C	20	2.5
	50	1.5
OPV	10	2.0
	20	1.0
TT in UNIJECT	1	25.0
Yellow fever	5	6.5
	10	2.5
	20	1.0

[a] The packed volume includes the vaccine vial, the packet containing the vaccine vial and any intermediate packaging (secondary packaging).

Table 8: Maximum recommended packed volume for diluents and droppers

Vaccine type	Dose per vial	cm^3 per dose
Diluent for BCG	20	0.70
Diluent for Hib	1	35.0
	10	3.0
Diluent for measles, MR, MMR	1	20.0
	10	4.0
Diluent for meningitis A&C	20	2.5
	50	1.5
Diluent for yellow fever	5	7.0
	10	6.0
	20	3.0
OPV droppers	n/a	17.0 (per unit)

Countries should use packed volume-per-dose to calculate cold-chain requirements if vaccines are to be kept in the cold chain in their secondary packaging. Storing vaccines in the shipping containers greatly increases the volume of cold storage needed, hence involves extra cost. However, this extra cost may be justifiable at higher-level stores where vaccine is kept alongside other refrigerated pharmaceuticals. In very large cold stores, where goods are stored and moved on pallets, vaccine should be stocked in their insulated shipping containers[4]. Bulking factors for insulated shipping containers for estimation of volume requirements are given in Annex 4.

WHO recommends that each international shipping carton should weigh less than 50 kg. It is important that individual boxes are not too heavy during transport as they are frequently loaded and offloaded manually at airports and intermediate stores.

[4] Shipping containers function as tertiary packaging.

4. Labelling and packaging[5]

Primary packaging constitutes the first level of container for the vaccine: the vaccine vial or ampoule itself.

Secondary packaging, the second level of packaging, comprises the intermediate packaging that contains the primary packages (the vials/ampoules of vaccines). It must be clearly labelled for the recipient, giving information on its contents *(see below)*.

Tertiary packaging, the third level of packaging, is the outer box, the shipping container that contains the secondary packages. It must be clearly labelled for international transport with the final address and other details (see below).

All labelling and packaging requirements listed in section 4 apply to both vaccine and diluent.

4.1. Labelling for secondary packaging

A label must be affixed either to the top and/or front surface of the secondary packages. It should indicate the type of vaccine, the name of the manufacturer, presentation, batch number, date of manufacture, date of expiry, quantity and storage conditions.

4.2. Labelling for tertiary packaging (insulated packaging)

The external surface of insulated packages should be either white or in the natural colour of corrugated carton. Dark colours must be avoided.

All labels on tertiary packaging must be attached to all four sides.

Vaccine Rush: A label must be affixed to all four sides of the vaccine package in a language appropriate to the country of destination (e.g., in English: "Vaccine Rush"; in French: "*Vaccin Urgent*"; in Spanish: "*Vacuna Urgente*"; etc.).

[5] Labelling and packaging in this section refers to secondary and tertiary packaging.

Do not freeze: For shipments of freeze-sensitive vaccines (DTP/DT/Td/TT, liquid Hib and hepatitis B vaccines, or combinations containing any of these) a **"Do not freeze"** sticker (again, in the appropriate language) should be attached to all four sides of the vaccine package.

Contents: A label with information on the contents of the box (name of manufacturer, type of vaccine, presentation, batch number, date of expiry, quantity, and storage conditions) should be affixed to all four sides of each box. The manufacture and expiry date on all labels should be written in full, not in a coded form (i.e. June 2005, *not* 06.05).

4.3. Numbering of tertiary packaging

All boxes should be numbered consecutively. Shipping documents should be included in the box labelled number 1, and this box should be clearly labelled with the words "**Containing vaccine shipping documents**".

5. Standard shipping and arrival procedures

The arrival of a vaccine shipment in a country, its subsequent clearance through customs and transportation to the central vaccine store are the most critical stages in the shipping procedure. These are frequently the times when mistakes and delays occur, resulting in damage to the shipments. The smooth arrival and handling of vaccine shipments depends on the manner in which each step in the delivery process is performed. Because numerous parties are involved (UNICEF Supply Division, other UN agencies, the manufacturer, the forwarder, the airline, the UN field office, customs authorities, clearing agents, or the national immunization service, etc.), and because of the need to communicate accurate, time-sensitive information, it is essential to have strict guidelines to determine and assign responsibilities at every step of the process. These are described in the general terms and conditions of the tender documents and are further detailed in individual contracts. The specific conditions depend on the country of destination.

The essential elements of the process are outlined below.

5.1. Route and arrival dates

Vaccines should travel by a direct route wherever possible. Where trans-shipment is unavoidable, the journey should be planned through airports that: a) have cold storage facilities, and b) are located in countries with a temperate climate. The maximum transit time from the manufacturer to arrival at the airport of final destination must not exceed 48 hours, unless this is unavoidable and has been specifically agreed to in writing in advance by UNICEF and/or the other UN agencies involved.

Shipments should be scheduled to arrive outside weekends and/or public holidays in the recipient country and airline bookings should be made well ahead of the date of departure. Any additional requirements regarding arrival times must be stated in the contract between UNICEF and/or the other UN agencies or manufacturers and the designated freight forwarder.

In addition to the above routing and booking procedures, the following general principles should be observed:

- Vaccines must not be transported with radioactive products, fish or meat;
- correct cold-chain procedures must be observed during transit, warehousing and shipping (i.e., all vaccines must be kept in temperature-controlled environments at all times throughout the shipment process);
- re-icing of shipments must be performed in accordance with the instructions of the supplier of each shipment whenever deemed necessary;

- consolidation or split consignments are not permitted unless approved in writing in advance by UNICEF and/or the other UN agencies;
- shipments must be dispatched as booked unless approved in writing in advance by UNICEF and/or other UN agencies;
- "house airway bills" are not permitted unless approved in writing in advance by UNICEF and/or other UN agencies.

5.2. Advance notice of arrival and advance shipping documentation

Copies of the documentation for the goods to be shipped must be sent at least seven days[6] in advance of arrival of the shipment. In the case of an individual contract for a specific destination that requires a longer period of advance notice, a longer period should apply.

The documentation must include the following:

- pre-advice defined by UNICEF and/or the other UN agencies;
- airway bill (AWB);
- supplier's invoice;
- packing list;
- lot release certificate (LRC) issued by the national regulatory authority (NRA) of the country of manufacture for each lot of vaccine supplied; and
- any other document, certificate or instruction specified in the individual order.

The documents should be sent by e-mail and fax by the freight forwarder or the manufacturer to the consignee, the UNICEF country office in the receiving country, the Immunization Team at the UNICEF Supply Division and any other parties specified in the individual contract.

The pre-advice must contain the following information:

- purchase order reference;
- consignee requisition reference;
- number of packages, gross weight (in kilograms) and volume (in cubic metres);
- type of vaccine, total number of vials and number of doses per vial/ampoule/tube;
- value of shipment (in US$);
- AWB and flight number(s);
- date and time for place of departure, transit (if applicable), and arrival;
- instructions for collection;
- any other information specified in the individual contract must also be included for the consignee.

[6] This period must include at least five working days.

The following information shall be stated on the airway bill:

- consignee's name, address and telephone number;
- purchase order reference;
- consignee's requisition reference;
- type of vaccine and quantity;
- instructions to: "Telephone consignee upon arrival *(repeat telephone number)";*
- handling information: "Medicines – Vaccine – For human use – Highly perishable – Not to be delayed.

For all vaccines other than oral polio vaccine (OPV), the following instruction should be stated in the AWB: "Throughout shipment, pending reshipment and prior to collection by the consignee, the vaccine must be stored at +2°C to +8°C (i.e., +35°F to +50°F)".

For OPV, the following instruction should be stated in the AWB: "Throughout shipment, pending reshipment and prior to collection by the consignee, the vaccine must be stored at -15°C to -25°C (i.e., +5°F to -13°F)."

5.3. Documents that accompany shipments

The following original documents must accompany the consignment when it is shipped, and a copy of these must also be placed in the box numbered "one":

- airway bill;
- supplier's invoice;
- packing list;
- lot release certificate issued by the national regulatory authority of the country of manufacture for each lot of vaccine supplied;
- any other documents, certificates or instructions specified in the individual contract.

The shipping carton containing the documents should be clearly labelled with the words "Containing vaccine shipping documentation".

The lot release certificate/s from the national regulatory authority (or from the national control laboratory) of the producing country should be included for each lot contained in the shipment. The lot release certificates are considered to be the only evidence that the lots received have been released by the regulatory authority of the producing country. Vaccines delivered without a lot release certificate cannot be accepted and must be kept on hold under appropriate storage conditions. In such cases, the lot release certificate/s should be requested and provided immediately by the manufacturer.

Inclusion of the lot release certificate is one of the most critical conditions for acceptance of the vaccine by the consignee and for its distribution in country[7]. Manufacturers' internal release documents and any other papers that may accompany a shipment **do not replace** and are **not a substitute** for the official lot release certificates issued by the national regulatory authority of the producing country.

5.4. Vaccine arrival report

The vaccine arrival report (VAR) provides a means of indicating inadequacies in the shipping process and problems relating to the condition of vaccines at the time of delivery *(see Annex 5).* The VAR is a means of monitoring international shipments of vaccines in order to ensure that shipping guidelines are followed and that vaccine quality is maintained. Indeed, it encourages increased involvement in the procurement process by all the parties implicated. UNICEF and/or WHO officers should collaborate with recipient governments to ensure that the VAR is duly completed by authorized staff, checked and verified by the immunization programme manager, and forwarded to the UNICEF country office within three days of the arrival of the vaccine. In the case of combined shipments, a separate report should be filled in for each vaccine in the shipment.

For countries receiving vaccines from UN agencies, all complaints should be sent immediately to the local country office of the procurement agency for them to follow up with their procurement organization. Depending on the nature of the complaint, the procurement agency may handle the issue itself or may request assistance from WHO. For countries procuring vaccine directly, all complaints should be handled directly with the vaccine manufacturer; WHO assistance can, however, be sought if required.

Table 9 sets out the vaccine arrival and complaints procedures for vaccines procured by UNICEF. These procedures may be adapted for other procurement routes.

[7] For the use of the recipient, Annex 3 lists the contact points for national regulatory authorities and national control laboratories in all vaccine-producing countries that supply UN agencies.

Table 9: Procedure for reporting vaccine arrivals

Arrival of vaccines and customs clearance.

↓

Inspection at airport or central cold stores. Vaccine Arrival Report (VAR) filled in and signed.

↓

Copy of VAR sent to UNICEF Country Office.

↓

Copy of VAR sent to UNICEF Supply Division, Copenhagen (SD)

↓

INDICATOR	OK	DEFECTIVE
Advance notification	Recorded	SD to follow-up with forwarder
Vaccine type/expiry	Recorded	SD to follow-up with manufacturer Eventual report to WHO/V&B for further investigation if necessary
Shipping documents	Recorded	SD to follow-up with forwarder or manufacturer Eventual report to WHO/V&B of problems related to release certificate
Quantities received	Recorded	SD to follow-up with forwarder/manufacturer
Status of temperature indicators	Recorded	SD to report to WHO/V&B, investigation to be carried out

Any defect in the process can lead to compensation claims and/or rejection of a shipment. Each individual situation will be investigated and dealt with by all involved parties.

If the quantity of damaged vaccine is substantial it could affect immunization delivery. In such cases, emergency measures will have to be taken to obtain sufficient vaccine to maintain the programme's scheduled activities.

Annex 1:
Guidelines to confirm that packaging complies with WHO recommendations

1. Introduction

This procedure referred to as "**validation**" is the measurement and/or confirmation that temperatures inside the shipping containers of every vaccine shipment remains within the defined temperature range (for the specific vaccine/s being transported) for a period of 48 hours.

As part of the WHO vaccine prequalification process, vaccine manufacturers must document the validation of their packaging.

Validation data should be produced for three successful consecutive tests at the defined ambient temperatures for at least 48 hours. If changes are introduced either in the packaging or the shipment procedures, the shipment must be validated again.

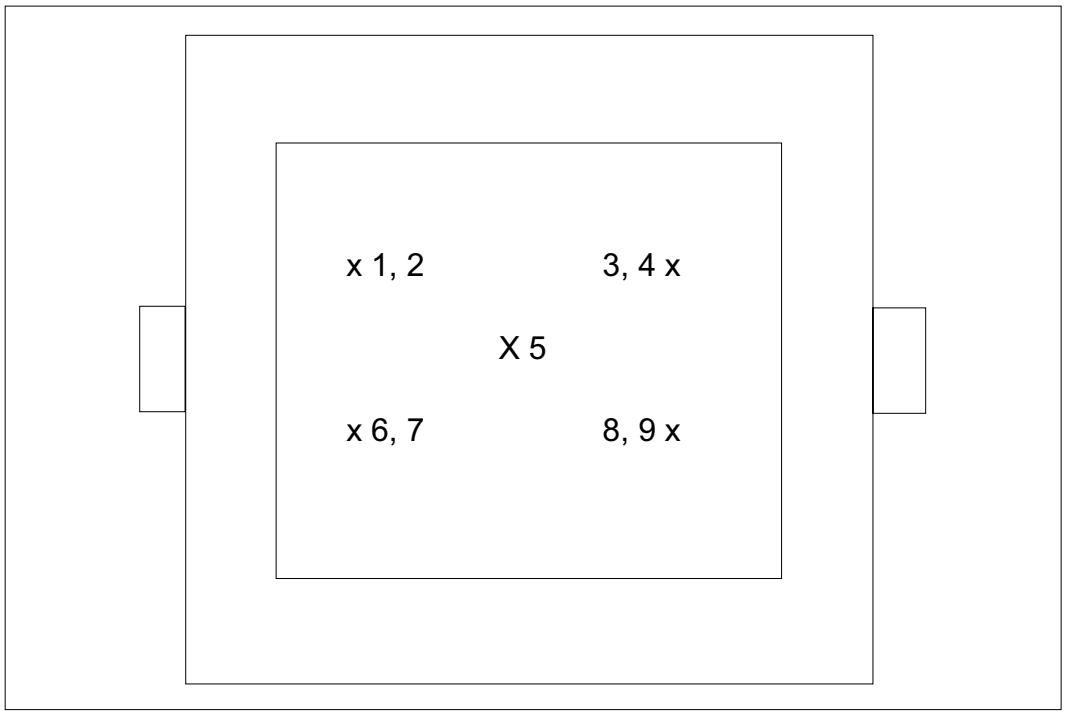
Test temperature and established criteria for class A, B and C vaccines for the validation of the packaging (for minimum of 48 hours)

Class	Type of vaccine	Ambient temperature	Minimum temperature allowed	Maximum temperature allowed
A	OPV	+43°C	no limit	+8°C
B	BCG Hib (freeze-dried) measles MR MMR meningococcal A&C yellow fever	+43°C	no limit	+30°C
C	DTP DTP–HepB DTP–Hib (liquid) DT	+43°C	+2°C	+30°C
	IPV HepB Hib (liquid) Td TT	-5°C	+2°C	+30°C

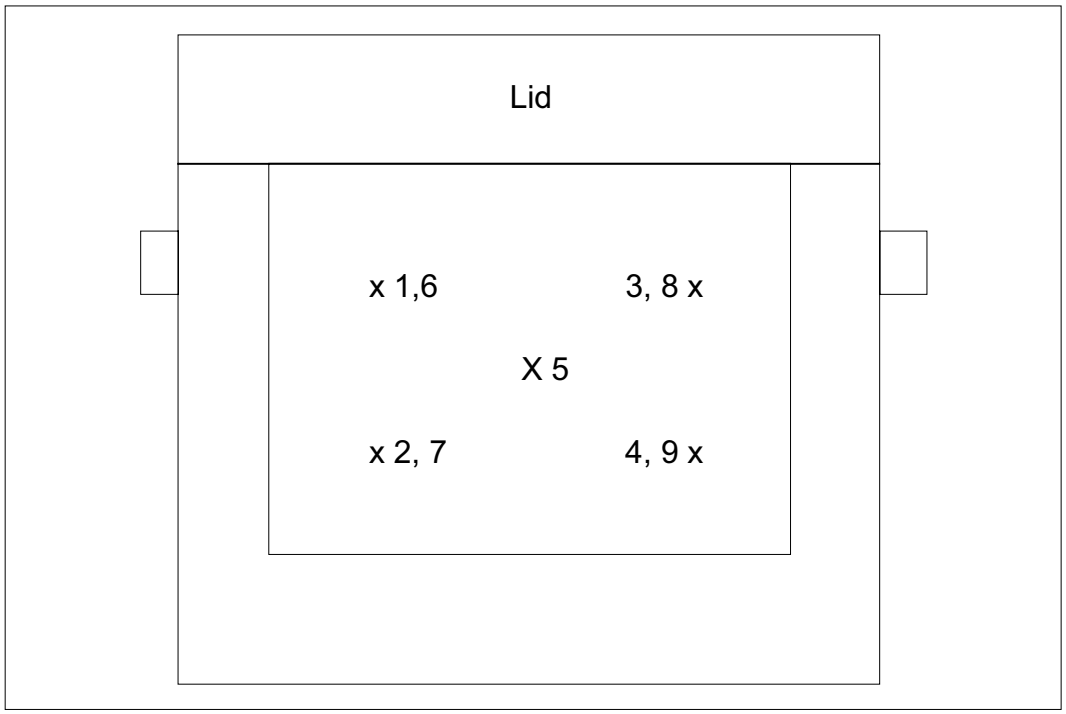
Temperatures within the container should be continuously monitored within an accuracy of ± 0.5ºC; the sensors used for this purpose must not be allowed to influence the test in any way. A minimum of 8 simultaneous temperature measurements are required for an insulated box *(see figure below).* The ambient temperatures at which the insulated box is tested must remain within a tolerance of ± 1ºC.

Locations of temperature sensors for insulated containers

a) Insulated container: top view



b) Insulated container: side view



2. Loading

Insulated boxes should be fully loaded with vaccine vials conditioned at +5ºC ±3ºC. Loads can be pre-fitted with thermocouples. Loading should be carried out as quickly as possible and the time taken for loading should be recorded for each container.

In the case of a vaccine manufacturer having more than one type of vaccine in one category, testing with any of the listed vaccine is acceptable. The validation does not need to be repeated with other presentations.

3. Temperature recording

The internal temperature of an insulated container is recorded at specified points within the load during the validation tests. The figure above shows the position of these points, each of which is 2.5/3.0 cm from the nearest icepack surface, with the exception of the central points.

Thermocouples should be attached to the outside of the vials and should **not be inserted** into the vials. Thermocouple leads can be introduced into the container either:

- through the seal – taking care not to affect the quality of the seal; or
- through a hole in the geometric centre of the lid or of one of the sides of the container – taking care to adequately seal the outer and inner openings.

4. Reporting

An initial validation report should be sent to WHO along with the dossier submitted for prequalification or reassessment. It should include:

- standard operating procedure (or test protocol) used for the validation;
- start date, end date and time of the three consecutive validation runs;
- detailed information on external and internal dimensions of insulated container, type of material it is made of, weight empty and weight fully loaded (total weight);
- detailed temperature history for all tests in tabular format (for all internal and external ambient channels).

Annex 2:
Shake test protocol

Purpose

The **shake test** is designed to determine whether adsorbed vaccines (DPT, DT, Td, TT, hepatitis B, Hib liquid, and/or combinations of these) have been affected by freezing. After freezing, the lattice (bond between adsorbent and antigen) gets broken. Separated adsorbent tends to form granules that get bigger in particle size and weight then gradually settle to the bottom after the vial has been shaken. The size of the granules seems to increase after repeated freezing and thawing cycles. Sedimentation occurs faster in a vaccine vial that has been frozen than in a vaccine vial (from the same manufacturer) that has never been frozen.

Individual batches of vaccine may behave differently from one another. The test procedure described below should, therefore, be repeated with all suspect batches. In the case of international arrivals, whenever there is an indication that temperatures have dropped below zero, the shake test should be conducted on a random sample of vaccines. However, if there is more than one lot of vaccine in the shipment, the random sample must include a vial taken from each and every lot.

Test procedure

1) Take a vial of vaccine of the same type and batch number as the vaccine you want to test, and made by the same manufacturer. This is your **control** vial.
2) Clearly mark the control vial: "**FROZEN**."
3) Freeze the **control** vial at -20°C overnight, until the contents are completely solid.
4) Let the **control** vial thaw. Do **not** heat it!
5) Take a "**test**" vial from the batch that you suspect has been frozen.
6) Hold the **control** ("**frozen**") vial and the "**test**" vial together in one hand.
7) Shake both vials vigorously for 10–15 seconds.
8) Place both vials on a flat surface side-by-side and start continuous observation of the vials until the test is finished. (If the vials have large labels that conceal their contents, turn both vials upside down and observe sedimentation in the neck of each vial.)
9) Use an adequate source of light to compare the sedimentation rates between vials.

Conclusion

If **sedimentation is slower** in the "**test**" vial than in the **control** ("**frozen**") vial, the vaccine **has not been damaged**. Use the vaccine.

If **sedimentation is similar** in both vials, **or** if sedimentation in the "**test**" vial is **faster** than in the **control** ("**frozen**") vial, the vaccine **has been damaged. Do NOT use the vaccine.** Notify your supervisor.

The figure below shows the difference between a **control** ("**frozen**") vial and a (**non-frozen**) **test** vial.

Seeing the difference in sedimentation rates during a shake test

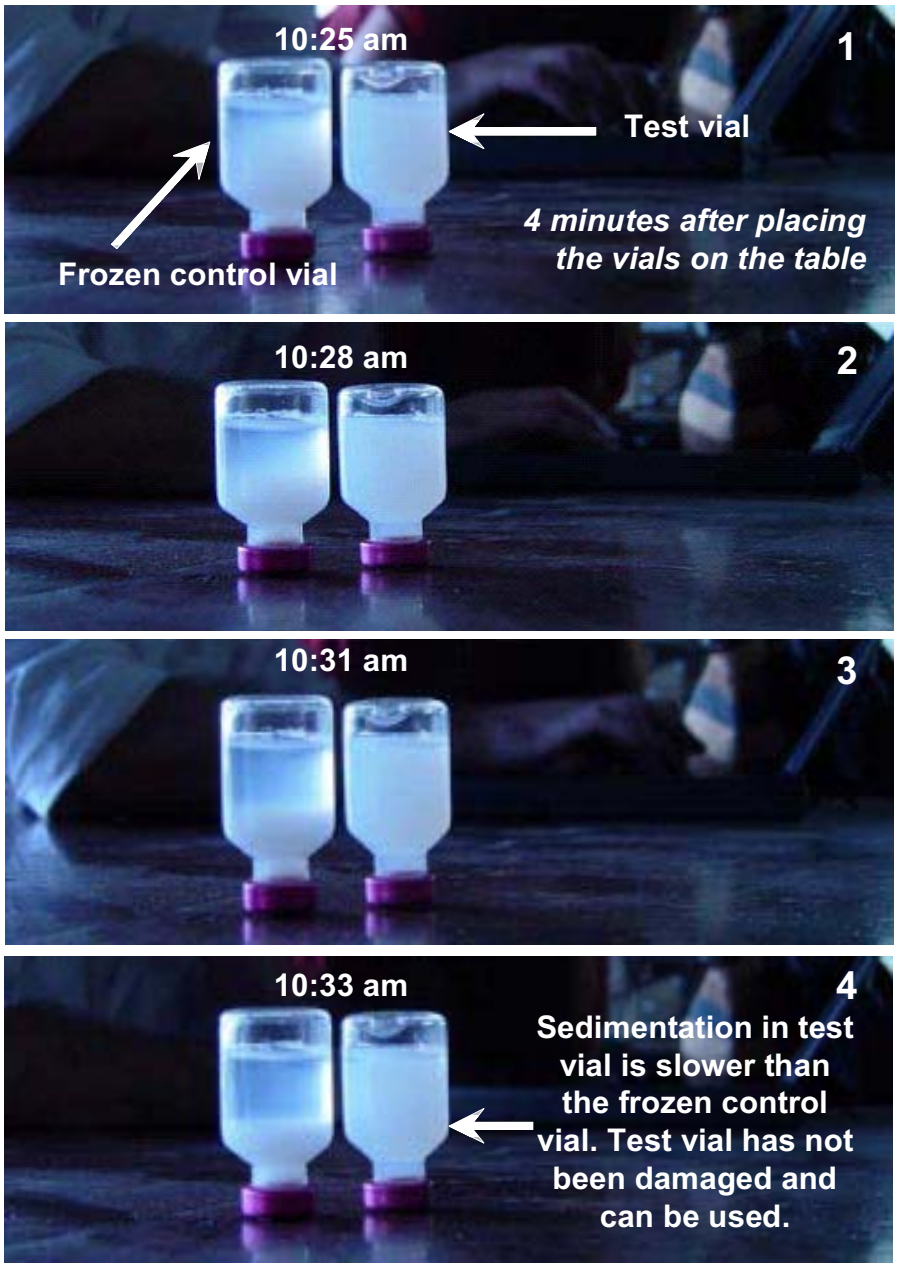


Photo: U. Kartoglu (WHO)

Annex 3:

List of contact points for national regulatory authorities in countries producing vaccines prequalified for purchase by United Nations agencies

Americas

Agencia Nacional da Vigilancia Sanitaria (ANVISA)
Esplanada dos Ministerios, Bloco G,
9o andar, sala 900
cep: 70058-900 Brasilia DF
Brazil

Bureau of Biologics and Radiopharmaceuticals (BBR)
Health Protection Branch (HPB)
Health Canada
L.C.D.C Building # 6 (0603 C)
Tunney's Pasture 0603C
Ottawa, Ontario K1A OL2
Canada

Centro para el Control Estatal de la Calidad de los Medicamentos (CECMED)
National Regulatory Authority of Cuba
Centro para el Control Estatal de la Calidad de los Medicamentos CECMED
Ave. 19, No 21002 entre 210 y 214
Atabey Playa
Ciudad Habana
Cuba

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 2000
Rockville, MD 20852
USA

Europe

General Pharmaceutical Inspectorate
Ministry of Social Affairs, Public Health and Environment
Bd Bishoffsheim 33
1000 Brussels
Belgium

Bulgarian Drug Agency
26 Yanko Sakazov Blvd
1504 Sofia
Bulgaria

Danish Medecines Agency
Axel heides Gade 1
2300 Kobenhavn 5
Denmark

Agence française de Sécurité Sanitaire des Produits de Santé
Direction de l'Inspection et des Etablissements
143-147 boulevard Anatole France
93285 Saint Denis Cedex
France

National Institute of Pharmacy
Zrinyi utca 3, Budapest
H - 1051
Hungary

Ministero della Salute
Lungo Tevere Ripa 1
00153 Roma
Italy

Paul-Ehrlich-Institut
Paul Ehrlich Strasse 51-59
Postfach 1740
D-63225 Langen
Germany

Medecines Evaluation Board (MEB)
PO Box 16229
2500 BE The Hague
T: 31-70 356 74 00
F: 31-70 356 75 15
Visitors address: Kalvermarkt-53
2511 CB The Hague
The Netherlands

Swissmedic
Swiss Agency for Therapeutic Products
Hallerstrasse 7
CH-3000 Bern 9
Switzerland

Medicines and Healthcare Products Regulatory Agency (MHRA)
Department of Health
Market Towers
1 Nine Elms Lane
London SW8 5NQ
United Kingdom

South-East Asia

Drugs Controller General of India, DCG(I)
Directorate General of Health Services
Ministry of Health and Family Welfare
Nirman Bhawan, New Delhi 110 011
Government of India
India

Directorate General of Drug and Food Control
Ministry of Health
Jalan Percetakan Negara 23
Jakarta Pusat 10560
Indonesia

Western Pacific

Therapeutic Goods Laboratories (TGAL)
Therapeutic Goods Administration
P.O. Box 100, Woden
ACT 2606
Australia

Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Chome, Kasumigaseki
Chiyoda-ku, Tokyo 100-8916
Japan

The Korea Food and Drug Administration (KFDA)
5 Nokbun-Dong Eunpyung-Ku
Seoul, South Korea
Republic of Korea

Annex 4:
Bulking factors for insulated packaging

Insulated packaging occupies up to 8.5 times the volume of the vaccine that it contains. If insulated boxes are to be re-used for further vaccine distributions in the country, they cannot be "nested". If they are to be kept, provide sufficient storage space so that they can be stacked. Bulking factors for insulated packaging based on the prequalified vaccines list (as of 1 April 2005) are given in the table below.

Bulking factors for insulated packaging

Vaccine type	Dose per vial	Bulking factor
BCG (freeze-dried)	10 or 20	5.5
DTP, DT, Td,TT	10	4.5
DTP, DT, Td,TT	20	5.5
DTP–HepB	2	3.0
	10	5.0
DTP–Hib	1	4.0
	10	3.5
DTP-HepB+Hib	1 or 2	3.5
HepB	1	4.0
	1 in UNIJECT	5.5
	2, 6, or 20	5.0
	10	7.5
Hib (liquid)	1 or 10	4.5
Hib (freeze-dried)	1	3.5
	10	4.0
Measles (freeze-dried)	10	5.0
MMR (freeze-dried)	1	4.0
	10	6.0
MR (freeze-dried)	10	5.0
Meningitis A&C	20 or 50	4.0
OPV	10 or 20	6.0
TT in UNIJECT	1	5.5
Yellow fever	5	6.5
	10	4.0
	20	5.0
Diluents and droppers	n/a	1.5

If the packaging volume is critical, countries should obtain accurate dimensions from the procurement agency or, in case of direct procurement, directly from the vaccine manufacturer.

Annex 5:
Vaccine Arrival Report

This report is to be filled in by authorized staff, ratified by the Store Manager or the EPI Manager, and forwarded to UNICEF **within 3 days** of vaccine arrival. Use one report for each vaccine in the shipment.[1]

Vaccine arrival report

COUNTRY	
REPORT No.	

Date of report	

Place, Date and Time of Inspection	Name of cold store, date and time vaccines entered into cold store

PART I-ADVANCE NOTICE

MAIN DOCUMENTS	Date received by consignee	Copy airway bill (AWB)	Copy of packing list	Copy of invoice	Copy of lot release certificate
Pre-advice					
Shipping notification		Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

List other documents (if requested)	

PART II- FLIGHT ARRIVAL DETAILS

AWB number	Airport of destination	Flight No	ETA as per notification		Actual time of arrival	
			Date	Time	Date	Time

NAME OF CLEARING AGENT: _____ ON BEHALF OF: _____

PART III- DETAILS OF VACCINE SHIPMENT

Purchase order No.	Consignee	Vaccine description (Type and doses/vial)	Manufacturer	Country

Vaccine				Diluent/droppers			
Lot number	Number of boxes	Number of vials	Expiry date	Lot number	Number of boxes	Number of units	Expiry date

(Continue on separate sheet if necessary)

	Yes	No	Comments
Was quantity received as per shipping notification?	☐	☐	
If not, were details of short-shipment provided prior to vaccine arrival?	☐	☐	

No. = number

[1] WHO recommends that all UN agencies, countries and non-governmental organizations procuring vaccines adopt this report.

Report No.	

PART IV-DOCUMENTS ACCOMPANYING THE SHIPMENT

Invoice	Packing list	Lot release certificate	Vaccine arrival report	Other
Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	
Comments				

PART V- STATUS OF SHIPPING INDICATORS

Total number of boxes inspected			
Coolant type:	Dry ice ☐	Icepacks ☐	No coolant ☐
Temperature monitors present:	VVM ☐	Cold chain card ☐	Electronic device ☐

PROVIDE BELOW DETAILS OF STATUS ONLY WHEN PROBLEMS ARE OBSERVED:

Box number	Lot number	Alarm in electronic device		Vaccine vial monitor				Cold Chain Monitor				Date/time of inspection
		Yes	No	1	2	3	4	A	B	C	D	

(Continue on separate sheet if necessary)

PART VI- GENERAL CONDITIONS OF SHIPMENT

What was the condition of boxes on arrival?	
Were necessary labels attached to shipping boxes?	
Other comments: (continued in separate sheet if necessary)	

PART VII- NAME AND SIGNATURE

Authorized Inspection Supervisor	DATE	Central Store or EPI Manager	DATE

For UNICEF Country Office use only

Date received by Country Office: _____ **Contact Person:** _____

Guidelines for completing the Vaccine Arrival Report

The Vaccine Arrival Report (VAR) is a comprehensive record of cold-chain conditions during transport and of compliance with shipping instructions. Recipient governments, UNICEF country offices and the UNICEF Supply Division are responsible for the report and for taking appropriate action if problems are reported (e.g., follow-up with the manufacturer, forwarding agent, WHO, etc.).

Use one report form for each shipment and for each vaccine in the shipment. In shipments containing diphtheria–tetanus–pertussis (DTP)–Hepatitis B (HepB) and *Haemophilus influenzae* type b (Hib) vaccines, use one form for DTP–HepB and a separate form for Hib. *In the case of short-shipments (where parts of the original quantities are not delivered), complete a separate report for each part delivered.*

Complete the form as described below. In the **header boxes** at the top of the form, enter the name of recipient country, report number and details of place and date of inspection and storage. The ***report number*** is an internal number for organizing records; compile it as follows: country code–year–number for each report (e.g., BUR–2005–001 for one vaccine; BUR–2005–002 for a second vaccine etc.). In the case of a short-shipment, the numbers for the separate deliveries would be, for example, BUR–2005–003.1, BUR-2005-003.2 etc.

Part I – Advance notice

I.1 Enter dates and details of documents received in advance of the vaccine shipment.

Part II – Flight arrival details

II.1 Fill in details of expected and actual arrival times for the shipment.

II.2 Fill in the name a) of the clearing agent and b) for whom the agent acts (e.g. the ministry of health or UNICEF).

Part III – Details of vaccine shipment

III.1 Fill in details of the order (purchase order number, consignee, vaccine description etc.).

III.2 For each batch of vaccine included in the shipment, record:
- a) the number of shipping boxes,
- b) the number of vials, and
- c) the expiry date.

The number of boxes you enter should always match the number of boxes shown in the packing list. If it does not, note (under *Comments*) if advance notice of a change in the quantity was provided. It is not necessary to count the number of individual vaccine packs in each shipping box for this report.

III.3 For the diluents and droppers (if included) with each batch of vaccine in the shipment, record:
- a) The number of shipping boxes,
- b) the number of vials, and
- c) the expiry date.

The information for III.2 and 3 is also in the packing list.

Note: Diluents for freeze-dried vaccine and droppers for oral polio vaccine (OPV) are integral parts of the vaccine, so always include them on the same form. If diluent/droppers are delivered separately, consider it a short-shipment.

Part IV – Documents accompanying shipment

The packing list should indicate which box contains the shipping documents (usually Box 1).

IV.1 If this information is not included in the packing list or in documents sent separately by courier, pouch or other means, note this under *Comments*.

IV.2 Verify that all necessary documents are present and complete the form accordingly.

Note: If the lot release certificate is missing, do not use the vaccines; keep them on hold in cold storage until the relevant document has been obtained from the vaccine manufacturer.

PART V – Status of shipping indicators

Inspect the temperature monitors in all boxes before putting vaccines into cold storage. For very large shipments, or when immediate storage in the shipping boxes is required, check a representative number of boxes before placing the shipment in the cold store. Complete inspection of all boxes the next day, or as soon as possible thereafter; under comments, note the date and time when the complete inspection took place.

Note: In this report, enter the information below (V.1) *only* for boxes in which the temperature monitor shows a change that indicates potential damage to vaccines (vaccine vial monitor = stage 3 and 4, cold chain monitor card as per vaccine/threshold table in card, or alarm indication in the electronic device).

V.1 Enter:
- a) the number of boxes inspected (this should equal the total number in the shipment),
- b) the type of coolant used, and
- c) details of any temperature exposure, if detected.

V.2 Photocopy or scan LCD screens in electronic devices that show alarm status and attach to report.

V.3 Clearly identify vaccines in boxes in which the indicator shows exposure to temperatures that risk damage and keep them in the cold room for further assessment of their condition. ***Do not discard vaccines until assessment is completed.***

PART VI – General conditions of shipment

VI.1 Indicate if the shipping boxes were received in good condition and if all necessary labels on the outside of the shipping boxes were present; add any comments.

PART VII – Name and signature

VII.1 The authorized person responsible for the inspection and the Central Store Manager or the EPI Manager should sign this report.

VII.2 Send the form, completed and signed, to the UNICEF Country Office within three days of arrival of the vaccine; they will forward it to the UNICEF Supply Division (Immunization Team Fax: +45 35269421).

The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested *(Initiative for Vaccine Research).*

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards *(Quality Assurance and Safety of Biologicals).*

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented *(Vaccine Assessment and Monitoring).*

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies *(Access to Technologies).*

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives *(Expanded Programme on Immunization).*

Department of Immunization, Vaccines and Biologicals
Family and Community Health

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Switzerland
Fax: +41 22 791 4227
Email: vaccines@who.int
or visit our web site at: http://www.who.int/vaccines-documents

World Health Organization