Interpretation of temperature monitoring devices in international shipments

1. Background

Temperature monitoring devices in international shipments are critical tools in confirming whether the product was exposed to any temperature above and/or below the defined temperature range. These devices help the consignee to identify the problem, provide information to understand the severity of the occurrence and together with UNICEF and furthermore with WHO to come to a decision of acceptance or rejection. All rejection acts should be either advised or endorsed by the WHO.

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 to during international transport, for a period of at least 48 hours (for more details please refer to WHO Guidelines on International Packaging and Shipping of Vaccines, WHO/IVB/05.23).

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

Temperature monitoring devices must be included in all vaccine shipments to document whether or not temperature limits have been exceeded. These devices should:

1. Serve as a quick reference guide to help recipient countries determine whether the shipment – or parts of the shipment – have been exposed to temperatures that could damage the vaccines; 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 deviation 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 deviation, take corrective measures, and avoid similar situations in future shipments; and b) for insurance purposes.

2. Temperature monitoring devices in international shipments

Electronic temperature devices provide the most reliable and accurate record of the above-mentioned information. WHO recommends that one electronic shipping indicator (meeting WHO PQS performance specifications, WHO/PQS/E06/TR07.1) 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) and/or freeze indicators in international shipments. CCM is used ONLY under exceptional circumstances where dry ice continues to be used.

Consistent with the development of this guideline, there are two PQS prequalified electronic shipping indicators. Therefore when you open the cartons, you will see either of these electronic devices (Figure 1).

Figure 1. WHO/PQS prequalified electronic shipping indicators

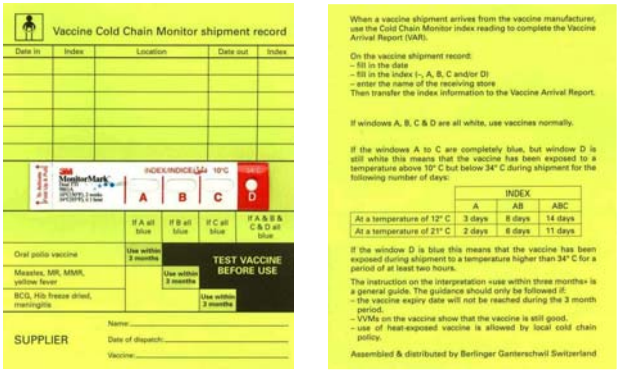
Q-tag2plus (Berlinger) PQS/E06.02

VaxAlert (Sensitech) PQS/E06.10

There are two types of electronic shipping indicators. Type I devices have a YELLOW backing card and are used for DTP, DT, TT, dT, HepB, IPV, liquid Hib and a combination of the above freeze-sensitive vaccines, while Type II devices have a BLUE backing card and are used for OPV, freeze-dried BCG, measles, MR, MMR, Hib, yellow fever and Meningitis vaccines.

If dry ice is used in the shipment of A or B classification (see Table 1), a CCM card should be found in each and every shipping carton instead of Qtag2plus or VaxAlert (Figure 2).

Figure 2. WHO/PQS prequalified Vaccine Cold Chain Monitor record (PQS/E06.04)



In addition, vaccines must have Vaccine Vial Monitors (VVM) either on the primary label or on the flip-off cap/neck of the ampoule depending on the type of the presentation.

Figure 3. Vaccine vial monitors on TT vaccine (PQS/E06.01)

Electronic shipping indicators ARE designed to monitor temperatures during transit. VVM is NOT designed as a transit indicator. VVM is NOT used in principle to evaluate the temperature exposure during an international shipment. However, it is also important that VVMs from different boxes should be checked upon arrival.

3. Interpretation of temperature monitoring devices in international shipments

This guide describes the steps to be followed when you receive an international shipment, particularly from the interpretation of temperature monitoring devices perspective.

1. In each shipment, box #1 should contain, along with shipping documents, a list of box numbers with the bar code/serial number of corresponding devices included in each box. When you open a box and remove the electronic device, you MUST also write down the box number on the backing card for easy reference.

2. You MUST open all boxes to read the electronic shipping indicators[1]. Once you open the box and find the electronic shipping indicator, FIRST you MUST stop the device, then you MUST also write down the box number on the backing card for easy reference as described in item 1.

3. After you have stopped the devices and recorded the box numbers, you MUST check the ALARM status of each device.

4. If there are no alarms, the shipment SHOULD be accepted. However, you should also check the VVM status and report this in the Vaccine Arrival Report (VAR). If there are no alarms, no changes are expected in VVM status in an international shipment. You should understand that the VVM inner square **start point colour** is NEVER white and normally it is approximately 10% of the outer circle colour (a slight bluish/purple colour). Some vaccines may arrive with VVM slightly darker than the **start point colour.** This depends on the VVM category and the time and temperature of storage prior to sending the international shipment.

5. If there are any alarms, **write down the time you stopped the device on the backing card.** This is important when you refer to the device after you stopped it. It will help you to calculate the precise time of deviation.

6. Make a photocopy or scan the device to document the ALARM status. In each image, indicate the number of the box that the device was in.

7. Include all necessary information in the **VAR.**

8. If there are any **ALARMS**, fill in the **Alarm Reporting Form** and attach it to the **VAR**.

9. Send the **VAR** with **photocopies** or **printed images** from scanned devices and the **Alarm Reporting Form** to the **"procurement agency".**

[1] *CCM card is used only with the shipments with dry ice and if there are no colour change of the ABC and/or D windows, vaccines should be accepted - there will NOT be any status change in the VVMs. In the case of any colour change in the ABC and/or D windows, it is very unlikely that any visible changes will occur in VVMs.*

In summary, the decision of accepting or rejecting the shipment due to a temperature exposure problem must be based on the electronic shipping indicator readings.

4. The relation of electronic shipping indicator readings with VVM

The relation of these readings and VVM status can be explained as follows:

- If there are no alarms, VVM cannot have a significant status change. Even if no change in the status in VVM is expected, VVMs still need to be checked to record the findings in the VAR.

- In the case of alarms, there cannot be any VVM status change with a <= -0.5°C alarm. VVM does not change any colour in negative temperatures.

- The alarm of >= 10°C is important for the OPV. In the case of >= 10°C, if the vaccines are other than OPV, the shipment should be accepted, and visible VVM status change is NOT possible with any of the vaccines with this alarm for the duration of the shipment.

- In the case of the >= 30°C alarm, shipment may be rejected, subject to confirmation by the WHO HQ. In most of these cases, the VVM status will not be compromised. However, depending on the number and severity of the higher temperature alarms, the VVM status change may be evident by visual inspection.

- In the case of the >= 45°C alarm, shipment should be rejected. Depending on the number and severity of the violation, the VVM status change may be evident by visual inspection.

5. Can a VVM really develop to 50% of the reference colour in an international shipment?

To date there were several complaints on the VVM status upon arrival in country with claims that it has reached stage 2 (50% of the reference colour) during an international shipment. WHO has not identified any quality-related issues with these complaints, and the conclusion was that the VVM reading at the country level was not accurate (staff assuming that the VVM start colour is white and claiming stage 2 if there is **any** colouring in the square). Table 2 displays the time and temperature required for a VVM to reach 50% of its start colour.

As seen in Table 2, VVM2 is the most reactive VVM. It is used only on OPV. It takes one full day at 37°C exposure for VVM2 to reach 50% of the reference colour. In theory, such exposure could take place, but this would also result triggering both >= 10°C and >= 30°C alarms.

Table 2: Time required for VVM to develop 50% of reference ring colour at different (constant) temperature exposures

TEMPERATURE	VVM TYPE	DURATION OF EXPOSURE REQUIRED FOR VVM TO REACH 50% OF REFERENCE RING COLOUR (IN DAYS)
5°C	VVM2	110
	VVM7	550
	VVM14	1,100
	VVM30	2,400
15°C	VVM2	23
	VVM7	100
	VVM14	200
	VVM30	430
25°C	VVM2	5
	VVM7	21
	VVM14	41
	VVM30	88
37°C	VVM2	1
	VVM7	3.5
	VVM14	7
	VVM30	15

In a theoretical case of VVM status being compromised in an international shipment without any alarms in electronic shipping indicators, the only possible explanation could be VVMs being compromised by the manufacturer before they are shipped. As indicated, this is a theoretical case, and has not happened at all since the introduction of VVMs in 1996. However, it is important that this scenario is also studied in this guide.

After labelling and affixing of VVM to OPV or a freeze-dried vaccine, the vaccine is stored at -20°C until it leaves the facility for shipment. Even if the manufacturer keeps these vaccines at -20°C for an extended period in the storage, the VVM status will NOT change significantly. If VVM colour after international shipment is substantial, the only explanations could be the manufacturer keeping the vaccines with VVM above -20°C prior to shipment or not storing VVMs properly before application to the vaccine. If OPV or a freeze-dried vaccine is stored at -20°C prior to shipment there will not be a significant change in VVM colour

Storage of vaccine with VVM7 at 2 to 8°C for prolonged periods of time will definitely cause development of colour in the VVM. Storage at 8°C, although within the compliant temperature range, will accelerate the colour development of the VVM. For VVM7, it takes about 550 days to reach 50% colour, while at 8°C, the time is reduced to about 320 days.

If the storage period until shipment exceeds 12 months and the temperature is always 8°C, the VVM develops >50% of its colour. If such vaccines are kept at 8°C for approximately 6 months, the VVM will develop > 25% of its colour which would easily be identified by visual inspection and could possibly cause the consignee to question the temperature during shipment. This situation should be avoided by the vaccine manufacturer as much as possible by storing the vaccine for the shortest period of time before international shipment.

A similar effect would require storage for about 1 year for VVM14 and 2 years for VVM30 at 8^{o}C before the shipment. Such events are extremely unlikely to happen.

6. Should a colour reflection densitometer be used to read the VVMs on arrival as part of the acceptance procedure?

X-rite Model 404 GS or GSX colour reflection densitometer, or later qualified model is used in verification tests specified in the VVM PQS verification protocol (WHO/PQS/E06//IN05/VP.1 dated 30 November 2006). The densitometer is also used routinely in acceptance tests conducted by the vaccine manufacturer whenever they receive a new VVM batch. A colour reflection densitometer cannot and should not be used in routine acceptance of international shipments. In addition to the above uses, WHO may use colour reflection densitometer in settling claims that has visual changes with accompanying serious and multiple alarms in electronic temperature monitors.

7. Responsibilities of the consignee upon arrival of vaccines

The standard procedure requires consignees to inspect vaccines upon arrival to cold store. UNICEF is contractually responsible for international transportation (48 hours - and sometimes more) up to the point of vaccine's arrival to the airport of destination; consignee is contractually responsible to collect and transport the vaccine from the airport to its cold store, and to inspect vaccine within a period of 48 hours from the receipt of the shipment at the airport. This adds more time to the period of between the start of the shipment and completion its inspection (i.e. VAR signed). This could double the exposure time for which WHO requires manufacturers to validate their export packaging as a minimum. Therefore it is important that the consignee works closely with customs and airport authorities to ensure expedited release of vaccines upon arrival. The Ministry of Health as consignee is responsible in ensuring the following:

1. Establish effective working arrangements with the customs authorities and with the National Regulatory Authority (NRA)
2. Ensure vaccine is cleared through customs without exposure to adverse temperatures
3. Ensure that the equipment and monitoring procedures in the holding store are satisfactory
4. Ensure that reliable transport is available to move vaccine from the holding store to the primary store
5. In hot climates, do not expose shipping containers to excessive temperatures during transport. In cold climates, do not expose shipping containers to temperatures below 0^{o}C during transport. If necessary, use warm packs to protect freeze-sensitive vaccines.
6. Where a clearing agent is used, sign a written contract (quality agreement) with the clearing agent

7. Monitor the performance and facilities of the clearing agent and monitor his temperature records

For further details on the responsibilities of the consignee upon arrival of vaccines, please refer to the *WHO-UNICEF Effective Vaccine Store Management Initiative, Modules 1-4* (WHO/IVB/04.16-20, UNICEF/Immunization 03 and 04.01-04, 2005).

Revision history		
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