Implementation of VVM at a Vaccine Manufacturer

Part 1
Steps to VVM Implementation Part 1

1. WHO process
2. Supplier equipment needed
3. Receipt, Control and Storage of VVMs
Steps to VVM Implementation (WHO)

1. Vaccine Manufacturer Submits Dossier to WHO for Prequalification which Includes Vaccine Stability Data
2. WHO Identifies the Approved Category of VVM based on the Stability Data of the Vaccine*
3. Vaccine Manufacturer Validates the VVM Reactivity & Performance
4. Determination of VVM Type (Dot or Full Label) and Placement on the Vial *(Artwork Approval Necessary for Full Labels)*
5. SOPs at Manufacturer for VVM Receipt, Storage and Use
6. Installation and Validation of VVM Application Equipment

* For use of HEATmarker outside of WHO/UNICEF programs, vaccine manufacturer makes the choice of category
Equipment Required at Vaccine Manufacturers

- Frozen storage (≤-24°C)
- Temperature monitoring and recording
- Temperature controlled water bath for validation and control
- Reflection densitometer for objective measurement of VVM color

- Water-proof Heat Sealable Pouches (Foil)
- 12” Heat Sealer Seals VVM in foil Pouches
- Automatic label application equipment
VVM RECEIPT, CONTROL and STORAGE at the MANUFACTURER
Verification of Proper Transport Conditions

The receiving inspection process begins on the day the HEATmarker VVM’s are delivered.

VVMs are normally shipped in an LD3 container with the VVMs packaged on a wooden pallet.

Alternatively, VVMs are sent in insulated shippers containing VVMs packaged with dry ice.
Verification of Proper Transport Conditions

• Due to the sensitivity of the VVM, proper transport conditions are imperative

• Vaccine manufacturers need to be prepared to react immediately upon arrival to verify proper transport conditions and move the VVM into frozen storage
Verification of Any Physical Damage During Transport

- Complete inspection should be made within 24 hours after the arrival
- Document any damage to the product with photos
- Contact the freight forwarding company immediately if damage is detected
- Notify TEMPTIME Corporation of any damage within 48 hours of delivery
The documentation package includes:

1. **HEATmarker Inspection Card for each lot**
   (Each carton containing HEATmarker Vaccine Vial Monitors also contains an Inspection Card)

2. **HEATmarker Vaccine Vial Monitor Receipt Form for each lot**

3. **Certificate of Analysis for each lot**

4. **Acceptance Form for the consignment**

5. **Commercial Invoice**

6. **Packing List**

7. **Other required documents, if needed.**
Location of Shipment Documents in LD3

The Shipping Documentation Package can be found in the right corner under the first layer of boxes in the LD3 Container.
The Shipping Documentation Package is located in the insulated shipper with the red sticker.

A copy of the Custom’s Documents are located above the black foam inside the shipper.
Location of Shipment Documents in Insulated Shippers

A copy of the Custom’s Documents AND HEATmarker Inspection Cards for each lot are located INSIDE the shipper. The Inspection cards are used to perform the Monitor of Transport calculation and Start Point Optical Density calculation during the receipt inspection process.
Inspection to Verify Presence of Dry Ice – LD3

The first level of inspection of transport is the presence of dry ice. In addition to dry ice being placed in the LD3 container outside the insulated carton, select boxes of dry ice inside the carton contain dry ice only (no product). These boxes are marked with a black and white dry ice label. Proper safety procedures and equipment must be used when handling dry ice.
Dry Ice in Insulated Shipper

Some dry ice should be present in the shipper when it is received.

Dry ice (solid form of carbon dioxide) does not leave any residue (other than incidental frost from moisture in the atmosphere). It sublimates at −78.5 °C; −109.3 °F. This extreme cold makes the solid dangerous to handle without protection, due to burns caused by frostbite.
Verification of Product Received

- Inspect each carton for physical damage.
- Document any damage with photos.
- Review the exterior information on each box of the HEATmarker VVM product to verify the VVM product shipped.
Labels on Each Carton

Each carton of VVMs has a Lot Number Label and a color-coded box label and information label.

Each information label contains:
1. Customer name
2. Customer PO
3. Customer Part #
4. Letter of Credit #
5. Total # of VVMs in box
6. Number of VVMs per roll
7. Number of rolls
8. TEMPTIME Lot #
9. Use-by-date
10. Ship date (month only)
11. Box number
12. Shipped density difference
Immediately Move Cartons of VVMs to Proper Frozen Storage

VVMs must be stored in the dark. VVMs can develop color changes very quickly when exposed to direct sunlight or indirect sunlight.

Indoor lighting can also have an impact over time on the VVMs. Therefore VVMs should be stored in the absence of light.

VVM box should be sealed to prevent ice build-up and UV Light exposure.
Storage Conditions

VVMs should be stored in packaging sufficient to avoid any deterioration of the physical properties of the VVMs.

VVMs should be stored in **sealed plastic bags** - avoid condensation.

VVMs should be stored in a **closed carton** to avoid physical damage.
Storage Conditions

VVMs should be stored at or below -24°C to minimize any measurable change in initial starting optical density.

- keep away from the door so as to minimize temperature variations
- Freezer temperatures should be maintained and recorded.
Recording Information from Shipment

Weigh (if possible) and record the amount of dry ice remaining in the shipment on the Lot Receipt Form. Sign and date the form.

**HEATmarker® Vaccine Vial Monitor (VVM) Lot Receipt Form**

| Customer: | BIBCOL |
|--------------------------------------------------|
| LC#: 0350FLC-5008-18 | Number of Cartons: 9 |
| PO#: (bOPV)/2017-18 | Number of Rolls: 66 |
| TEMPTIME Part Number: 10491 | Number of Indicators/Roll: 7000 |
| Customer Part Number: N/A | TOTAL Number of Indicators: 462000 |
| Lot Number: 17R222/1 | Shipped Density Difference: 0.07 (OD Indicator - OD Background) |
| Date of Manufacture: 2017-06-10 | Use By Date: 2021-08-10 |

*Instructions: 1) Fill out receipt information. 2) If any test results do not conform to the specifications, contact your supervisor immediately.*

Received by: [Signature]

Date: [Signature]

Time: [Signature]

Location: [Signature]

Test | Result | Requirement | Conform/Non Conform
--- | --- | --- | ---
1. Dry Ice | Yes/No | Yes | ______
2. Dry Ice Weight | ____ kg | For Information only | ______

Sign, date, record the dry ice weight
Verification of Monitor of Transport Conditions

The second level of control of inspection is the verification of the Monitor of Transport Conditions of the VVM as shown on the HEATmarker Inspection Card included with the shipment (one for each lot).
Verification of Monitor of Transport Conditions

Locate the HEATmarker VVM Inspection Card(s) in the documentation Package (one for each lot shipped) and verify the pre-filled information.

Use a calibrated X-Rite 504 densitometer to measure the active surface (square) of the VVM at least two times. Calculate the average and record the result.

Use a calibrated X-Rite 504 densitometer to measure the reference surface (ring) of the VVM at least two different places (top or bottom and side – be sure there is no printing. Calculate the average and record the result.

Calculate the measured density difference (AVE REF – AVE IND) and record the result.

Calculate the Monitor of Transport Conditions (Shipped density difference printed on card - Measured density difference from your calculation above) 0.57-0.14=0.43

The value should be within the tolerance on the Inspection Card.

Calculate the Average Starting Value. The WHO minimum specification Start Point OD is ≥ 0.025 +/-0.02.
Verification of Monitor of Transport Conditions

• If the calculated Monitor of Transport Conditions value is not within the tolerance on the Inspection Card, the measurement should be repeated. If it is still not within the tolerance, a supervisor should be notified to authorize additional inspection.

• Should the results of the Monitor of Transport Conditions acceptance value not be met, there are HEATmarker inspection cards in each carton that can be measured to verify conformance. In addition samples can be removed from individual rolls, removed from the liner, placed on the inspection card and measured. All readings should be recorded.

This card can be found inside each box. A master inspection card for each lot can be found in the documentation package.
Verification of End Point OD with WHO Specification

Verification of End-Point Optical Density at 37°C

- A Certificate of Analysis is supplied for each lot of VVM. This certificate can be used as documentation for conformance to the specification.

- The vaccine manufacturer may choose to do additional tests. These tests should be performed according to the procedures approved by WHO found in Chapters 2 and 3 of “Information Package for All HEATmarker VVMs.”
The Certificate of Analysis (CoA) for each lot shows Temptime’s results.

WHO has approved Temptime Corporation’s Testing protocol #P023C “Protocol for Testing and releasing a lot of HEATmarker VVMs at 37 degrees C”

Vaccine manufacturers must develop a standard procedure to measure the color development of VVMs after a predetermined time at 37C to test compliance with the specification. The measurements can be input into a spreadsheet for analysis, or analysis can be performed manually.

Acceptance criteria for the lot are shown on the CoA.
In Process Inspection & Use

• Prior to application on vaccine products, the VVMs should be inspected to verify that there has been no change in Optical Density during storage. Measure the starting initial reflectance density to verify the continuing conformance of the VVM to the acceptance criteria.

• Remove only the necessary quantity of rolls of VVMs from the freezer vault for some hours of use.

• Store the VVMs in a freezer or at least a refrigerator in or near the labeling room for in-use storage of VVMs.

• The VVMs are sensitive to light and should be properly protected from light during the labeling process.

• The roll number on each roll of VVMs provides traceability. It is important to record the roll numbers used during production.
Actions to Take if a Problem Occurs

• If there is any problem with the shipment due to physical damage, deterioration, delayed arrival (for more than 48 hours) or any other issue that may have an impact on the quality of the VVMs, immediately put the shipment into proper frozen storage.
• Initiate full documentation of the problem with the shipment (including detailed observations, descriptions, photographs and any other appropriate documentation)
• Immediately contact the freight forwarding agent and alert them of a possible claim. Document all conversations and information.
• Contact TEMPTIME Corporation immediately and especially within 48 hours to preserve any rights under the General Conditions of Sale. Copy TEMPTIME Corporation on any documentation to the freight forwarding agent.
Actions to Take if a Problem Occurs

- Temptime has a Complaint Process that the manufacturer should follow.
- Minimum information needed to help determine root cause of the problem should be entered on the Complaint Form and sent to Temptime as soon as possible.
Thank you!!!