Innovations in Temperature Monitoring
VVMs and Beyond
Agenda

• Vaccine Stability and VVM Selection
• Why should vaccine manufacturers use VVMs
• Innovations in the vaccine supply chain
Vaccine Temperature Sensitivity

Heat sensitivity

most sensitive
2
7
14
30

Days at 37°C

least sensitive

Freeze sensitivity

least sensitive
most sensitive

Measles
OPV
DTP
DTP/HepB
Hib Lyo
Hib Liq
Rubella
JE PHK
Rotavirus
Hep A
HPV
Cholera/Typhoid
Live
DTaP + combos
Cholera/Typhoid
Killed
Vaccines

Influenza
Varicella
Mumps
IPV
Measles
DTP
Hep A
Hep B
Varicella
Monitor Cumulative Heat with HEATmarker VVM

- The Active Square is the color changing reactive portion
- It is light at the start and progressively and irreversibly darkens
- The color change is faster at higher temperatures
- End point is reached when the color of the Active Square area is equal to the Reference Circle
The HEATmarker TTI Is Easy To Read

The Active Square is lighter than the Reference Circle.

If the expiry date is not passed, USE the vaccine.

The Active Square matches or is darker than the Reference Circle.

DO NOT USE the vaccine.
The Chemistry of the HEATmarker TTI

Polymerization Reaction

- The principle of operation is based on the solid-state polymerization of substituted diacetylenic monomers
- The combined effects of time and temperature cause a gradual, predictable, cumulative and irreversible color change from clear to dark
The VVM (Vaccine Vial Monitor) is the TTI used by WHO/UNICEF in the global immunization program. Temptime has more than 17 different categories of TTIs available from days at refrigerated temperature to years at room temperature.
# HEATmarker VVM for Use on Vaccines

<table>
<thead>
<tr>
<th>Pharmaceutical Product</th>
<th>Indication</th>
<th>Customer</th>
<th>Temptime Product</th>
<th>Value Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Immunization Campaigns for a range of contagious diseases:</td>
<td></td>
<td></td>
<td></td>
<td>Prevents immunization with heat damaged vaccines</td>
</tr>
<tr>
<td>• BCG</td>
<td></td>
<td></td>
<td></td>
<td>Expands reach of immunization programs to remote populations</td>
</tr>
<tr>
<td>• Diphtheria</td>
<td></td>
<td></td>
<td></td>
<td>Increases immunization programs efficiency</td>
</tr>
<tr>
<td>• Tetanus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pertussis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DTP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hep B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HiB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Meningococcal A and C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Measles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mumps, Pneumococcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• OPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rotavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tetanus Toxoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Yellow Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Campaigns:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rabies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Typhoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GSK, Sanofi Pasteur, Merck, Crucell, Pfizer, Novartis, Serum Institute of India, Biofarma, Japan BCG, BB-NCIDP, Bharat Biotech, Statens Serum Institute, Biological E, Bharat Serums and Vaccines, Haffkine, plus others</td>
<td>VVM2, VVM7, VVM14, VVM30</td>
<td></td>
</tr>
</tbody>
</table>
WHO e-VVM Based Vaccine Management Course

http://www.epela.net/epela_web/
WHO e-VVM Based Vaccine Management Course

http://www.epela.net/epela_web/
Selective vaccine use
Rotating stocks
Pinpointing cold chain problems
Increasing access
Preventing freezing
Reducing vaccine wastage
Signaling whether to use the vaccine for subsequent session
2007 UNICEF/WHO Joint Policy Statement Urging Member States, Donor Agencies and NGOs to Include VVMs As Minimum Requirement for Purchase of Vaccine

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification

Vaccine vial monitor (VVM) | All vaccines |
--- | --- |
Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type approved by WHO(WHO/V&I/99.187, WHO/I/07.048).

Signed declaration, as part of the cover letter submitted along with the file for prequalification confirming that the manufacturer will apply a VVM to the vaccine, and has the technical capacity to do so if requested by the purchasing specifications.
Steps to VVM Implementation

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
Accelerated Stability Studies for WHO Prequalification

● GOAL

- Accelerated stability data must be generated that allows the choice of the highest stability VVM category possible.

● RATIONALE

- At elevated temperatures, the highest category VVM which reaches its end point before the vaccine stored at the same temperature becomes sub-potent should be chosen. This ensures that the product is still suitable to use while minimizes wastage through premature discard of vaccine that is still potent.
The temperature sensitivity of vaccine characteristics, particularly potency, has a major impact on the success of global immunization programmes. WHO has acknowledged the importance of clearly defining the stability characteristics of a vaccine.

Chapter 10. Labeling states:

“If Vaccine Vial Monitors (VVM) are to be used, adequate stability data should be generated to support selection of appropriate VVM for a vaccine in question. Further details on the use of VVM for different types of products are available elsewhere.”


2 WHO Temperature Sensitivity of Vaccines (WHO/IVB/06.10) http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.10_eng.pdf
The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).

In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation occurs is measured and analyzed in accordance with the Arrhenius equation.

Vaccines should be tested to failure at these accelerated temperatures.

Vaccines do not need to follow the Arrhenius equation exactly to have a suitable VVM applied.

3 http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.10_eng.pdf
Chapter 7 in this Guideline provides specific requirements for inclusion in the product dossier submission regarding stability.

Chapter 7.2 addresses accelerated stability testing of the final product to define the VVM category to be used with the specific vaccine:

“Tables of accelerated stability data are required to define the VVM category to be used with the specific vaccine (stability at 2 different temperatures are required and these are usually 2-8°C and 37°C or 45°C), However real time data establishes the expiry dating. Conclusions on stability and the claimed shelf life of the vaccine(s) should be presented.”

Manufacturers are strongly encouraged to include 25°C as one of the accelerated test temperatures.

4 http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.16_eng.pdf
WHO PQS Performance Specification – Vaccine Vial Monitor (WHO/PQS/E06/IN05)\(^5\)

**VVM Reaction Rates**

<table>
<thead>
<tr>
<th>Category (Vaccines)</th>
<th>No. of days to end point at +37 °C</th>
<th>No. of days to end point at +25 °C</th>
<th>Time to end point at +5 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM 30: High Stability</td>
<td>30</td>
<td>193</td>
<td>&gt; 4 years</td>
</tr>
<tr>
<td>VVM 14: Medium Stability</td>
<td>14</td>
<td>90</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>VVM 7: Moderate Stability</td>
<td>7</td>
<td>45</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td>VVM 2: Least Stable</td>
<td>2</td>
<td>N/A*</td>
<td>225 days</td>
</tr>
</tbody>
</table>

- The four categories of VVM are VVM2, VVM7, VVM14 and VVM30.
- The number following “VVM” corresponds to the upper limit in days at 37 °C for at least 95% of VVMs to reach the end point.
- This Table lists the upper limit in days at 25 °C for 95% of each VVM category to reach the end point, except for VVM2.
- The critical temperatures for VVM2 are 37 °C and 5 °C. VVM2 is only used for Oral Polio Vaccine and is not included in further discussion.

These test times are coincident with the upper limit times in the VVM Performance Specification.

These test times should be considered as the minimum requirement.

Additional testing is encouraged.

Tests should be continued until product failure, if possible.

- For example, do not stop the test after 7 days at 37°C, continue testing at 14 days and 30 days.
- Do not stop the test if a single assay is below the product specification.

Some vaccine formulations are very stable towards heat exposure. Manufacturers should consider extending tests at 37°C to 45 and 60 days or longer as appropriate. Similarly extended test periods at 25°C should also be considered.

<table>
<thead>
<tr>
<th>Test Temperature (°C)</th>
<th>Test Times (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>7, 14 and 30</td>
</tr>
<tr>
<td>25</td>
<td>45, 90 and 193</td>
</tr>
</tbody>
</table>

Minimum Stability Data to Support Choice of VVM Category (except OPV)
Step 1: Summarize stability data

- 2 to 8°C\(^1\): 3+ years (1600 days)
- 25°C: 90 days
- 37°C: 8 days
- Expiry Date: 2 years

Step 2: Compare Stability Data with VVM Categories

\(^1\)2 to 8°C is treated as 5°C
Product A: VVM Choice and Rationale

VVM14 and VVM30 – Reach End Point After Vaccine is Sub-potent

VVM2 – Reaches End Point Too Fast

VVM30
VVM14
VVM7
VVM2
Product A Stability Data and VVM Categories

CHOOSE VVM7
Summary – Vaccine Stability and VVM Category

• VVM is a critical characteristic for WHO prequalification

• Sufficient stability data needs to be included in the Product Summary File to support the choice of the longest VVM category available

• Accelerated degradation studies must be carried out for sufficient duration to reach end of product life at the accelerated temperature

• Stability data and VVM category request submitted to WHO in Product Summary File

• WHO approves the VVM category for a particular vaccine

• Notification of VVM category is provided to manufacturer and Temptime
Why Should a Vaccine Manufacturer Implement VVM?

• VVM helps improve global health!
• VVM is good for business!
  – VVM is a critical characteristic for WHO prequalification
    • Case Study – Rotateq/Rotarix
  – VVM is has been adopted and is being introduced in countries outside of PQS requirement
    • Case Study – China
    • US consideration
Case Study: Rotarix and RotaTeq Vaccines

A Cost Effectiveness and Capacity Analysis for the Introduction of Universal Rotavirus Vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines

Albert Jan van Hoek¹, Mwanajuma Ngama²*, Amina Ismail³, Jane Chuma³, Samuel Cheburet⁴, David Mutonga³, Tatu Kamau⁵, D. James Nokes⁶

Conclusion:

– Vaccination against rotavirus disease is cost-effective for Kenya irrespective of the vaccine.
– Of the two vaccines Rotarix was the preferred choice due to
  • a better cost-effectiveness ratio
  • the requirement of fewer doses
  • less storage space
  • proven thermo-stability and
  • presence of a vaccine vial monitor (VVM)

¹PLoS One, Vol.7 (No.10). e47511. ISSN 1932-6203
http://wrap.warwick.ac.uk/52019/
Case Study: China
Shanghai CDC Implements HEATmarker® VVM on Pneumococcal Vaccine

- Decision in October 2013 to implement VVM on pneumo
- Shanghai CDC extending the use to five vaccines
Beijing CDC Launches HEATmarker® VVM for 2014 Flu Vaccine Program

NCDC to launch a study covering 5 vaccines in three provinces
Vulnerabilities in Vaccine Management
Office of Inspector General
June 2012

82 million VFC vaccine doses were administered to an estimated 40 million children at a cost of $3.6 billion in 2010.

Study
- Vaccine storage unit temperatures were monitored in 45 providers for a 2-week period.

Finding
- 76 percent of the 45 selected providers were exposed to inappropriate temperatures for at least 5 cumulative hours during that period.

National Vaccine Advisory Committee – Minutes of September 2013 meeting to Assistant Secretary of Health

“Visual indicators of quality on the packaging may be further explored. The World Health Organization (WHO) already uses vaccine vial monitors in warm climates. Freeze threshold indicators could address the most common problem in U.S. clinics.”

1 https://oig.hhs.gov/oei/reports/oei-04-10-00430.pdf
Developments in US Policy for VVMs and FREEZEmarker

National Vaccine Advisory Committee – February 2014 meeting
- National Vaccine Program Office (NVPO) is organizing Vaccine Storage and Handling Forum with VVMs and freeze indicators on agenda
- CDC and American Academy of Pediatrics (AAP) are supportive to participate in the forum
- NVPO contacted WHO to ask for representation and speak on VVM technology and value
- Temptime is asking for assistance to identify AAP members with VVM knowledge who could share their positive experience with VVM
Innovations
Vial Level Freeze Risk Indicator

Current FREEZEmarker 80 µL

Vial Level FREEZEmarker 2 µL
The NEXT little big thing!

- Unambiguous grey to black color change
- Clearly demonstrates that even 2µL volume is easily distinguished
- This is not a final design, simply proof of concept
The Next Challenge – Controlled Temperature Chain (CTC)

Objective: **on-label** use of vaccines in a CTC allowing specific vaccines to be kept and administered at ambient temperatures, up to 40°C for one, limited period of time

- **First pilot conducted on MenAfriVac in Banikoara, Benin in November 2012.**
  - Over 155,000 people vaccinated using MenAfriVac in a CTC
- **VVM on each vial**
  - **And Temptime’s LIMITmarker™**
    in each vaccine carrier

Before Exposure to 40°C  
After Exposure to 40°C
New Product Concept – VVM+
VVM plus Peak Indicator
Temptime is BMGF GCE Grant Awardee

VVM
• VVM active square is translucent and the substrate color is seen through the monomer

Reactive Substrate
• Substrate develops color quickly at high temperature

Response after short exposure to 40°C

VVM

VVM+™
Comparison of VVM+ and VVM at 40°C
Not presently available for sale.
Not cleared for sale as a medical device in the U.S.
Typical Product and Information Flow

MedTracker - Vaccine Public Market Pilot

Vaccine Manufacturer → National Store → Regional Store → District Store → Facilities

User smart phone interprets barcode and indicator. Information sent to host computer.

Host computer communicates with user.

Captive Database
Web Portal
Thinfilm and Temptime Collaborate to Deliver Printed Electronic Temperature Indicators for Use in Distribution, Storage and Management of Sensitive Medical Products

- Printed Electronics Technology
- Credit Card Sized Device
- Indicates High or Low Excursion
- Irreversible & Disposable
- Lower Cost than Standard Electronics
Printed Electronics to Detect Temperature Excursions

TransTracker®
ELECTRONIC

Press to Activate
ON

Heat Limit Exceeded

Cold Limit Exceeded

www.temptimecorp.com

TransTracker®
ELECTRONIC

Press to Activate
ON

Heat Limit Exceeded

Cold Limit Exceeded

www.temptimecorp.com

TransTracker®
ELECTRONIC

Press to Activate
ON

Heat Limit Exceeded

Cold Limit Exceeded

www.temptimecorp.com

Graphics and messaging TBD
Integrated wireless facility and transport monitoring solution

Cobalt wireless Datalogging solution from Oceasoft France

System Configuration

Cobalt radio Modules with sensor

Cobalt Radio Receiver and Repeater

Thermo software (server/client based)
Integrated wireless facility and transport monitoring solution

Facility Monitoring Solution
- Wireless Datalogging System
Integrated wireless facility and transport monitoring solution

Multiple location Real time Monitoring Solution
Cobalt – Real time monitoring snap view
Cobalt – Real time monitoring snap view
THANK YOU!