DCVMN VVM Overview Webinar

July 2018
Temptime Vision and Mission

Vision: “Temptime elevates the quality of global health”

Mission: “We innovate cost-effective monitoring solutions for environmentally sensitive products to ensure supply chain integrity, protect patients and benefit communities globally”
Driving Principles

• “Sometimes it’s the simple ideas that make all the difference. Making it super easy for a rural health worker to know whether a vial of vaccine is still effective by scaling up the VVMs has saved hundreds of thousands of lives.”

  Bill Gates - February 21st, 2017

• “I have always been struck by the brilliance of the VVM approach: a marker that changes color to reflect the state of the vaccine. Now, with electronics and imaging entering a new regime of cost-to-performance, it is exciting to see Temptime add fine-grain recording and geo-tracking in the supply chain, and innovative 2D barcodes which can be read with smartphones.”

  Sanjay Sarma, Vice President Open Learning, MIT - April 13th, 2017
The Challenge: Develop a low-cost, highly reliable, easy-to-interpret, unit-level temperature sensor that improves product quality and patient confidence and safety, reduces wastage, and spares product that is still viable for administration – at the very end of the very last mile of the most challenging supply/cold-chains...

to assist:

• the World Health Organization
• UNICEF
• PATH
• Gavi (the Global Alliance for Vaccines & Immunisations)
• The Bill & Melinda Gates Foundation

with...
Improving vaccine effectiveness...
Enabling vaccine outreach...
Expanding vaccine coverage...
Preventing vaccine wastage...

Yogyakarta, Indonesia earthquake - 2006

D. Kristensen
PATH
Facilitating stock management...
Helping to eradicate diseases...
And helping to save lives!

“Time temperature indicator known as vaccine vial monitor (VVM) absolutely vital to eradication effort, allowing health workers to know vaccine has not been exposed to excessive heat.”
Time-Temperature Indicator/ VVM ↔ Arrhenius

• Color change based on Arrhenius curves/equations

\[ k = A_0 e^{- \left( \frac{E_a}{RT} \right)} \]

- \( k \): rate coefficient
- \( A_0 \): frequency factor
- \( E_a \): activation energy (J mol\(^{-1}\))
- \( R \): universal gas constant (8.314 x 10\(^{-3}\) kJ mol\(^{-1}\) K\(^{-1}\))
- \( T \): Kelvin temperature (K)

Gradual  Predictable  Cumulative  Irreversible

Measure of MKT
The Vaccine Vial Monitor (VVM) – Cornerstone of Portfolio

Technology:
- The principle of operation is based on the solid-state polymerization of substituted diacetylene monomers.
- The combined effects of time and temperature cause a gradual, predictable, cumulative and irreversible color change from clear to dark.
- The white square is the active color changing reactive portion.
- End point is reached when the color of the Active Square area is equal or darker than to the Reference Circle.

Scale: Temptime manufactures and sells more than 600 million VVM’s per year.
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

Polymerization

(Colorless)

\[
R-C\equiv C - C \equiv C - R \\
R-C\equiv C - C \equiv C - R \\
R-C\equiv C - C \equiv C - R \\
\]

(Black)
Vaccine Temperature Sensitivity

Heat sensitivity

most sensitive

Days at 37°C

least sensitive

Freeze sensitivity

most sensitive

Freeze sensitivity

least sensitive

Principles and considerations for adding a vaccine to a national immunization programme FROM DECISION TO IMPLEMENTATION AND MONITORING
http://apps.who.int/iris/bitstream/10665/111548/1/9789241506892_eng.pdf?ua=1

World Health Organization
Four WHO VVM categories

**VVM category chosen is correlated to vaccine stability**
WHO Prequalified and FDA 510k Clearance

- Temptime's quality management system is consistent with FDA's Quality System Regulations (QSR) 21 CFR 820 (GMP for medical devices)

- ISO 9001:2008
- ISO 13485:2003
- WHO Prequalified Device
# HEATmarker VVM for use on vaccines

Over 650 million VVMs used last year

<table>
<thead>
<tr>
<th>Pharmaceutical Product</th>
<th>Indication</th>
<th>Customer</th>
<th>Temptime Product</th>
<th>Value Delivered</th>
</tr>
</thead>
</table>
|                        | Children’s Immunization Campaigns for a range of contagious diseases:  
• BCG  
• Diphtheria  
• Tetanus  
• Pertussis  
• DTP  
• Hep B  
• Hib  
• Meningococcal A and C  
• Measles  
• Mumps, Pneumococcal  
• OPV  
• Rotavirus  
• Rubella  
• Tetanus Toxoid  
• Yellow Fever  
Other Campaigns:  
• HPV  
• IPV  
• Rabies  
• Typhoid | GSK, Sanofi Pasteur, Merck, Crucell, Pfizer, Novartis, Serum Institute of India, Biofarma, Japan BCG, BB-NCIPD, Bharat Biotech, Statens Serum Institute, Biological E, Bharat Serums and Vaccines, Haffkine, Bio-Manghuinos, plus others | VVM2, VVM7, VVM14, VVM30 |  
• Prevents immunization with heat damaged vaccines  
• Expands reach of immunization programs to remote populations  
• Increases immunization programs efficiency |
## 2011 Honduras Technical and Operational Guidelines for Pneumococcal Conjugate

### Lineamientos técnicos y operativos de vacunación con Neumococo conjugada

#### Febrero, 2011

**Tegucigalpa, Honduras C. A.**

<table>
<thead>
<tr>
<th>Monitoreo de exposición al calor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>✔️ Esta vacuna tiene un sensor (VVM siglas en inglés) (Vial Vaccine Monitor) que es una etiqueta que contiene material sensible al calor, ubicado en el frasco de vacuna para registrar la exposición al calor acumulada a lo largo del tiempo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Vacuna Neumococo con sensor ubicado en parte superior del frasco</strong></td>
</tr>
</tbody>
</table>

**El Sensor se lee así**

- Cuando el cuadrado intenso es más claro que el cuadrado estanco, USE la vacuna.
- A medida que el tiempo pasa, si el color del cuadrado intenso todavía es más claro que el cuadrado estanco USE la vacuna.
- Cuando el color del cuadrado intenso es igual al del cuadrado estanco o el color del cuadrado intenso es más claro que el cuadrado estanco:
  - No lo utilice como criterio para descartar la vacuna
  - Se deben utilizar las mismas estandarizadas para el descarte de la vacuna.
  - Coa firme de documentación infime al nivel correspondiente si algún monitor VVM de la vacuna ha cambiado de color.

#### Tiempo de utilización de la vacuna

Considerando que la presentación de esta vacuna es de una doble, una vez que se retire el tapón del frasco debe aplicarse inmediatamente. Esta vacuna no debe congelarse.

Peak Threshold Indicators

- Single use threshold indicators.
- Multiple unit secondary packages or shipping boxes.
- Ability to customize temperature thresholds.

**LIMITmarker F/L™**
Formulated to signal short excursions above the set response temperatures: 9°C, 17°C, 21°C, 25°C (all +/- 1°C).

**LIMITmarker I™**
Formulated to immediately signal upon excursions above the set response temperatures: 40°C ±1°C, 44°C ± 1°C, and 50°C ±2°C

Before Exposure to 40°C

After Exposure to 40°C

USE

DO NOT USE

USE

DO NOT USE
Temptime Continues to Invest in Product Innovations

- VVM: new categories
- CTC & VVM+®: combined VVM and peak threshold indicator
- Hybrid 2D Bar Codes with embedded VVM active area or threshold indicator: improve patient safety and address evolving international anti-counterfeiting/track & trace and serialization requirements
Four WHO VVM Types to Monitor Vaccines with Different Heat Sensitivities

VVM11 and VVM250 added on 18 May 2018 for six VVM types
VVM Line Extensions to Address Programmatic Needs: VVM11

- **Why VVM11**
  - Some vaccines have stability > VVM7 but < VVM14
  - Some vaccines have moved to 3 year expiry date but with < 14 days at 37°C
  - Change to statistical modeling of vaccine stability can possibly lead to use of a lower VVM type
    - e.g., VVM14 now would revert to VVM7
- **VVM11 fills the gap between VVM7 and VVM14**
  - Provides ≥ 2.5 years at 5°C
  - Project initiated based initially on potential IPV stability
- **Status**
  - Included in newly published VVM spec
- **No premium charge for VVM11**

**Table 1: VVM reaction rates by type**

<table>
<thead>
<tr>
<th>Type (Vaccines)</th>
<th>Maximum time to end point at +37°C</th>
<th>Maximum time to end point at +25°C</th>
<th>Maximum time to end point at +5°C</th>
<th>Time to end point at +5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM30: High Stability</td>
<td>30 days</td>
<td>193 days</td>
<td>NA*</td>
<td>≥4 years</td>
</tr>
<tr>
<td>VVM14: Medium Stability</td>
<td>14 days</td>
<td>90 days</td>
<td>NA*</td>
<td>≥3 years</td>
</tr>
<tr>
<td>VVM11: Intermediate stability</td>
<td>11 days</td>
<td>71 days</td>
<td>NA*</td>
<td>≥2.5 years</td>
</tr>
<tr>
<td>VVM7: Moderate Stability</td>
<td>7 days</td>
<td>45 days</td>
<td>NA*</td>
<td>≥2 years</td>
</tr>
<tr>
<td>VVM2: Least Stable</td>
<td>2 days</td>
<td>NA*</td>
<td>225 days</td>
<td>NA*</td>
</tr>
</tbody>
</table>

*VVM (Artemius) reaction rates determined at two temperature points*
Four-Five WHO VVM Categories – VVM11 is now approved

VVM11
The Next Challenge – Controlled Temperature Chain (CTC)

Current definition of CTC

• Allowing specific vaccines to be kept and administered at ambient temperatures, up to 40°C
  • For one, limited period of time (length of time will vary by antigen and setting) immediately preceding administration
  • For vaccines meeting a number of pre-determined conditions
    ▶ Up until this excursion, the vaccine should continue to be kept in the traditional 2°C-8°C cold chain.

[Current focus: vaccines administered during campaigns and special strategies, in ‘single antigen’ settings.]
Temptime’s Peak Threshold Indicators used in WHO pilot to spare new heat-stable Meningococcal vaccine (stable up to 40°C)
New Product Innovations Address High Temperature Excursions and CTC Requirements

VVM+™

• Combined VVM response and high temperature threshold in a single indicator
HEATmarker VVM+
VVM Plus Peak Indicator in Same Device

- VVM+ reacts like a VVM up to 37°C
- At 40°C, VVM+ reaches the end point rapidly to show exposure to critical peak temperature
Over 5 years and $5 Million Dollars Invested

• What are the next steps to launch VVM+?
  • HPV
  • Oral cholera
  • Hep B
  • Rotasiil lyophilized
  • Others?
VVM Challenge – Highly Stable Rotavirus Vaccine
540 days at 37°C

Stability of heat stable, live attenuated Rotavirus vaccine (ROTASII®)
Sameer P. Naik, Jagdish K. Zade *, Rajendra N. Sahale, Sambhaji S. Pise, Ravi Menon, Subhash G. Bankar, Sunil Gaikwad, Rajeev M. Dhere
Serum Institute of India Pvt. Ltd., Pune- 411001, India

...are up to six hours as, at higher temperatures, any microorganism introduced during the reconstitution process could multiply.

The thermo-stability of ROTASII®, ironically, has thrown up a new challenge in terms of vaccine vial monitors (VVM). The presently available VVM portfolio (Max VVM30: 30 days at 37 °C) does not begin to cover the extreme thermo stability of ROTASII which is 18 months- (540 days) at 37 °C. Efforts to develop a more appropriate VVM are on-going.

It has been already noted that there is remarkable reduction in mortality from diarrheal disease after vaccine introduction in
VVM Line Extensions to Address Programmatic Needs
VVM250 – Technology Capability

Temptime has supplied TTIs for use by US Military with 3 year life at 26°C for more than 20 years and a more stable category for use on Rapid Skin Decontamination Lotion.

Additionally, the Joint Program Executive Office for Chemical and Biological Defense has developed a time temperature indicator (TTI) to include on RSDL packets when manufactured. TTIs incorporate MKT to accurately determine the service life limits of RSDL exposed to various temperatures. TTIs, therefore, assist with RSDL management by providing visible information reflecting product quality. An example TTI is shown in Figure 3.
Rotasiil Team was Concerned with Exposures Above 40°C

VVM+250 confirmed by WHO and SII

VVM+250
VVM 250 Specifications

PQS performance specification

<table>
<thead>
<tr>
<th>TITLE: Vaccine Vial Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specification reference:</td>
</tr>
<tr>
<td>Product verification:</td>
</tr>
<tr>
<td>Issue date:</td>
</tr>
<tr>
<td>Date of last revision:</td>
</tr>
</tbody>
</table>

Table 1b: VVM reaction rates by type

<table>
<thead>
<tr>
<th>Type (Vaccines)</th>
<th>Maximum time to end point at +55°C</th>
<th>Maximum time to end point at +45°C</th>
<th>Approximate Maximum time to endpoint at +37°C</th>
<th>Time to end point at +25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM250: Very High Stability</td>
<td>17 days</td>
<td>73 days</td>
<td>250 days*</td>
<td>≥900 days</td>
</tr>
</tbody>
</table>

*VVM (Arrhenius) reaction rates determined at 55°C and 45°C, the 37°C values are approximate.
The Challenge: Cold Chain Problems are Global

Vaccines – US San Francisco Bay Area 10 County Region (2006)

<table>
<thead>
<tr>
<th>Category</th>
<th># of Incidences</th>
<th>Loss (dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigeration Problems</td>
<td>16</td>
<td>$42,958</td>
</tr>
<tr>
<td>Shipping/Receiving</td>
<td>4</td>
<td>$34,772</td>
</tr>
<tr>
<td>Improper Storage</td>
<td>6</td>
<td>$187,133</td>
</tr>
<tr>
<td>Expired Vaccines</td>
<td>51</td>
<td>$127,289</td>
</tr>
<tr>
<td>Total Losses</td>
<td>77</td>
<td>$392,717</td>
</tr>
</tbody>
</table>

Extrapolation to state

$2,352,426

Source: California Department of Public Health
Office of Inspector General
June 2012

- Vaccines for Children (VFC) program provides free vaccines to eligible children
- 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

Impact
- Exposure to inappropriate temperatures can reduce vaccine potency and efficacy, increasing the risk that children are not provided with maximum protection against preventable diseases.

1 https://oig.hhs.gov/oei/reports/oei-04-10-00430.pdf
Global Temp-Monitoring Requirements – 2018

Last Updated: April 2018

National requirements for VVM on all public sector vaccines (3: Pakistan, India, Indonesia)

Gavi requirements for VVM on all public sector vaccines (54 Gavi-eligible countries in 2017)

Regional requirements for VVM on all public sector vax (6 GCC countries - unimplemented)

Provincial requirements for VVM on all private sector vaccines (9 – Beijing, Shanghai, Fujian, Anhui, Jiangsu, Shandong, Hebei, Heilongjiang, Zhejiang)

**Argentina** – 2009 law requiring temp-monitoring of all temp-sensitive human/animal medical products; gradual implementation in 2017 on vaccines/carton-level

**Peru** – 2015 law requiring documentation of all temp-excursions during distribution, resulting remediation plans, and empowerment of MoH to enforce remediation plans

**Brazil** – 2016 policy requiring Nat’l Mail Service to distribute all temp-sensitive medicines, vaccines, diagnostic kits, and medical supplies for Nat’l Health Agency
The Solution: Add Another Dimension to 2D Barcodes with Embedded Temperature Sensors
The solution: 2D Barcode with Embedded Temperature Sensor - Digitization of Chemical Indicators & Unit Level Data Connection

What it is; how it works...

- **Enhance the value of 2D barcodes** (for patient safety and anti-counterfeiting) by incorporating temperature integrity

- Specific area has indicator ink – e.g. cumulative (VVM) or threshold printed as part of barcode
- Rapid reading with phone or scanner
- Connect with cloud or web-based databases
- Use on primary, secondary and tertiary packaging
GS1 2D Data Matrix with Threshold Sensor

- **Threshold Indicator** – rapid, irreversible color change when peak temperature threshold is exceeded

![Threshold Indicator Diagram]

- Exceed threshold temperature
- Below threshold temperature

Exceed Threshold Temperature
GS1 2D Data Matrix with Time Temperature Indicator (TTI)

- **Time temperature indicator** – gradual, irreversible color change from light to dark develops with cumulative time and temperature exposure.

![Before heat exposure](HEATmarker® VVM30)

![After excessive heat](HEATmarker® VVM30)

![Time and temperature exposure](QR code image)
GS1 2D Data Matrix with Other Potential Indicators

**Reversible Threshold 2D Barcode**

**Anti-Counterfeiting 2D Barcode**

**Dual 2D Barcode**
(any combination)
Dynamic 2D Barcode Indicator

- GS1 compliant 2D barcode with temperature-sensitive monitor to provide machine-readable, variable, environmental information that supplements other static data
New Technology Development:
2D Barcodes w/Integrated Temperature Indicators

What it is; how it works – *continued*

• **Serialized** barcodes on individual saleable units provide enabling technology for global identification and tracking regulations
• Merges unit serialization and **temperature-monitoring** in a single scan
• Technology adaptable for **anti-counterfeiting** applications
• Significantly enhances product integrity, patient safety, supply security and temperature compliance from *point of manufacture to point of use*

End-to-end unique identifier and unique temperature monitor
Dynamic Barcodes Allow Unit Level Data Connection from Manufacture to End Use

- **Product Flow**
- **Package Level**
- **Monitoring Device**
- **Data Capture**
- **Information Flow**

Manufacturer → National Distributor → Local Distributor → Health Provider → Patient → Data Capture → Information Flow
Thank you!