Agenda

• What is VVM and how does it work
• How to choose a VVM type including Covid vaccines
• Implementation at manufacturer
• Barcode innovation
Zebra acquired Temptime to expand their Global Health product offering.
Diverse Portfolio of Temperature Monitoring Solutions

VVM is the main product, but we have a range of SOLUTIONS to help identify when temperature sensitive products like vaccines or blood or hormones or RDTs are exposure to unsafe temperature events.
VVM inspiration

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

Bill Gates
February 21\textsuperscript{st}, 2017
What is a VVM and How Does It Work
Vaccine Vial Monitor (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** is equal to the **Reference Circle**.

Square darkens with cumulative heat exposure.
The HEATmarker 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.
Vaccine Vial Monitor (VVM) – Faster color change at higher temperatures

Slower color development at lower temperature

Faster color development at higher temperature

Before heat exposure

After heat exposure
The Arrhenius Equation

HEATmarker TTs contain a heat-sensitive material that integrates cumulative heat exposure over time that:

- Is based on a chemical reaction (polymerization) following the Arrhenius equation

\[ k = A_0 e^{-\frac{E_a}{RT}} \]

- Darkens, irreversibly, with time and temperature (cumulative) and faster when the temperature increases
- HEATmarker is a Mean Kinetic Temperature (MKT) indicator

**k** rate coefficient

**A₀** frequency factor

**Eₐ** activation energy (J mol⁻¹)

**R** universal gas constant (8.314 x 10⁻³ kJ mol⁻¹K⁻¹)

**T** Kelvin temperature (K)
VVMs have a well-defined Arrhenius temperature relationship over time

HG282/2 VVM7

Time for VVM to reach end point
VVM Response is Correlated with Vaccine Stability

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.

- VVM should reach endpoint before vaccine potency drops below efficacy requirements
- Dossier with these stability data supports VVM7
- For WHO prequalified vaccines, WHO makes decision on VVM category and sends letter to vaccine manufacturer and Temptime
- For other applications, vaccine manufacturer makes VVM category decision
# HEATmarker VVM for Use on Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Disease indication</th>
<th>Customer</th>
<th>Temptime Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine or campaign:</strong></td>
<td></td>
<td>DCVMN</td>
<td>VVM2, VVM7, VVM14, VVM30, VVM11, VVM250, VVM0.5</td>
</tr>
<tr>
<td><strong>Newer Vaccines:</strong></td>
<td></td>
<td>IFPMA</td>
<td></td>
</tr>
<tr>
<td>HPV, IPV, Cholera, Typhoid, Ebola, COVID</td>
<td></td>
<td>GSK, Sanofi Pasteur, Merck, Pfizer, Novartis, Japan BCG</td>
<td></td>
</tr>
<tr>
<td><strong>Future Vaccines:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria, Dengue, Rabies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stability Studies and Choice of VVM Category
Temperature Sensitivity of Vaccines (2015)

Vaccines to the left of the line are not damaged by freezing.

Vaccine formulation:
- Freeze dried
- Liquid, no adjuvant
- Liquid, with alum adjuvant

*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.

B. Schreiber, D. Chang Blanc, TechNet Bangkok 2015
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.
## Characteristics That Define Vaccine Suitability

<table>
<thead>
<tr>
<th>Type of characteristic</th>
<th>Compliance</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory</td>
<td>Pre-qualification process proceeds</td>
<td>Rejection of application for prequalification evaluation.</td>
</tr>
<tr>
<td>Critical*</td>
<td>Pre-qualification process proceeds</td>
<td>Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
</tr>
<tr>
<td>Unique and innovative</td>
<td>Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>Pre-qualification evaluation proceeds.</td>
<td></td>
</tr>
</tbody>
</table>

*VVM is a critical characteristic for vaccine prequalification*
UNICEF/WHO Policies on Criticality of VVMs (UNICEF TENDER ANNEX)

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

- 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&B/99.187, WHO/IVB/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.
WHO Guidelines on Stability Evaluation of Vaccines¹

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


²WHO Temperature Sensitivity of Vaccines (WHO/IVB/06.10)
WHO Temperature Sensitivity of Vaccines

- 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.

3http://www.who.int/vaccines-documents/DocsPDF06/847.pdf
NEW WHO PQS Performance Specification: Vaccine Vial Monitor (WHO/PQS/E006/IN05)⁵

**VVM reaction rates**
(new categories added: VVM11 and VVM250)

<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 (Arrhenius) reaction rates determined at two temperature points

⁵http://www.who.int/immunization_standards/vaccine_quality/who_pqs_e06_in05_1.pdf
Implementation of VVM at Vaccine Manufacturer
Part 1
Steps to VVM Implementation Part 1

1. WHO process
2. 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
Implementation of VVM at Vaccine Manufacturer

Part 2
Steps to VVM Implementation Part 2

1. WHO process
2. Receipt, Control and Storage of VVMs
3. Calibration of X-Rite 500 Series Spectrodensitometer
4. VVM Acceptance Testing
5. Application of VVM to Vials
VVM Acceptance Testing

• Vaccine manufacturers are responsible to develop SOPs related to VVM consistent with their quality system requirements
• SOPs for receiving, inspecting, storing and releasing of a lot of VVMs must be developed
• Some manufacturers rely solely on the Certificate of Analysis provided with a lot to support their release process
• Other manufacturers perform additional tests and verifications, including the 37°C water bath test as routine or on random lots
• These processes should suit the vaccine manufacturers’ quality system and risk management practices
GUIDANCE on APPLICATION of VVM
VVMs are Applied During Final Labeling

- Preferred to apply VVM in line during final labeling operation
- Possible to apply VVM as a secondary process
- Ambient temperature and lighting (avoid excessive light exposure)
- Some manufacturers have local cold storage of VVM in labeling area

Kartoglu - WHO
Lesson Learned

Adhesion of VVM to cap strongly dependent on cap composition and texture

- Field complaint of poor adhesion of VVM to cap – VVMs lifting or coming off
  - Raised lettering on plastic cap and matte finish should be avoided
  - Best surface is flat and glossy (shiny)

- 2nd field complaint with different manufacturer
  - Cap changed and no test of adhesion performed prior to use

- No reported problems with metal caps. No other adhesion problems reported
Conclusions

• Successful GMP implementation of VVM at large and small vaccine manufacturers around the world independent of size of manufacturer

• VVM implementation by local manufacturers for local distribution in India and Indonesia

• SOPs (including training) must be put in place for receipt (IQA), storage and application of VVM

• Adhesion of VVM to cap must be verified

• Application of VVM to vials can be accomplished at room temperature by hand or by automatic equipment
VVM innovation

1. mRNA VVM types
2. VVM+ (combination of VVM and THRESHOLD indicators)
3. Digital VVM (chemistry in or next to a 2D Bar code)
4. VVM App to help HCWs
HEATmarker VVM+
Combined VVM and Peak Threshold 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
VVM+® - Combined VVM and Threshold Indicator Addresses High Temperature Excursions and CTC Requirements

- Combined VVM response and high temperature threshold in a single indicator
- No additional training required for field personnel
Launch of VVM+250 on Rotasiil in Early 2019

VVM+250 Includes Both Innovations: Room Temperature Stable Vaccine and Peak Threshold

VVM+ addresses the risk that vaccines stored at room temperature may be subjected to high temperature excursions which can cause rapid vaccine degradation.
Next Generation Supply Chain with Digital VVM

2D Barcode with Embedded Temperature Sensor

- No additional space needed for vial-level use
Global Standard Development 全球标准的发展

GS1 Optically Readable Sensor Indicator

AI Definition for Threshold Indicator and Cumulative Time-Temperature Indicator 自动识别技术
Transformational Innovation: 2D Barcode with Temperature Sensor Digitize Chemical Indicators with Unit of Sale Level Data Connection

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

- Specific area has cumulative (VVM) and/or threshold ink printed as part of barcode
- Rapid reading with phone or scanner
- Connect with cloud based data set of other sensors
GS1 2D Data Matrix with Vaccine Vial Monitor (VVM)

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

Before heat exposure

After excessive heat

Time and temperature exposure
Digitized Temperature Sensor – VVM or “eVVM”

2D barcodes on vials PLUS use of cell phone to scan:

- Reduce time in recording BN, EXP date, vaccine
- Automatic link to child data (when combined w/ immu. card)
- Date, time and location of immunization and vaccinator
- Product authentication
- Serialized supply chain tracking

Adding digitized temperature sensors will provide:

- Automated capture of VVM status
- Warning to HCWs
- View of heat exposure across whole cold chain
- Additional product authentication
Digital Innovation: VVM App Built into WHO EVM App
WHO App vs. Future Innovations by Zebra

What this App does versus future options

Currently, we have the VVM tool within EVM App, which uses a human eye to judge actual VVM on vial and match with the image

Confirms “use” or “discard”
Provides a time estimate in days/months remaining on the VVM

This app does not scan the VVM
In the future, Temptime is working on a scannable VVM (next slide) that will allow a phone to compliment the human eye
VVM lessons learned during COVID
COVID Lessons Learned: VVM manufacturing capacity can support pandemic quantities

Early on, we assumed demand would be 1-2 billion vaccine doses through COVAX potentially needed, with a mix of 10, 5 and 1 dose vials

Actions taken:

• Increased headcount in manufacturing and QC
• Expanded our ability to make and store indicators
• Secured new shipping routes and containers
• Increased inventory levels to meet demand

Temptime made and shipped over 1 billion indicators for routine and COVID vaccines in 2021 alone = VVM can be made in pandemic quantities
VVM does not delay access to novel or pandemic-quantity

One out of 11 suppliers has put VVM on COVID vaccine

Urgency for supply, a worry over delaying the process, and not having sufficient stability data were rationales for not applying

Sinopharm ordered 200 million VVMs for single dose vials

Our production for Sinopharm was about 12 million VVMs/day

VVM was included on 20% of 2021 vaccine deliveries, to COVAX
Lessons Learned:

VVM selection only requires accelerated stability data.

Selecting a VVM type is not an interdependency

New VVM types for mRNA vaccines more heat labile than OPV are available (VVM1/2, VVM1/4)

During the pandemic, WHO TPP moved VVM to the preferred category. Left the decision to manufacturers.

KAP studies in LMICs confirmed VVM value for COVID vaccines
Thank you!!!