VVM Implementation and Innovation

DCVMN
March 2023

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*

Printing Supplies

RFID Products

Locating Systems
Hardware and Software

Tablets

Industrial Machine Vision
and Fixed Scanners

Interactive Kiosks

Accessories

Software

OEM

Temperature Monitoring
and Sensing

ZEBRA

Video

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

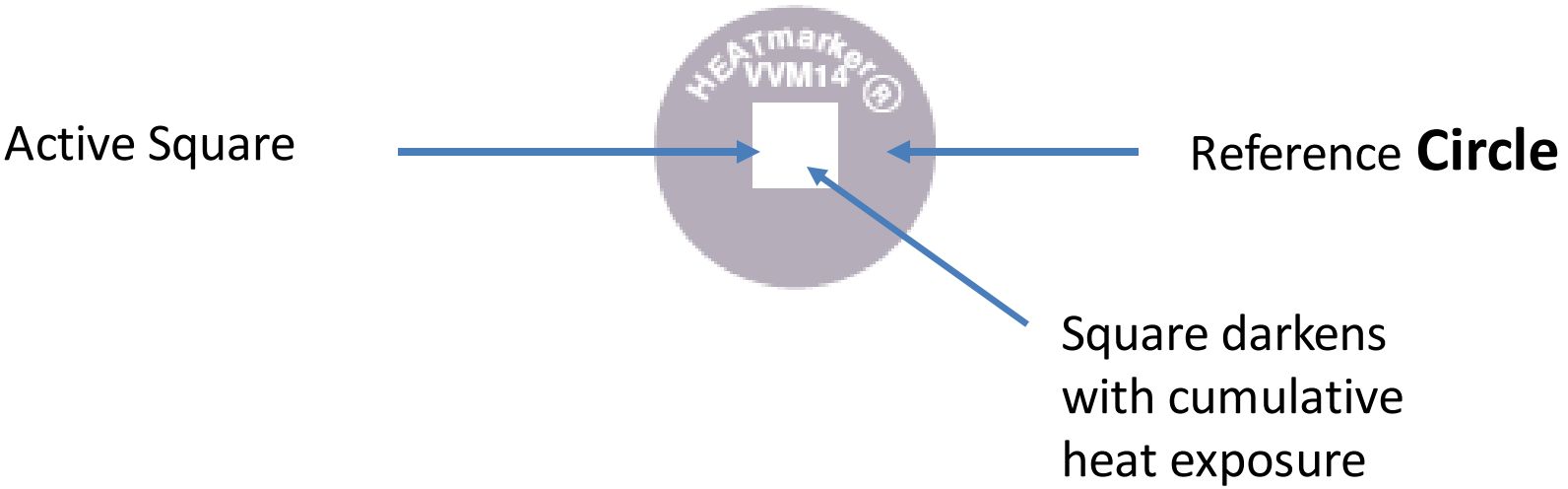
VVM inspiration

"…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 21st, 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**

The HEATmarker Is Easy To Read

The Active Square is **lighter** than the Reference Circle.

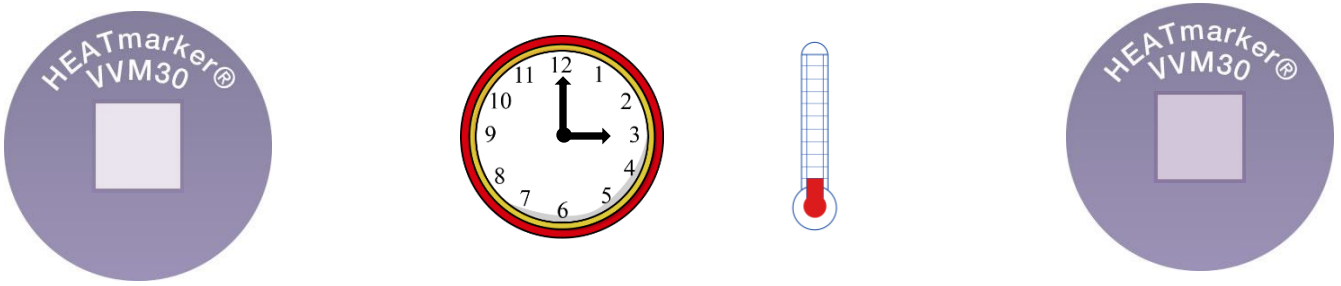
If the expiry date is not passed, ***USE*** *the vaccine.*

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

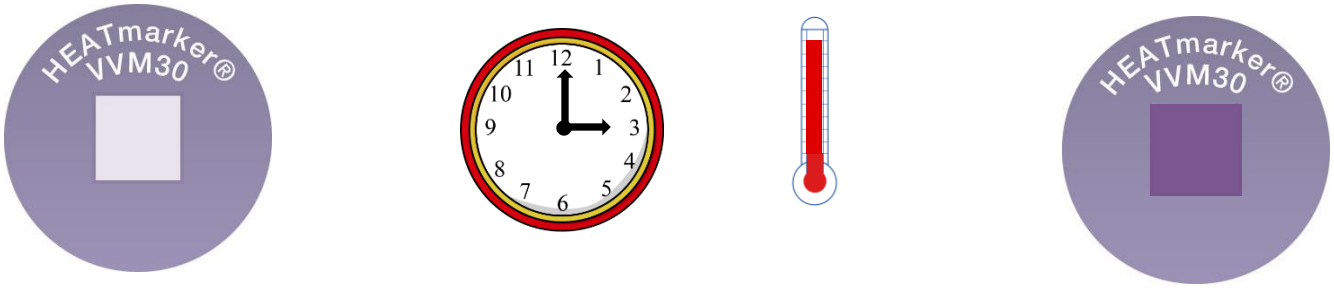
DO NOT USE *the vaccine.*

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:

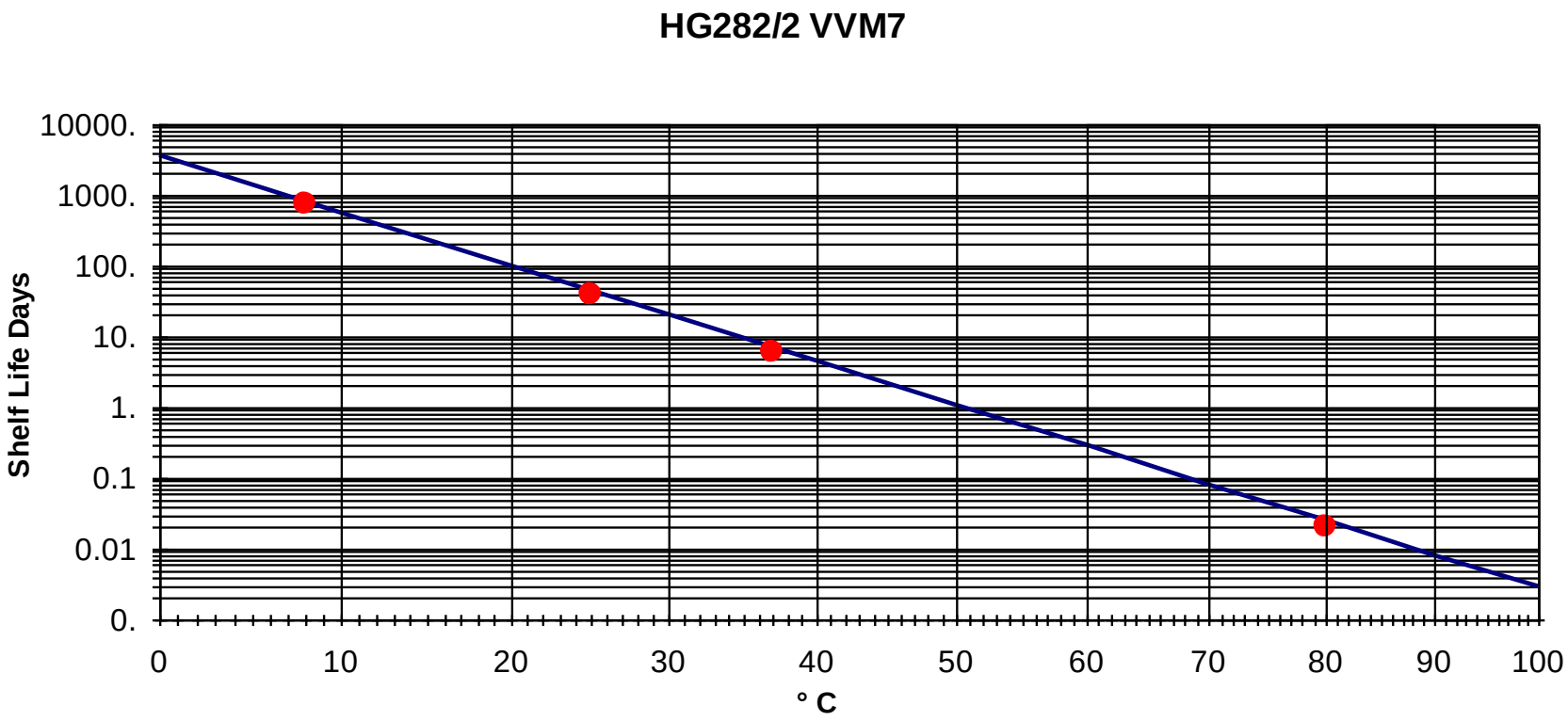
- Is based on a chemical reaction (polymerization) following the Arrhenius equation

$$k = A_0 e^{-\left(\frac{Ea}{RT}\right)}$$

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

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

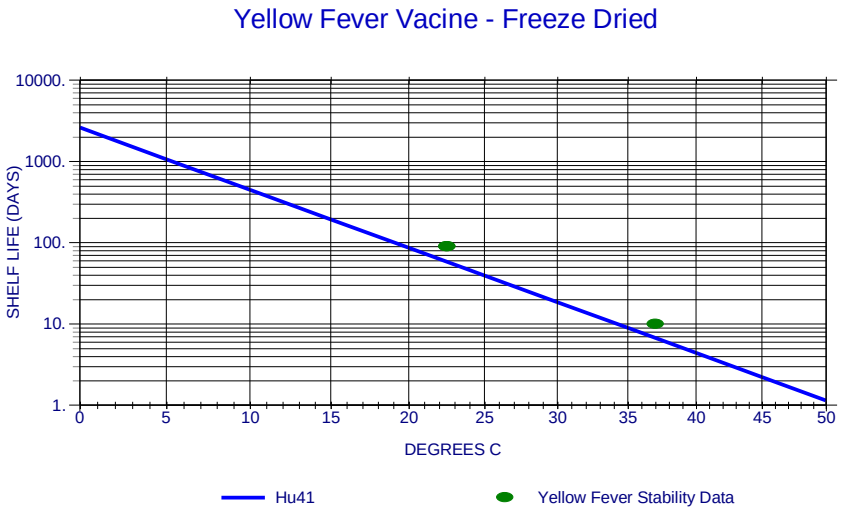
VVMs have a well-defined Arrhenius temperature relationship over time

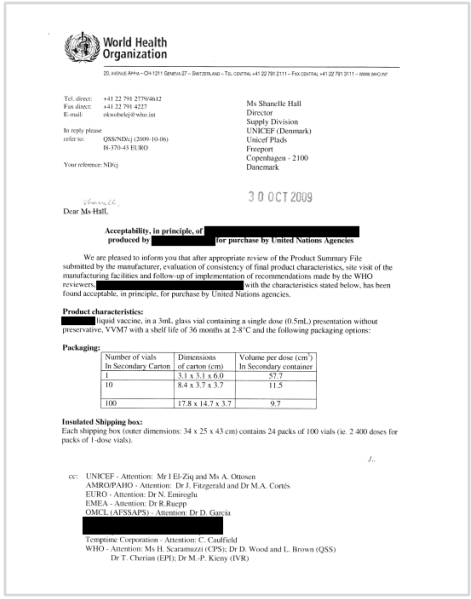


● Time for VVM to reach end point

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.





World Health Organization

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Fax direct: +41 22 791 4227
E-mail: oknoebels@who.int

In reply please refer to: QSS/NDL(-) (2009-10-06)
B-370-43 EURO

Your reference: NDL(-)

Ms Shanelle Hall
Director
Supply Division
UNICEF (Denmark)
Unicef Pladz
Freeport
Copenhagen - 2100
Danemark

30 OCT 2009

Dear Ms Hall,

Acceptability, in principle, of [redacted] produced by [redacted] for purchase by United Nations Agencies

We are pleased to inform you that after appropriate review of the Product Summary File submitted by the manufacturer, evaluation of consistency of final product characteristics, site visit of the manufacturing facilities and follow-up of implementation of recommendations made by the WHO reviewers, [redacted] with the characteristics stated below, has been found acceptable, in principle, for purchase by United Nations agencies.

Product characteristics:
[redacted] liquid vaccine, in a 3mL glass vial containing a single dose (0.5mL) presentation without preservative, VVM7 with a shelf life of 36 months at 2-8°C and the following packaging options:

Packaging:

Number of vials In Secondary Carton	Dimensions of carton (cm)	Volume per dose (cm³) In Secondary container
1	3.1 x 3.1 x 6.0	57.7
10	8.4 x 3.7 x 3.7	11.5
100	17.8 x 14.7 x 3.7	9.7

Insulated Shipping box:
Each shipping box (outer dimensions: 34 x 25 x 43 cm) contains 24 packs of 100 vials (ie. 2 400 doses for packs of 1-dose vials).

cc: UNICEF - Attention: Mr I El-Ziq and Ms A. Ottosen
AMRO/PAHO - Attention: Dr J. Fitzgerald and Dr M.A. Cortés
EURO - Attention: Dr N. Emiroglu
EMEA - Attention: Dr R.Rupp
OMCL (AFSSAPS) - Attention: Dr D. Garcia
[redacted]
Temptime Corporation - Attention: C. Caulfield
WHO - Attention: Ms H. Scaramuzzi (CPS); Dr D. Wood and L. Brown (QSS)
Dr T. Cherian (EPI); Dr M.-P. Kieny (IVR)

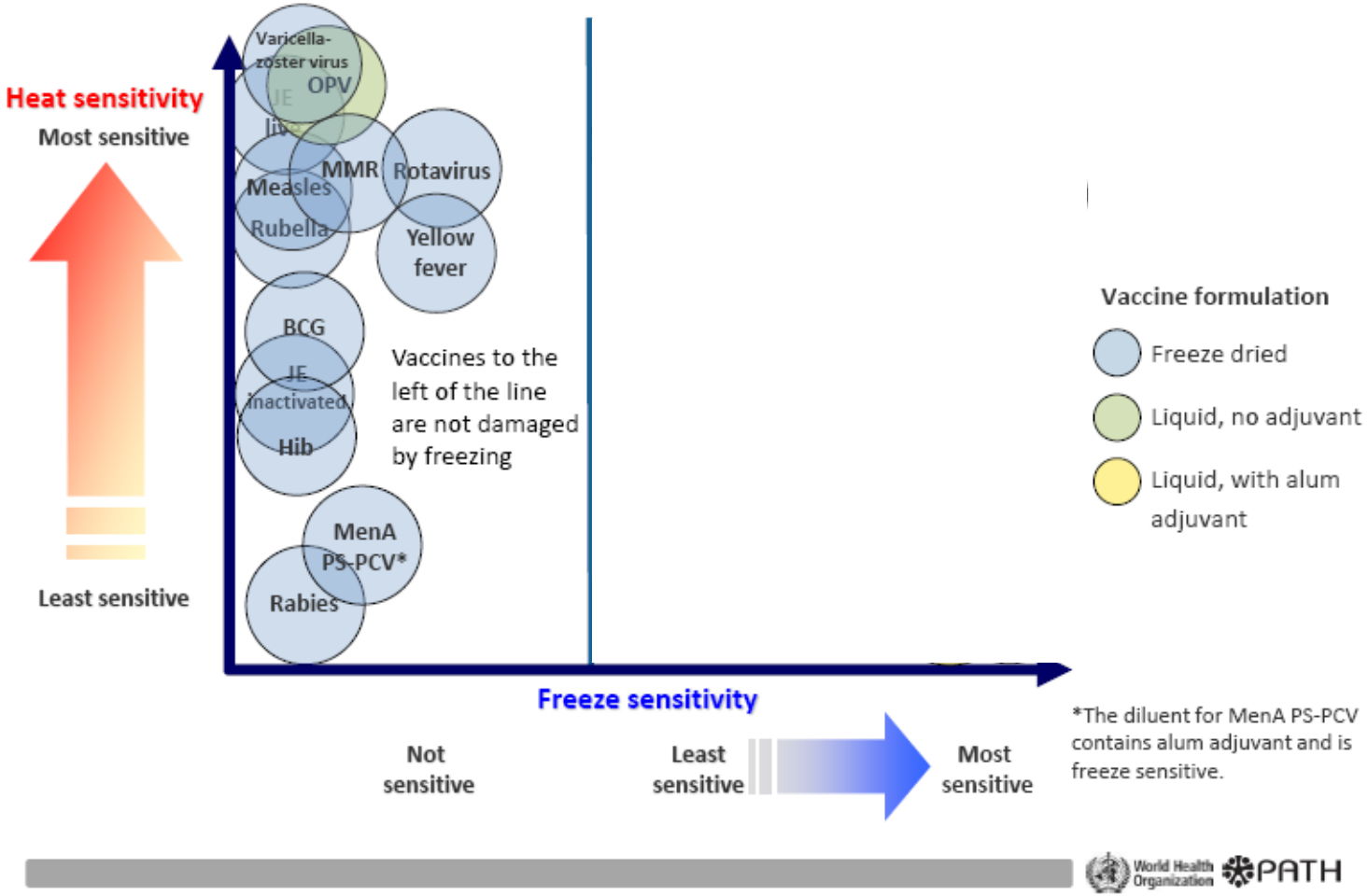
- VVM should reach endpoint before vaccine potency drops below efficacy requirements
- Dossier with these stability data supports VVM7
- For WHO prequalified vaccines, WHO makes decision on VVM category and sends letter to vaccine manufacturer and Temptime
- For other applications, vaccine manufacturer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

HEATmarker VVM for Use on Vaccines

Vaccine	Disease indication	Customer	Temptime Product
	**Routine or campaign:** • OPV, BCG, DTP, TT, Td, • Hep B, HiB • Measles, Measles Rubella • Meningococcal A and C • Yellow Fever • JE vaccine • Pneumococcal conj. • Rotavirus **Newer Vaccines:** • HPV • IPV • Cholera, Typhoid • Ebola • COVID **Future Vaccines:** • Malaria • Dengue • Rabies	**DCVMN** SII, Biofarma, Bharat Biotech, Biological E, Sinopharm, Sinovac, Biomanguinhos, Chumakov… AJ Vaccines, Bavarian Nordic… **IFPMA** GSK, Sanofi Pasteur, Merck, Pfizer, Novartis, Japan BCG	 VVM2 VVM7 VVM14 VVM30 VVM11 VVM250 VVM0.5

Stability Studies and Choice of VVM Category

Temperature Sensitivity of Vaccines (2015)



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

Type of characteristic	Compliance	Deviation
Mandatory	Pre-qualification process proceeds	Rejection of application for prequalification evaluation.
Critical*	Pre-qualification process proceeds	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.
Unique and innovative	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.	
Preferred	Pre-qualification evaluation proceeds.	

*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

WHO/IVB/07.04
ORIGINAL: ENGLISH

WHO-UNICEF policy statement on the implementation of vaccine vial monitors:

The role of vaccine vial monitors in improving access to immunization

World Health Organization (WHO) and United Nations Children's Fund (UNICEF),

Marking the 10 years of successful implementation of vaccine vial monitors (VVMs);

Referring to the WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services (WHO/V&B/98.18), Making use of vaccine vial monitors (WHO/V&B/00.14), Getting started with vaccine vial monitors (WHO/V&B/02.35), WHO-UNICEF joint statement on effective vaccine store management (WHO/IVB/03.14), and Monitoring vaccine wastage at country level (WHO/IVB/03.18/Rev.1);

Emphasizing the Global Immunization Vision and Strategy aiming to protect more people against more diseases by expanding the reach of immunization to every eligible person, including those in age groups beyond infancy, within a context in which immunization is high on every health agenda;

Determined to reach every mother and child for vaccination against vaccine-preventable diseases;

Noting the challenges in immunization service delivery especially in areas with weak or no cold chain infrastructure;

Acknowledging with appreciation the dedication of health workers throughout the world to overcome challenges in reaching all mothers and children with life saving vaccines;

Recognizing the cooperation of vaccine manufacturers in applying vaccine vial monitors on WHO prequalified vaccine products;

Acknowledging that the VVM is the only tool among all time and temperature indicators that is available at all times – in the process of storage, distribution and at the time the vaccine is administered – indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged;

Further noting that since its introduction in 1996 with oral polio vaccine, the VVM has contributed to the success of national immunization days as well as to overcoming access problems in areas with weak or no cold-chain infrastructure and reduction of vaccine wastage;

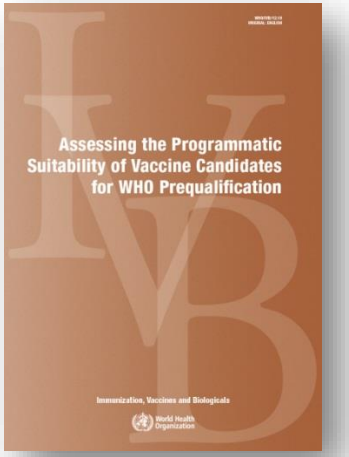
Appreciating the evidence produced by many field studies on the positive impact of the VVM on field operations, both routine and supplemental;

Recognizing that the benefits of VVM in overcoming the cold chain challenges and reaching the hard-to-reach populations will not be realized if they are not available;

Noting the use of VVMs to support policies for storage and administration of vaccines outside the cold chain to reach infants in rural and remote areas, such as for the hepatitis B vaccine birth dose for newborns;

Stressing the need that health workers require a consistent supply of vaccine with VVMs in order to be able to rely upon them as a tool;

2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification



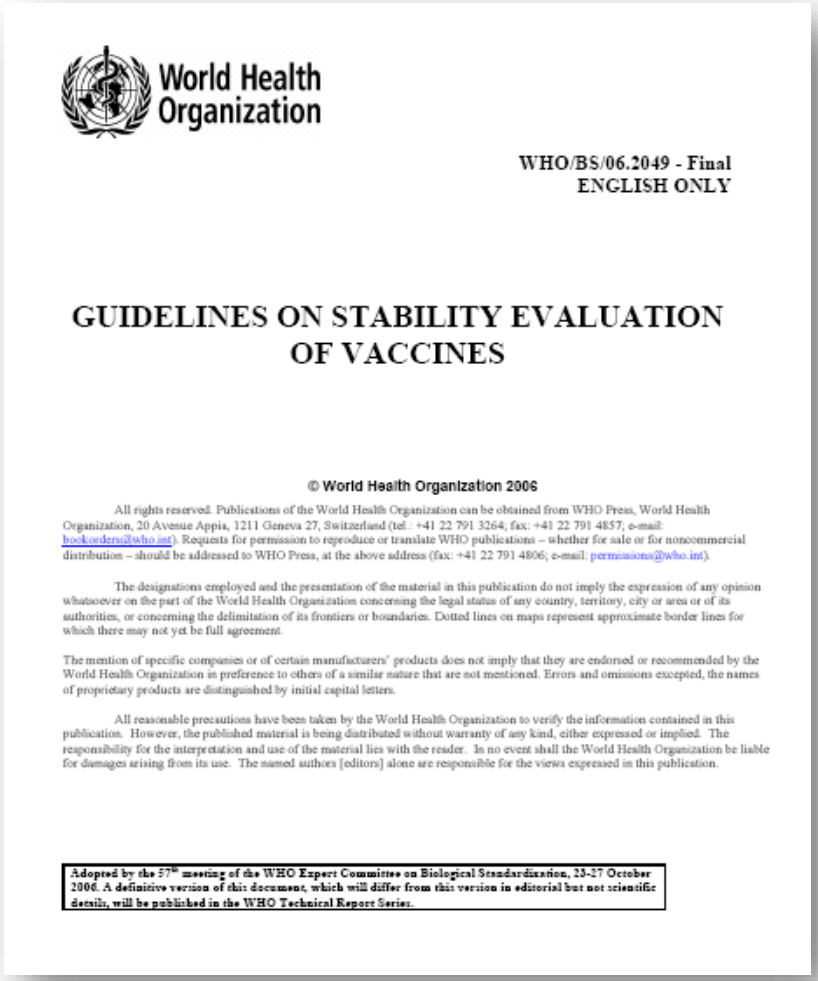
Vaccine Vial Monitor (VVM)	**Vaccines**	Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. - The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type approved by WHO(WHO/V&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 Vaccines[1]

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]



World Health Organization

WHO/BS/06.2049 - Final
ENGLISH ONLY

GUIDELINES ON STABILITY EVALUATION OF VACCINES

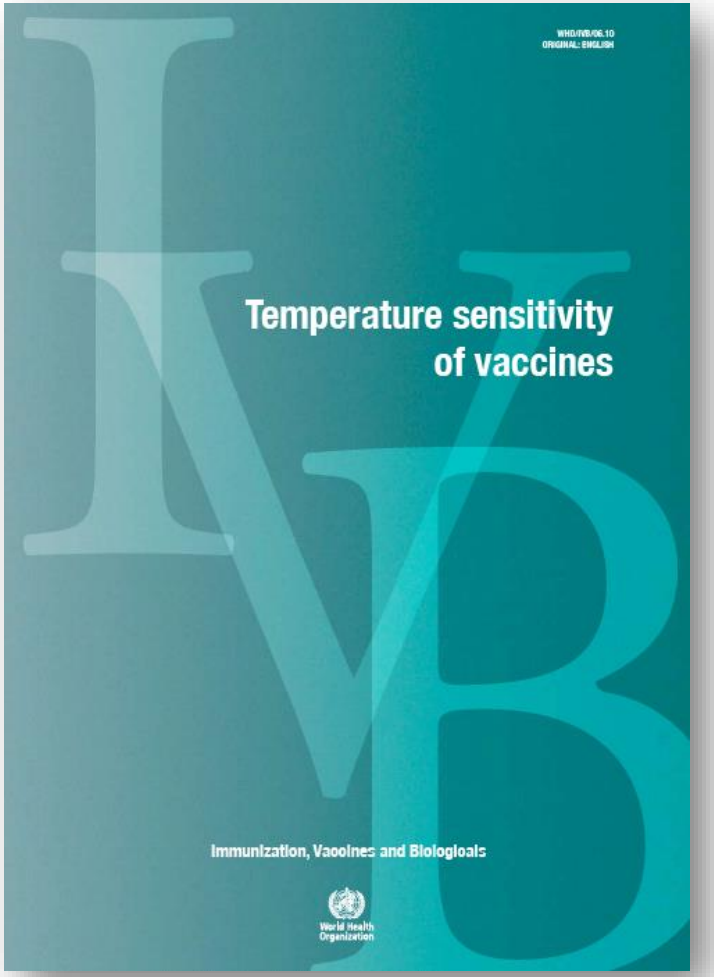
Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

1 http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049.Stability.final.09_Nov_06.pdf

[2]WHO *Temperature Sensitivity of Vaccines* (WHO/IVB/06.10)

WHO Temperature Sensitivity of Vaccines[3]

- 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://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 1a: VVM reaction rates by type

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

**VVM (Arrhenius) reaction rates determined at two temperature points*

[5]http://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

Play 3min 40 secs

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

Play 1 min

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

Temptime Innovation

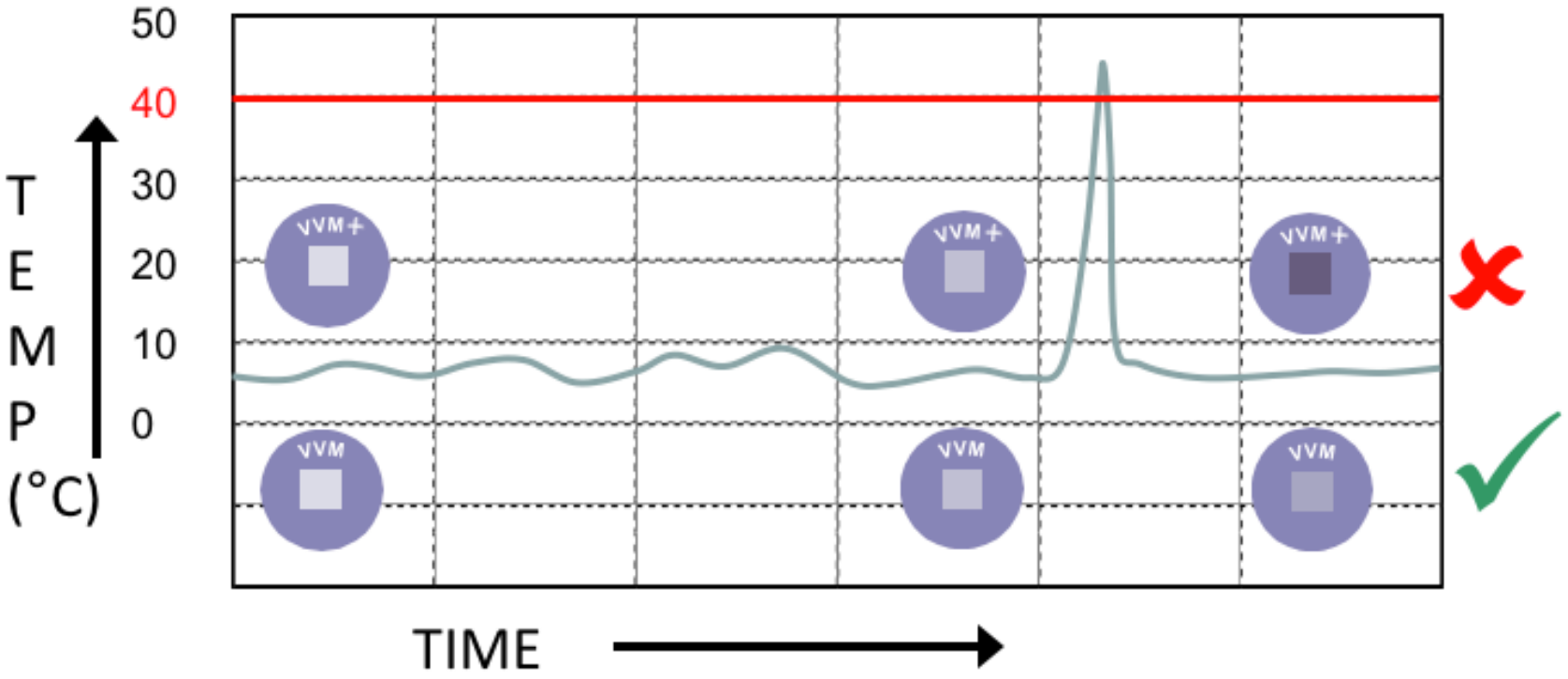
VVM innovation

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+

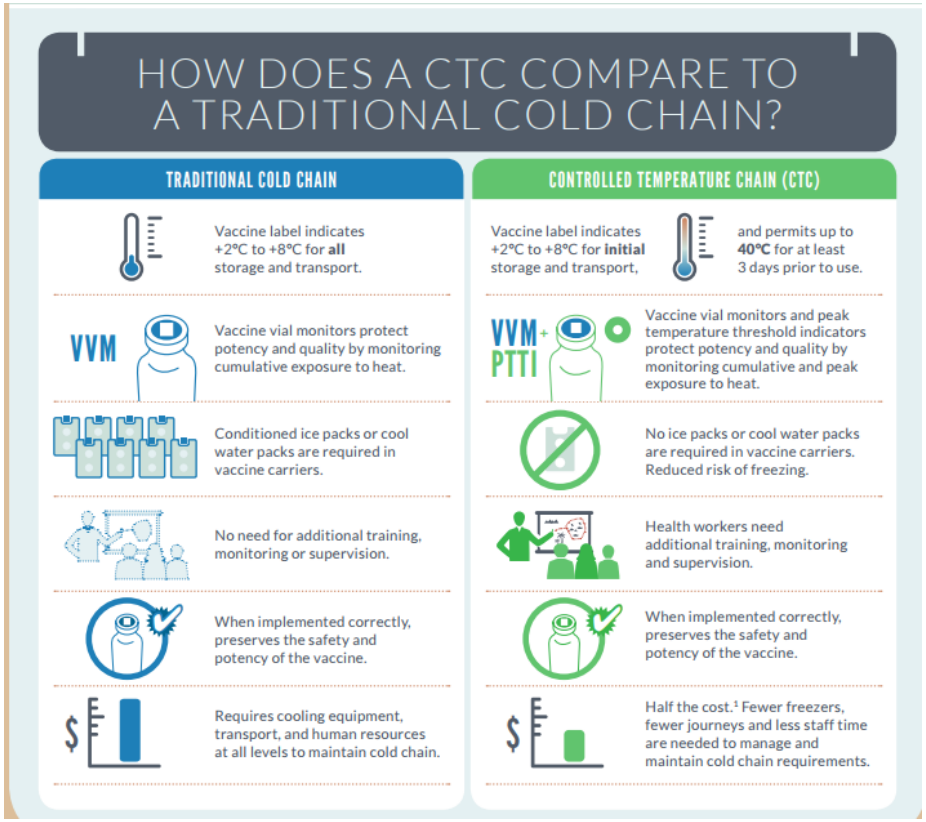
Combined VVM and Peak Threshold Indicator in Same Device

- 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

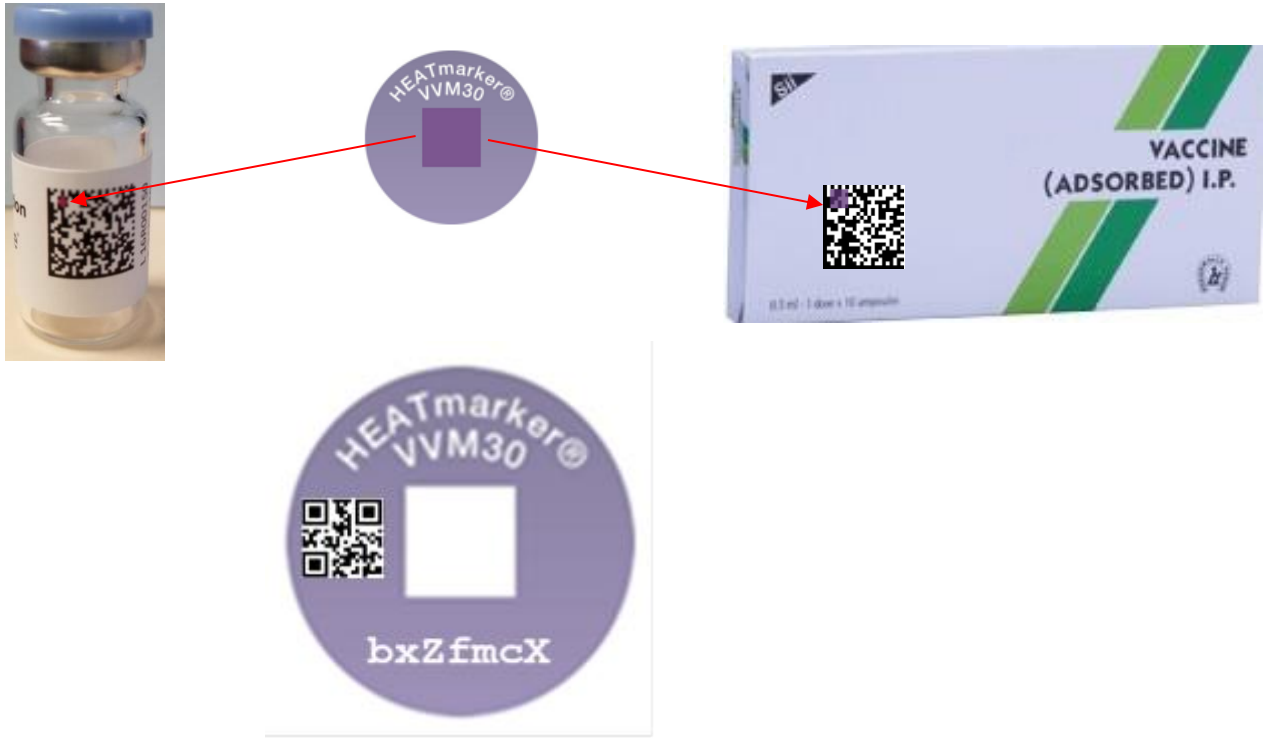
VVM+250 Includes Both Innovations: Room Temperature Stable Vaccine and Peak Threshold

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

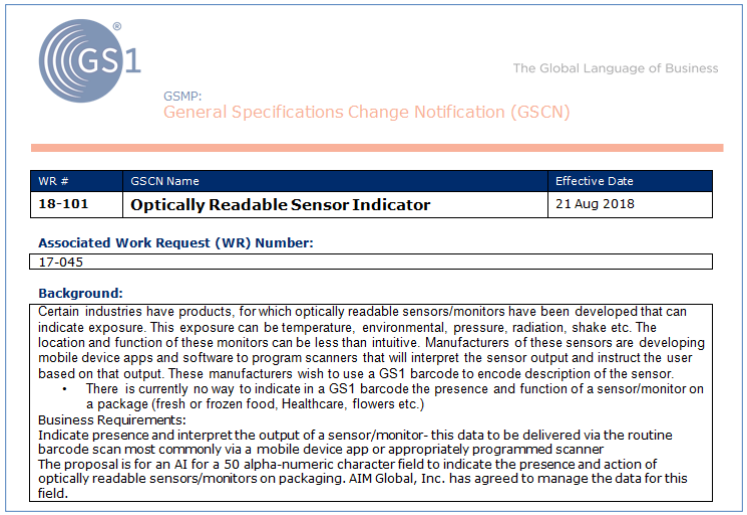
2D Barcode with Embedded Temperature Sensor

- No additional space needed for vial-level use



Global Standard Development 全球标准的发展

GS1 Optically Readable Sensor Indicator



GS1

The Global Language of Business

GSMP:
General Specifications Change Notification (GSCN)

WR #	GSCN Name	Effective Date
18-101	**Optically Readable Sensor Indicator**	21 Aug 2018

Associated Work Request (WR) Number:
17-045

Background:
Certain industries have products, for which optically readable sensors/monitors have been developed that can indicate exposure. This exposure can be temperature, environmental, pressure, radiation, shake etc. The location and function of these monitors can be less than intuitive. Manufacturers of these sensors are developing mobile device apps and software to program scanners that will interpret the sensor output and instruct the user based on that output. These manufacturers wish to use a GS1 barcode to encode description of the sensor.

- There is currently no way to indicate in a GS1 barcode the presence and function of a sensor/monitor on a package (fresh or frozen food, Healthcare, flowers etc.)

Business Requirements:
Indicate presence and interpret the output of a sensor/monitor- this data to be delivered via the routine barcode scan most commonly via a mobile device app or appropriately programmed scanner
The proposal is for an AI for a 50 alpha-numeric character field to indicate the presence and action of optically readable sensors/monitors on packaging. AIM Global, Inc. has agreed to manage the data for this field.

AI Definition for Threshold Indicator and Cumulative Time-Temperature Indicator 自动识别技术

aim

THRESHOLD TEMPERATURE EXPOSURE INDICATOR:

AI (8009) 01

aim

CUMULATIVE TIME-TEMPERATURE EXPOSURE INDICATOR (TTI):

AI (8009) 02

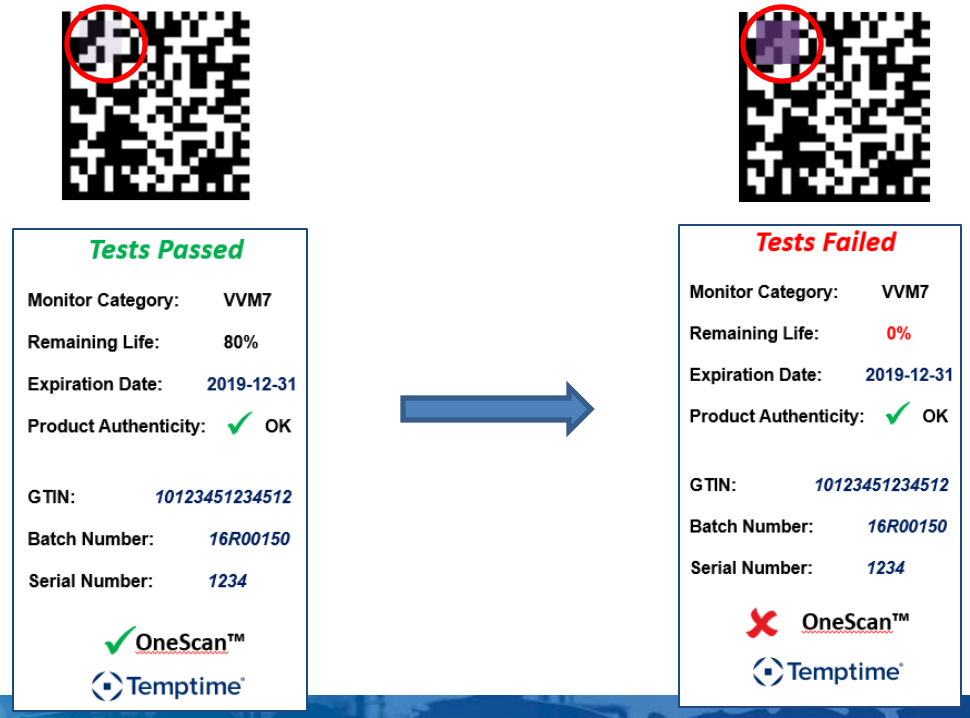
DRAFT 2 v6

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)

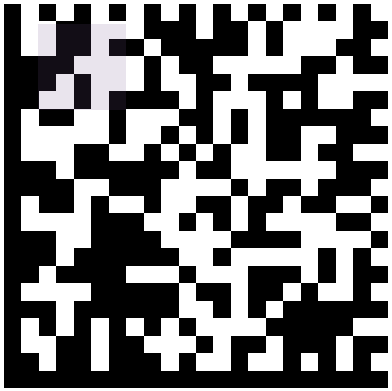
- Specific area has cumulative (VVM) and/or threshold ink printed as part of barcode
- Rapid reading with phone or scanner
- Connect with cloud based data set of other sensors



GS1 2D Data Matrix with Vaccine Vial Monitor (VVM)

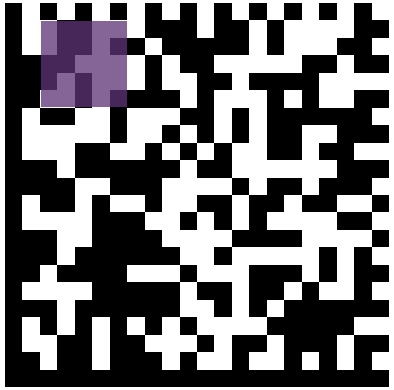
- **VVM** – gradual, irreversible color change from light to dark develops with cumulative time and temperature exposure

Before heat exposure



Time and temperature exposure

After excessive heat



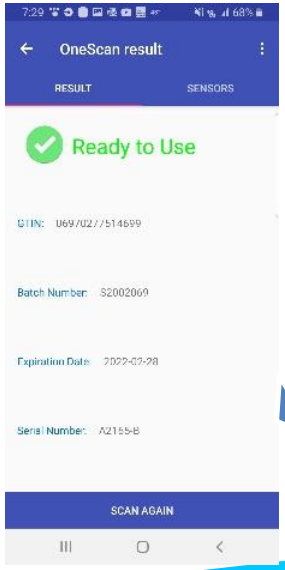
Digitized Temperature Sensor – VVM or “eVVM”

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:

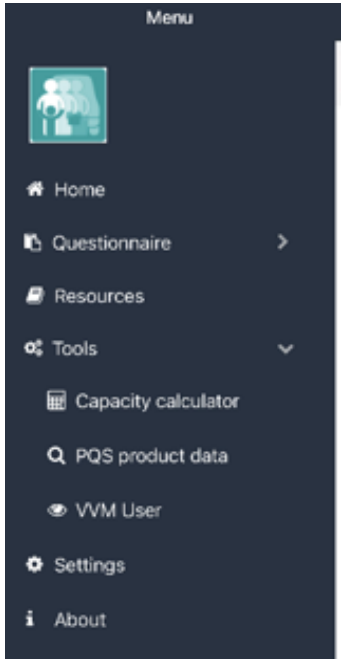
- ***Automated capture of VVM status***
- ***Warning to HCWs***
- ***View of heat exposure across whole cold chain***
- ***Additional product authentication***

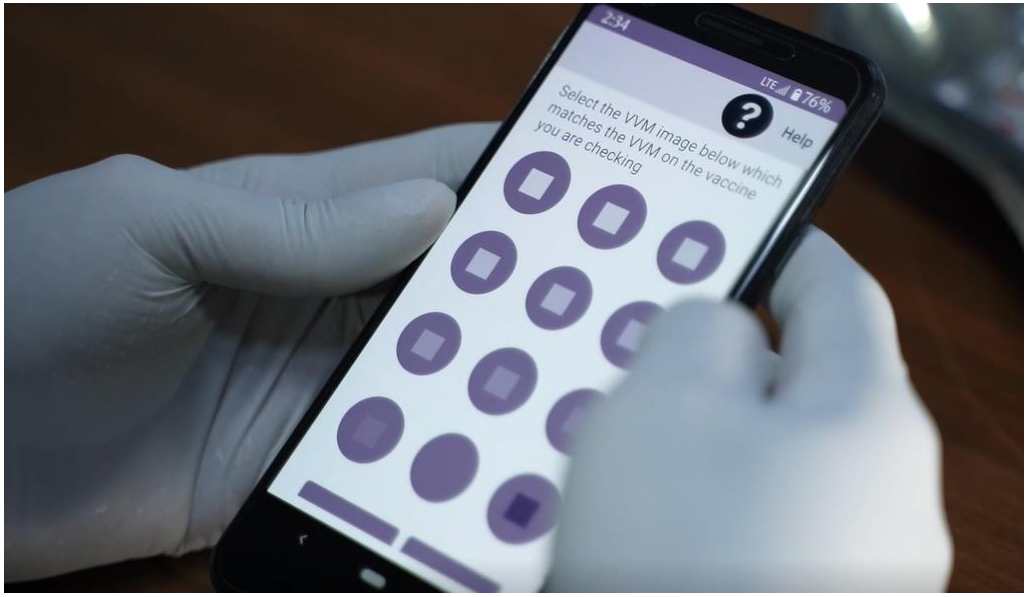


Digital Innovation: VVM App Built into WHO EVM App

EVM

Setting a standard for the vaccine supply chain





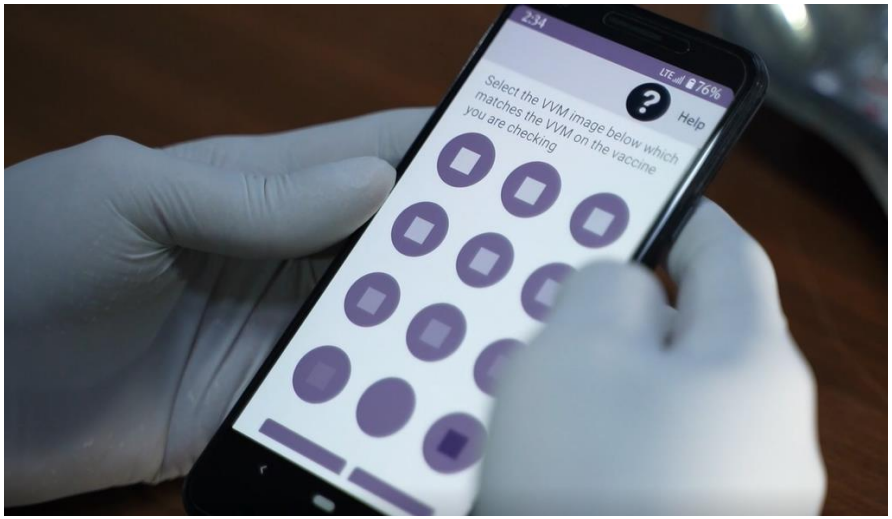
WHO App vs. Future Innovations by Zebra

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



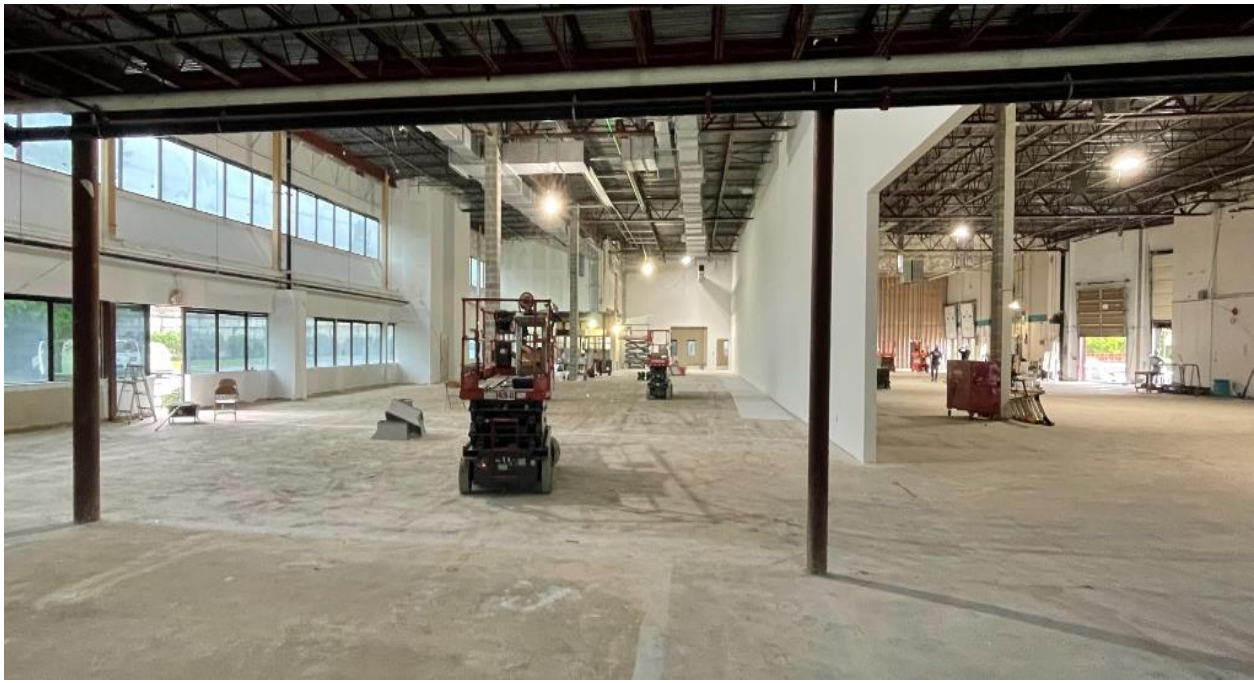
VVM lessons learned during COVID

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!!!