# DCVMN VVM Overview Webinar



July 2018



# **Temptime Vision and Mission**

<u>Vision</u>: *"Temptime elevates the quality of global health"* 

<u>Mission</u>: "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 13<sup>th,</sup> 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...

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# Preventing vaccine

# wastage...

Yogyakarta, Indonesia earthquake - 2006

# Facilitating stock management...

D. Kristensen PATH

# Helping to eradicate diseases...

UI WATE

D. Kristensen PATH

# 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."



Ümit Kartoğlu - WHO

D. Kristensen PATH

# Time-Temperature Indicator/ VVM ← → Arrhenius

Color change based on Arrhenius curves/equations

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

 ${\bf k}$  rate coefficient  ${\bf A}_0$  frequency factor  ${\bf E}{\bf a}$  activation energy (J mol^-1)  ${\bf R}$  universal gas constant (8.314 x 10^-3 kJ mol^-

<sup>1</sup>K<sup>-1</sup> )

Cumulative

T Kelvin temperature (K)

Gradual

Predictable

Irreversible





#### 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 <u>Active Square</u> area is equal or darker than to the <u>Reference Circle</u>

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

## The Chemistry of the HEATmarker TTI

(Colorless)

 $R-C\equiv C-C\equiv C-R$ 

R-C=C-C=C-R

R-C=C-C=C-R

**Polymerization Reaction** 

- The principle of operation is based on the solidstate 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



# Vaccine Temperature Sensitivity



# Four WHO VVM categories

HEATmarker VVMs - Time to VVM Endpoint



World Health Organization



## 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 13485:2003



#### WHO Prequalified Device

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# HEATmarker VVM for use on vaccines Over 650 million VVMs used last year

<u>Pharmaceutical</u> <u>Product</u>	<b>Indication</b>	<u>Customer</u>	<u>Temptime</u> <u>Product</u>	<u>Value</u> <u>Delivered</u>
	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	<ul> <li>Prevents immunization with heat damaged vaccines</li> <li>Expands reach of immunization programs to remote populations</li> <li>Increases immunization programs efficiency</li> </ul>

# 2011 Honduras Technical and Operational Guidelines for Pneumococcal Conjugate



http://www.bvs.hn/Honduras/PAI/LTOVNC2011.pdf



# **Peak Threshold Indicators**

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



# Temptime Continues to Invest in Product Innovations

- VVM: new categories
- CTC & VVM+<sup>®</sup>: 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 anticounterfeiting/track & trace and serialization requirements





# Four WHO VVM Types to Monitor Vaccines with Different Heat Sensitivities



#### HEATmarker VVMs - Time to VVM Endpoint

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

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 <u>end</u> <u>point</u> 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*

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

\*VVM (Arrhenius) 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**

TechNet Meeting | Dakar, Senegal | February 5, 2013 Simona Zipursky | zipurskys@who.int

•Allowing <u>specific</u> vaccines to be kept and administered at ambient temperatures, <u>up to 40°C</u>

- 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.

<u>Current focus</u>: 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)





Anna-Lea Kahn - WHO-HQ/ EPI 14<sup>th</sup> TechNet Conference - Bangkok, Thailand 13 May 2015

# New Product Innovations Address High Temperature Excursions and CTC Requirements

 $VVM+^{TM}$ 

• 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

	ARTICLE IN PRESS	
	Vaccine xxx (2017) xxx-xxx	
and the second s	Contents lists available at ScienceDirect	≍ Vaccine
28 M	Vaccine	-
ELSEVIER	journal homepage: www.elsevier.com/locate/vaccine	

Stability of heat stable, live attenuated Rotavirus vaccine (ROTASIIL®)

Sameer P. Naik, Jagdish K. Zade \*, Rajendra N. Sabale, Sambhaji S. Pisal, Ravi Menon, Subhash G. Bankar, Sunil Gairola, Rajeev M. Dhere

Serum Institute of India PVT LTD, 212/2, Hadapsar, Pune 411028, India

organism introduced during the reconstitution process could



multiply. The thermo-stability of ROTASIIL<sup>®</sup>, 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 ROTASIIL 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



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. 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





Figure 3. Time Temperature Indicator



#### Rotasiil Team was Concerned with Exposures Above 40°C

VVM+250 confirmed by WHO and SII



VVM+250

# VVM 250 Specifications



PQS performance specification

WHO/PQS/E006/IN05.3 Original: English Distribution: General

TITLE: Vaccine Vial Monitor					
Specification reference:	E006/IN05.3				
Product verification:	E006/IN05.VP.3				
Issue date:	15 May 2018				
Date of last revision:	19 January 2012				

#### Table 1b: VVM reaction rates by type

Type (Vaccines)	Maximum time to end point at +55°C	Maximum time to end point at +45°C	Approx- imate Maximum time to endpoint at +37°C	Time to end point at +25°C
VVM250: Very High Stability	17 days	73 days	250 days*	≥900 days

\*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)

Category	# of Incidences	Loss (dollars)
Refrigeration Problems	16	\$42,958
Shipping/ Receiving	4	\$34,772
Improper Storage	6	\$187,133
Expired Vaccines	51	\$127,289
Total Losses	77	\$392,717
Extrapolation to state		\$2,352,426



## Source: California Department of Public Health 34

# US Vaccines for Children Program Vulnerabilities in Vaccine Management<sup>1</sup>

#### Office of Inspector General June 2012

Department of Health and Human Services OFFICE OF INSPECTOR GENERAL

VACCINES FOR CHILDREN PROGRAM: VULNERABILITIES IN VACCINE MANAGEMENT



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

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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.

# Ice on box of influenza vaccine



# Global Temp-Monitoring Requirements – 2018

Last Updated: April 2018

Peru – 2015 law requiring documentation of all temp-excursions during distribution, Brazil - 2016 policy requiring resulting remediation plans, and empowerment Nat'l Mail Service to distribute all of MoH to enforce remediation plans temp-sensitive medicines, vaccines, diagnostic kits, and medical supplies for Nat'l Health Agency Argentina – 2009 law requiring National requirements for VVM on all public sector vaccines (3: Pakistan, India, Indonesia) temp-monitoring of all temp-sensitive human/animal medical products; gradual implementation in 2017 Gavi requirements for VVM on all public sector vaccines (54 Gavi-eligible countries in 2017) on vaccines/carton-level 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)

## 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



Temptime\*
 Improving Global Health

#### 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



#### 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*

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Manufacturer	item	Case	Pallet	Transport	Distributor	Transport	Pallet	Distribution Centre	Transport	Case	Item	Retailer	Consumer



End-to-end unique identifier and unique temperature monitor



Provider

Operator



Caregive

#### Dynamic Barcodes Allow Unit Level Data Connection from Manufacture to End Use





# Thank you!



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