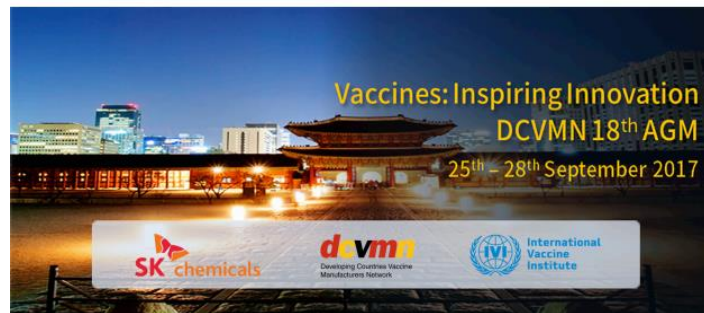




Innovations in Thermostability Monitoring: VVM200, VVM+, and Hybrid 2D Bar Codes with embedded VVMs

DCVMN
AGM – Seoul, S. Korea

Michael Rush
Executive Director - Global Health Policy

25 September 2017

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 – to improve patient safety and address evolving international anti-counterfeiting/track & trace, and serialization requirements



Inspiration

- *“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.”*

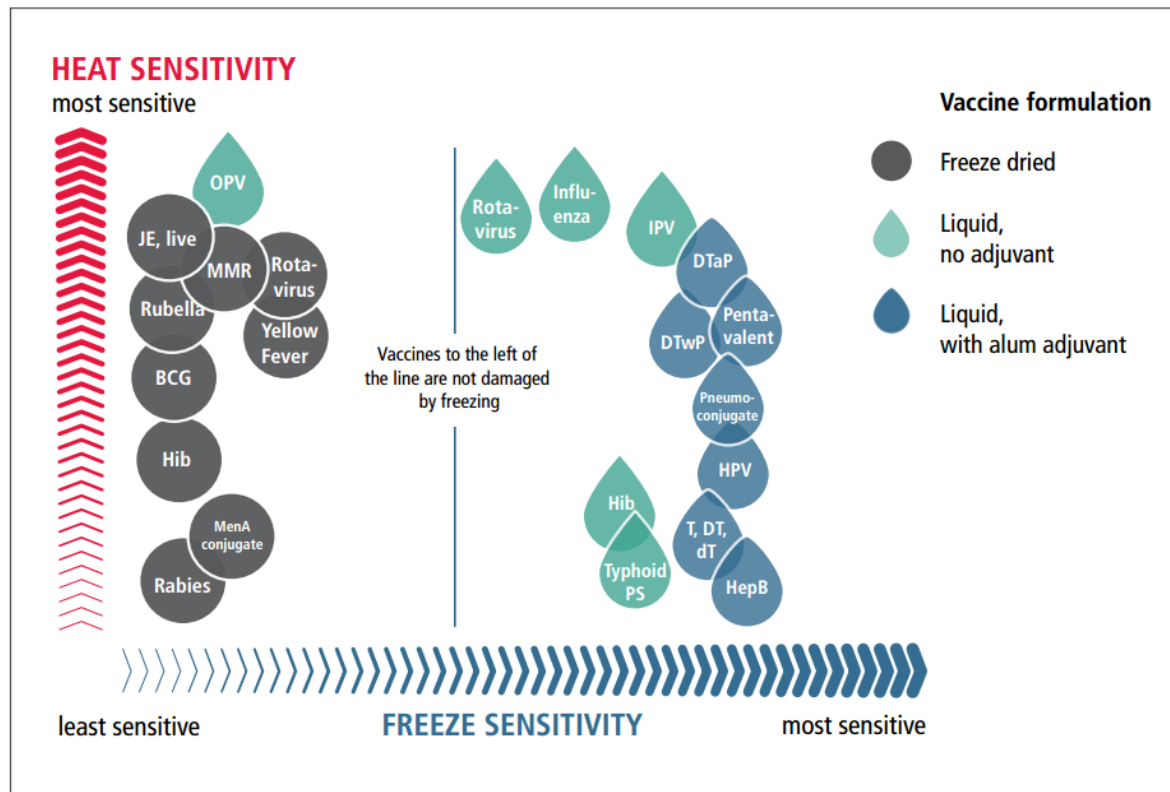


Bill Gates - February 21st, 2017

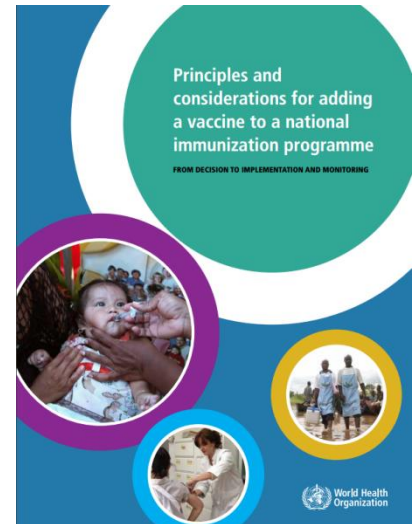
- *“I have always been struck by the brilliance of the VVM approach: a marker that changes color to reflect the state of the vaccine. Now, with electronics and imaging entering a new regime of cost-to-performance, it is exciting to see Temptime add fine-grain recording and geo-tracking in the supply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

Sanjay Sarma, Vice President Open Learning, MIT - April 13th, 2017

Temperature sensitivity of vaccines



Note: This graphic illustrates relative sensitivity across antigens, as the same type of vaccine from different manufacturers may have different vaccine vial monitors (VVMs). For more information, see → Section 3.3.4.



WHO PQS Performance Specification – Vaccine Vial Monitor (WHO/PQS/E06/IN05)⁵

VVM Reaction Rates

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

- 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.

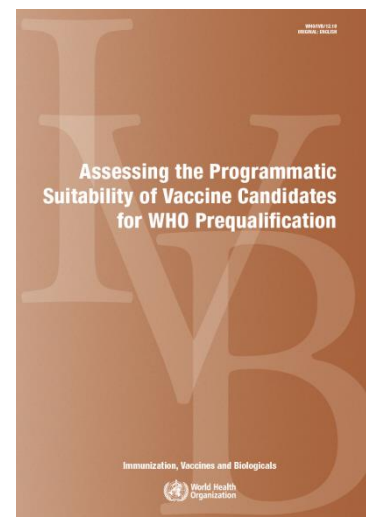
⁵ http://www.who.int/immunization_standards/vaccine_quality/who_pqs_e06_in05_1.pdf

UNICEF/WHO Policies on Criticality of VVMs

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&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.
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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

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

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



WHO/BS/06.2049 - Final
ENGLISH ONLY

GUIDELINES ON STABILITY EVALUATION OF VACCINES

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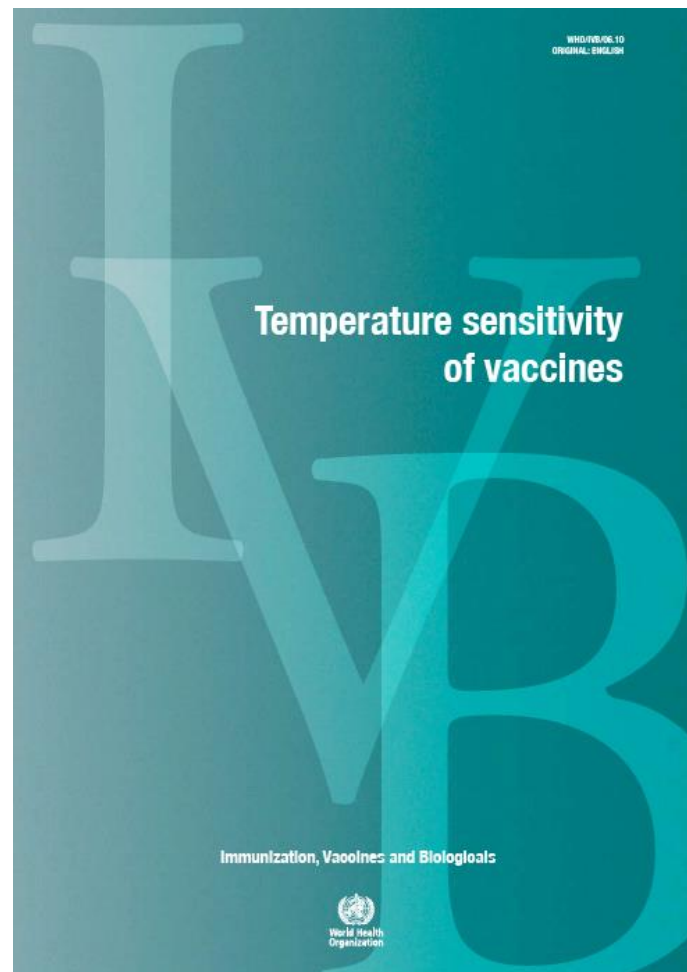
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Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the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

WHO Temperature Sensitivity of Vaccines³

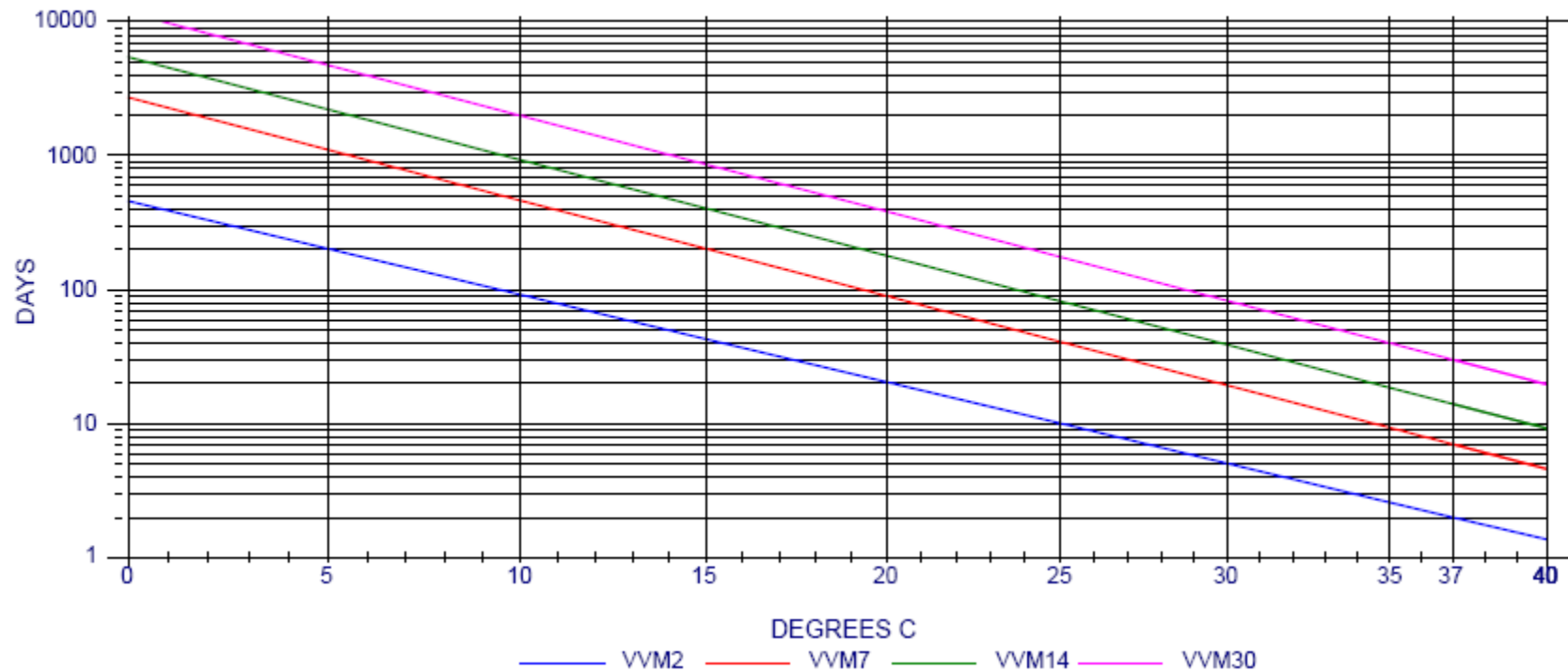
- The basis for choosing a VVM category for a given vaccine is the Accelerated Degradation Test (ADT).
- In this test samples are subjected to a range of elevated temperatures at which significant and readily detectable degradation is induced in a relatively short time. The rate at which degradation 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>

Four WHO VVM categories

HEATmarker VVMs - Time to VVM Endpoint



WHO PQS VVM Specification is currently under revision

VVM Line Extensions to Address Programmatic Needs

VVM11

- Why VVM11
 - VVM7 has slightly greater than 2 year minimum life
 - Some vaccines have stability > VVM7 but < VVM11
 - Some vaccines have moved to 3 year expiry date
 - If change to statistical model of vaccine stability, possibility that a lower VVM category might be chosen.
 - VVM14 might revert to VVM7
- VVM11 fills the gap between VVM7 and VVM14
 - Provides ≥ 2.5 years at 5°C
 - Project initiated based on Sanofi Pasteur IPV stability potential
- Status:
 - Specs proposed to PQS and added to VVM specification revision in progress
 - Accredited independent lab testing completed
 - Interest by Sanofi Pasteur, GSK and SII

VVM Line Extensions to Address Programmatic Needs

Improved VVM7

- Improved VVM7 with ≥ 2.5 years at 5°C vs. 2 years for current VVM7
- Vaccines with only 7 days of stability at 37°C will benefit
- In discussion with PQS whether new category is needed
 - Improved VVM7 will meet current requirements

Table 3: VVM reaction rates by category of heat stability

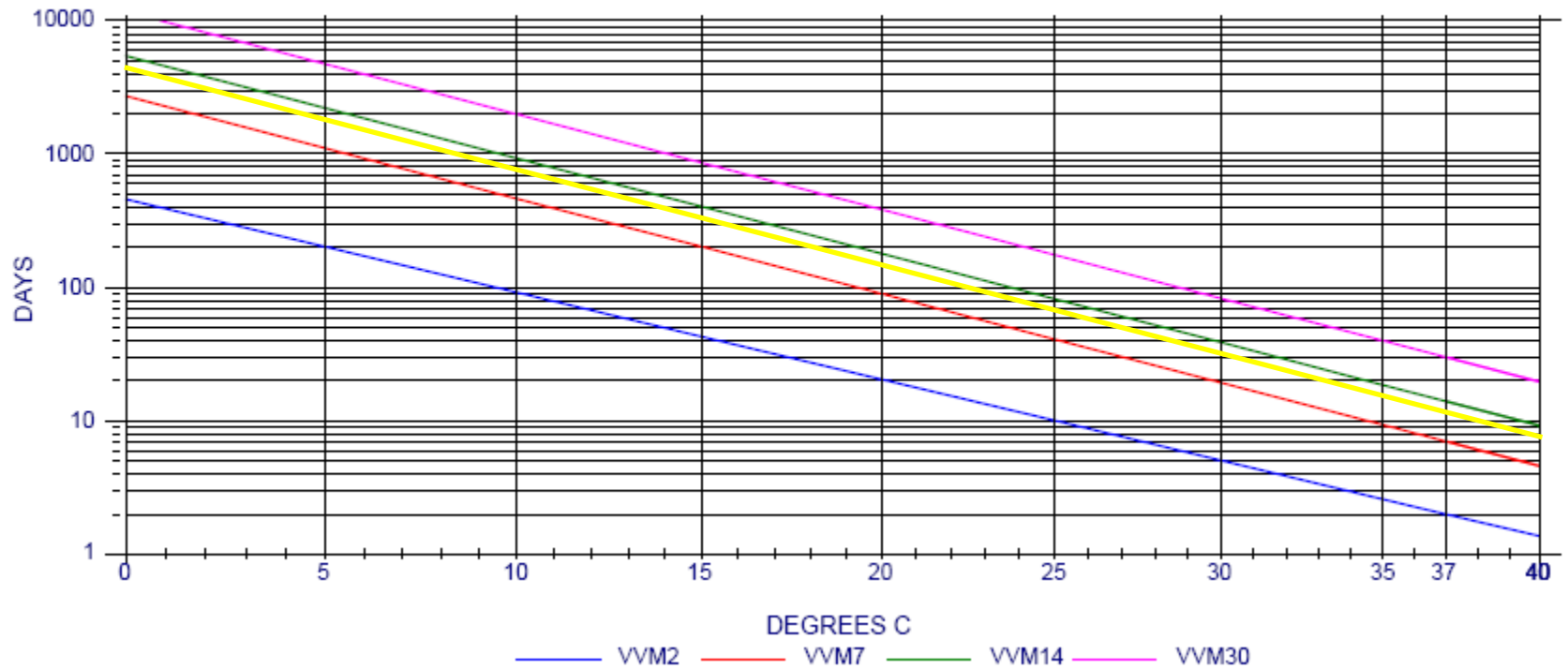
Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
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VVM 14: Medium Stability	14	90	> 3 years
VVM 7: Moderate Stability	7	45	> 2 years
VVM 2: Least Stable	2	N/A*	225 days

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

- Candidate formulations moved forward into the qualification stage; potential commercialization in Q2 2018

Four Five WHO VVM categories

VVM11 In Progress



— VVM11

VVM Challenge – Highly Stable Rotavirus 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. Dhare

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

8 °C up to six hours as, at higher temperatures; any micro-organism introduced during the reconstitution process could multiply.

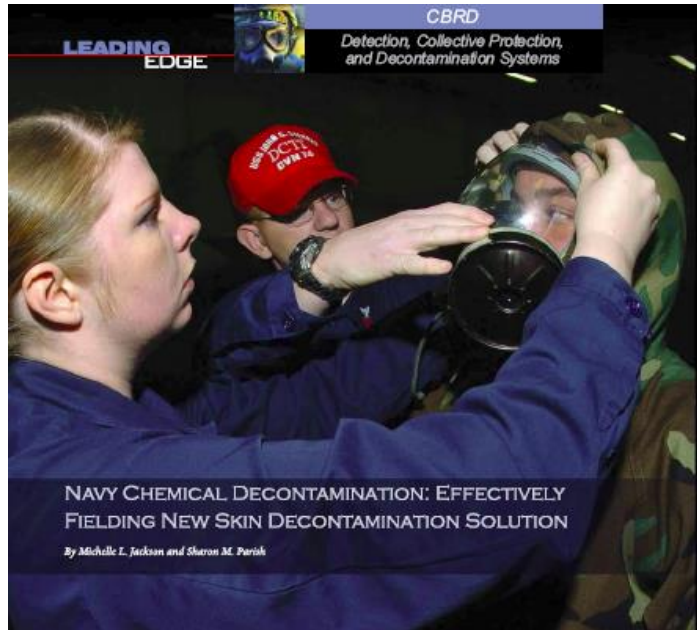
The thermo-stability of ROTASIIL®, ironically, has thrown up a new challenge in terms of vaccine vial monitors (VVM). The presently available VVM portfolio (Max VVM30: 30 days at 37 °C) does not begin to cover the extreme thermo stability of ROTASIIL which is 18 months- (540 days) at 37 °C. Efforts to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

VVM200 – 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 Lo

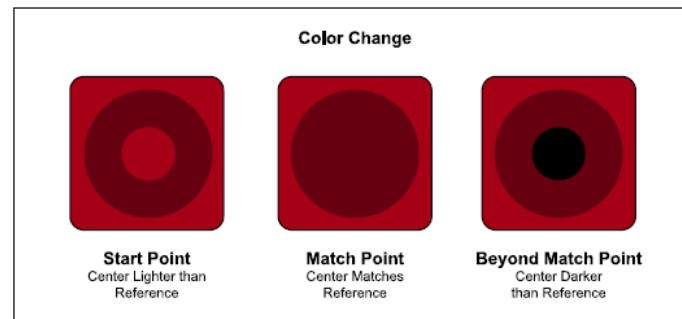


Figure 3. Time Temperature Indicator

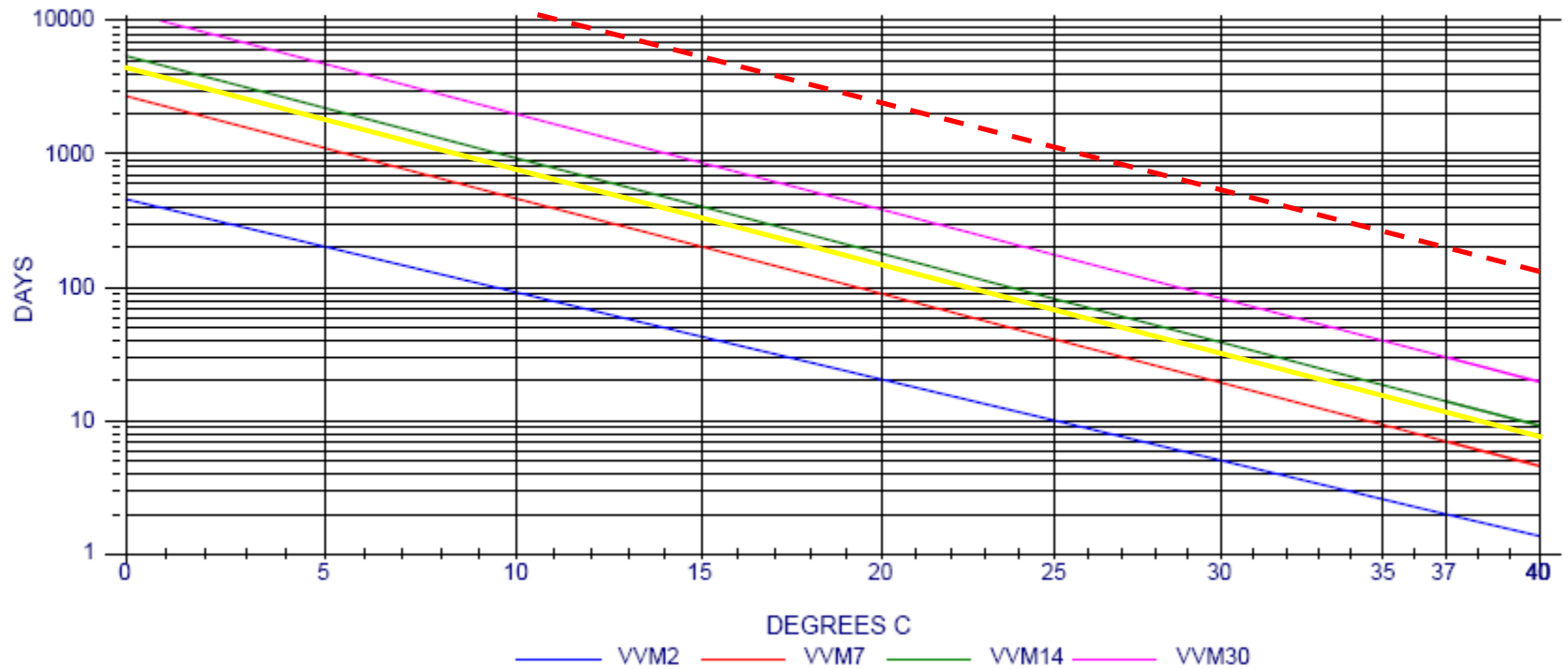
VVM Line Extensions to Address Programmatic Needs

VVM200

- ROTASIIL Stability
 - Information provided by the manufacturer indicates 30 months up to 25°C as package insert storage condition
 - Dossier submitted to WHO
- VVM Status
 - WHO PQS is considering addition of a VVM180 in the VVM specification under revision
 - Temptime has made VVM format runs for stability testing

Six WHO VVM categories

VVM200 In Progress



— VVM11

- - VVM180

New Product Innovations to Address High Temp Excursions

- VVM+
 - Combined VVM response and high temperature threshold in a single indicator

The innovation of the Controlled Temperature Chain (CTC) – where do we go from here?



**World Health
Organization**

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

Programmatic incentive of CTC

- **CHALLENGE:** The logistics for campaigns– from surge cold chain capacity to ice pack freezing are extremely complex and time consuming
- **BENEFITS:** Allowing more cost-effective & efficient immunisation programmes, particularly in the last mile of outreach efforts.



HOW DOES A CTC COMPARE TO A TRADITIONAL COLD CHAIN?

TRADITIONAL COLD CHAIN



Vaccine label indicates +2°C to +8°C for **all** storage and transport.

VVM



Vaccine vial monitors protect potency and quality by monitoring cumulative exposure to heat.



Conditioned ice packs or cool water packs are required in vaccine carriers.



No need for additional training, monitoring or supervision.



When implemented correctly, preserves the safety and potency of the vaccine.



Requires cooling equipment, transport, and human resources at all levels to maintain cold chain.

CONTROLLED TEMPERATURE CHAIN (CTC)

Vaccine label indicates +2°C to +8°C for **initial** storage and transport.



and permits up to 40°C for at least 3 days prior to use.

VVM + PTTI



Vaccine vial monitors and peak temperature threshold indicators protect potency and quality by monitoring cumulative and peak exposure to heat.



No ice packs or cool water packs are required in vaccine carriers. Reduced risk of freezing.



Health workers need additional training, monitoring and supervision.



When implemented correctly, preserves the safety and potency of the vaccine.



Half the cost.¹ Fewer freezers, fewer journeys and less staff time are needed to manage and maintain cold chain requirements.

The Next Challenge – Controlled Temperature Chain (CTC)

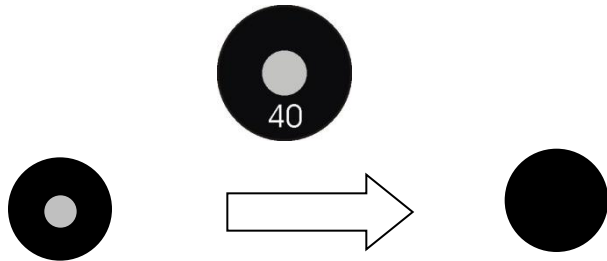
Objective: **on-label** use of vaccines in a CTC allowing specific vaccines to be kept and administered at ambient temperatures, up to 40°C for one, limited period of time

- All CTC pilot studies with

- 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



+



VVM

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

Peak Temperature Threshold Indicator

- Reacts rapidly to peak temperature

Response after short exposure to 40°C



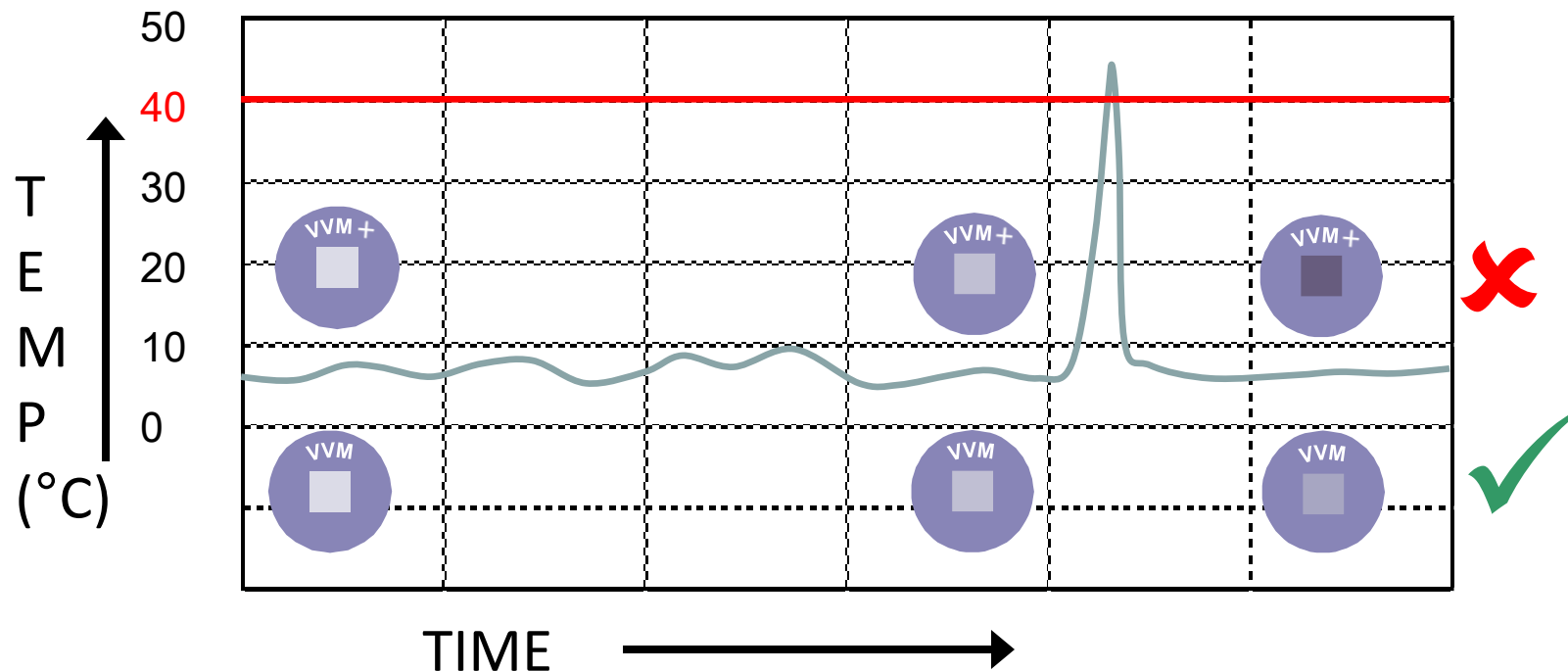
VVM+™



HEATmarker VVM+

VVM plus Peak Indicator in Same Device

VVM+ reacts like a VVM up to 37°C. At 40°, VVM+ reaches the endpoint rapidly to show exposure to critical peak temperature.

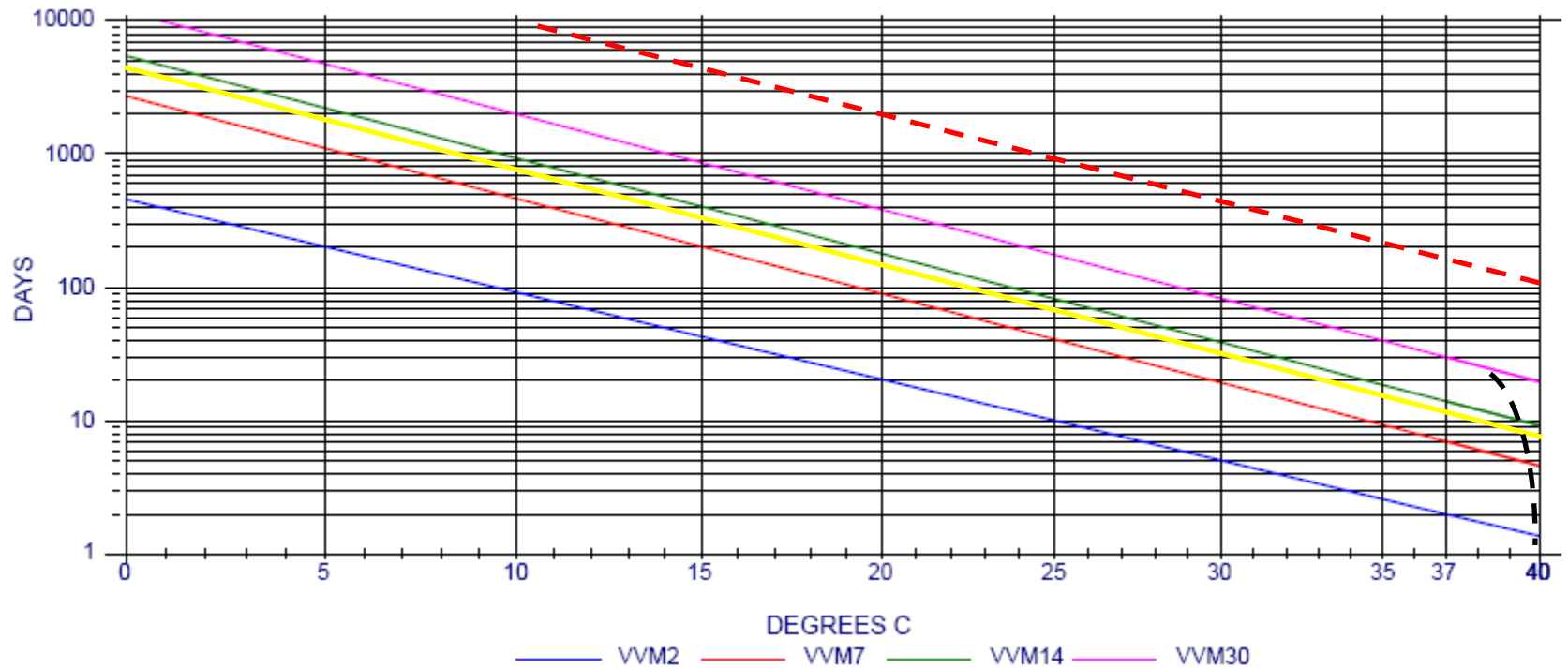


Comparison of VVM+ and VVM at Threshold Temperature



Four Five Six WHO VVM categories and VVM+

VVM+ In Progress



— VVM11

-- VVM180

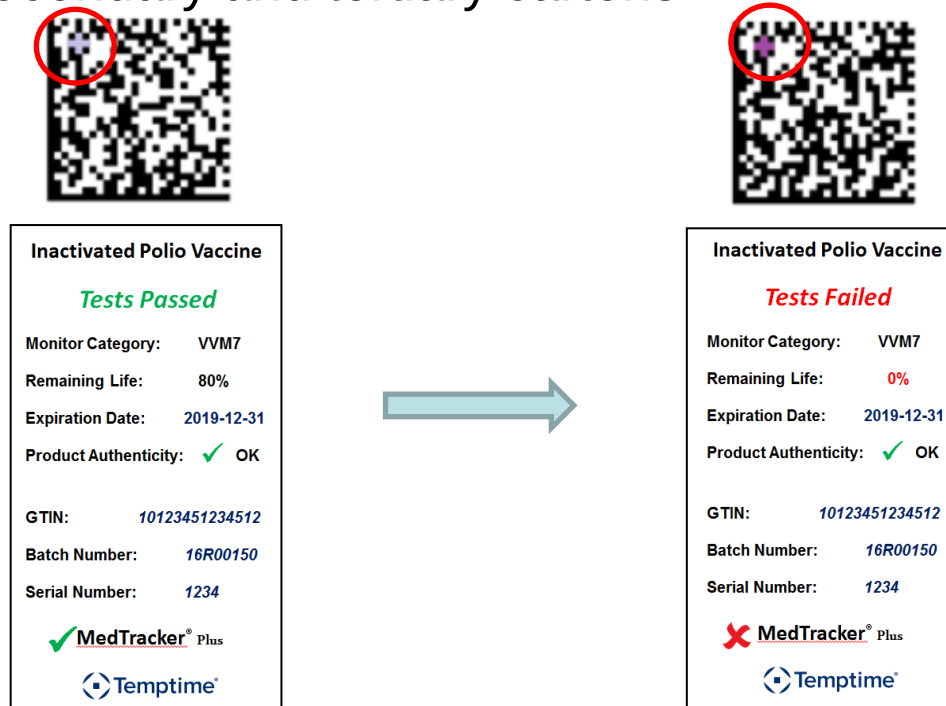
-- VVM+

In Development

2D Barcode with Embedded VVM

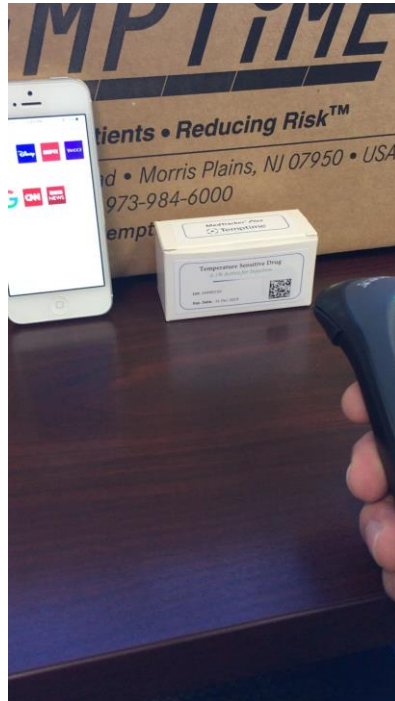
Enhance the value of 2D barcodes by integrating temperature integrity

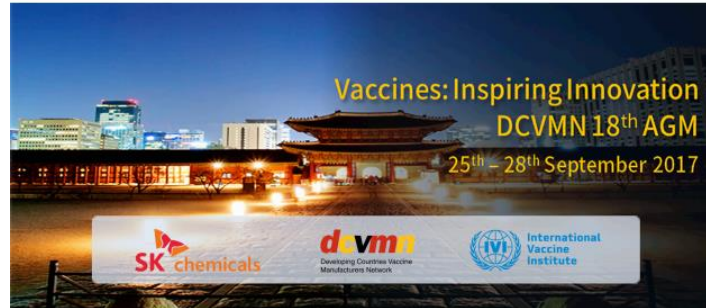
- Specific area has VVM or threshold ink printed as part of barcode
- Rapid reading with phone or scanner
- Measure color level of VVM
- Use on secondary and tertiary cartons



Demo of Data Matrix Processing - Status

- Developed and demonstrated algorithm on computer to decode binary change or measure color shades
- Developing app for phone or scanner
- GS1 organized a Working Group to create the Application Identifiers



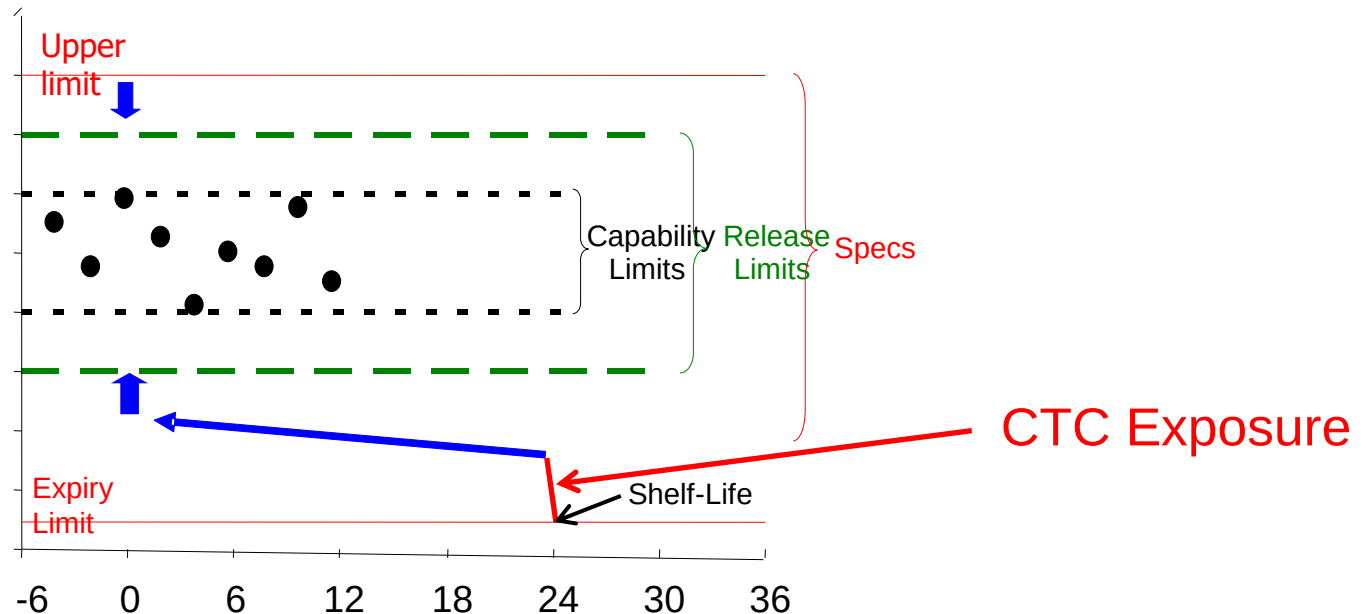


Thank You - 고맙습니다

Back-Up Slides

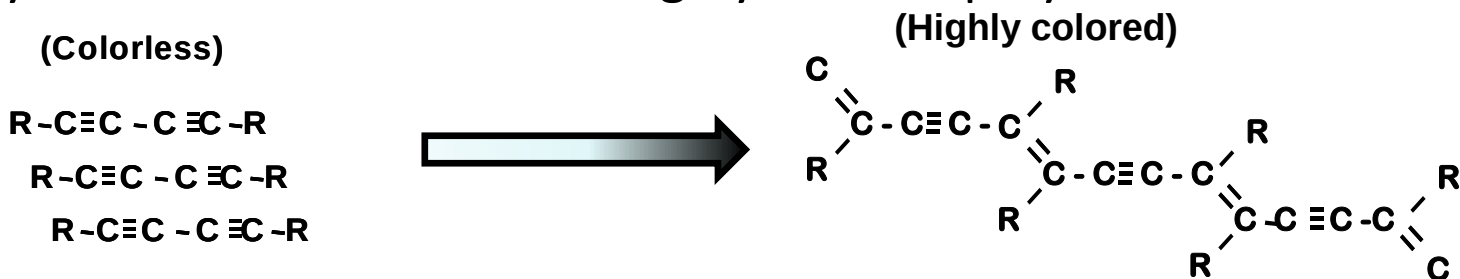
Impact of CTC on Vaccine Stability Studies

- Manufacturers will need to provide additional stability data to support CTC on-label approval



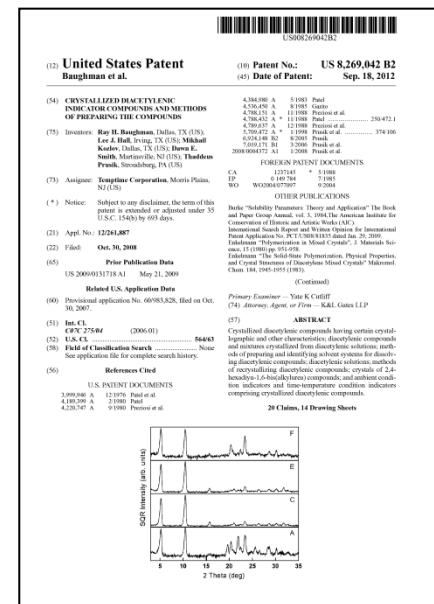
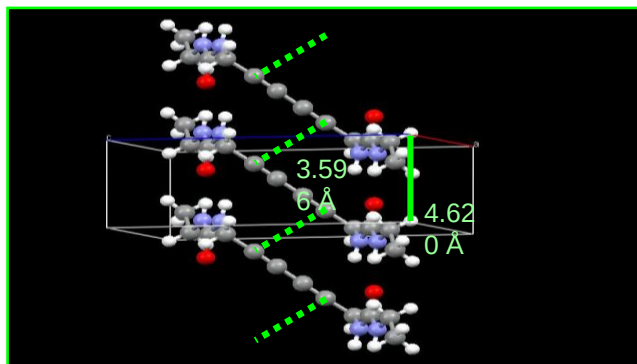
The Chemistry: Polymerization of the Monomer

- The color-changing chemistry is based on the solid state polymerization of colorless diyne diurea monomers to highly colored polymers

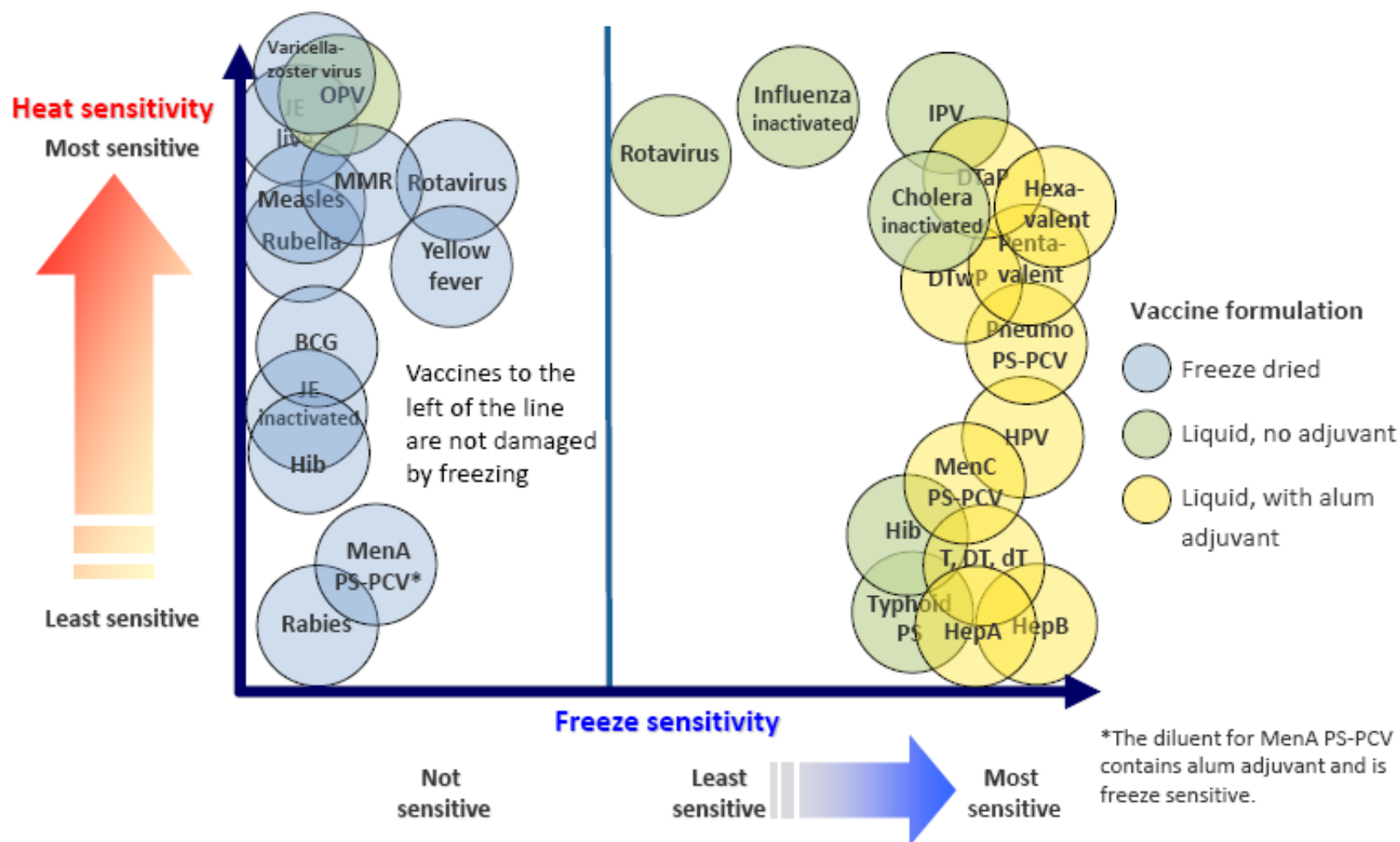


- The crystal structure of KE monomer was solved (Baughman et al)

- Basis of a key US patent (issued 18 September 2012)



Temperature sensitivity of vaccines (2015)

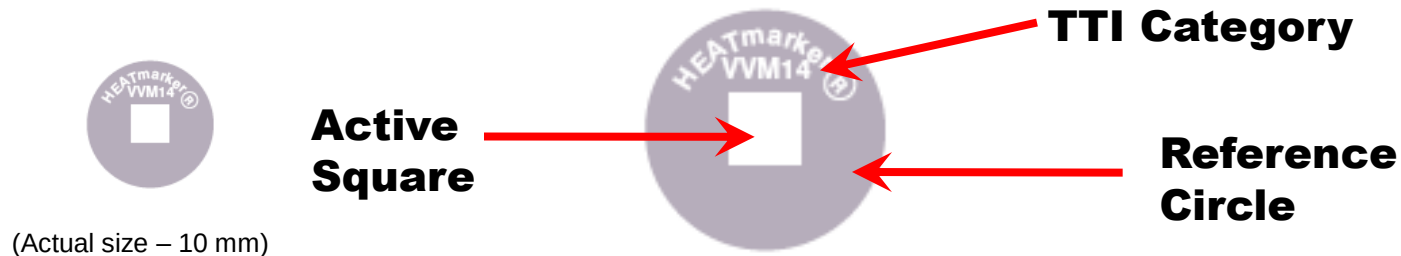


What is a HEATmarker?

- HEATmarker is the brand name for Temptime's Time-Temperature Indicators for monitoring heat in the Life Sciences field of use
 - **VVM** (Vaccine Vial Monitor) is the first HEATmarker created in 1996 that is defined by WHO's specifications
 - It can be printed on a vial label, applied on the vial cap or on an ampule neck.
 - There are 4 categories defined by the number of days at 37°C to reach the end point: VVM2, 7, 14 and 30.



HEATmarker Time-Temperature Indicator (TTI)



- 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
- Following Arrhenius kinetics, the combined effects of time and temperature cause a **gradual, predictable, cumulative and irreversible color change** from lightly colored to dark
- **HEATmarker TTIs can be correlated to product stability**
- **HEATmarker shows a Health Care Worker if a product has been exposed to excessive heat over time**

The HEATmarker is Easy to Read and Has Proven Benefits

How To Read the HEATmarker ¹

The Active Square is lighter than the Reference Circle.

If the expiry date is not passed, USE the vaccine



USE



USE



DO NOT
USE



DO NOT
USE

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

DO NOT USE the vaccine.

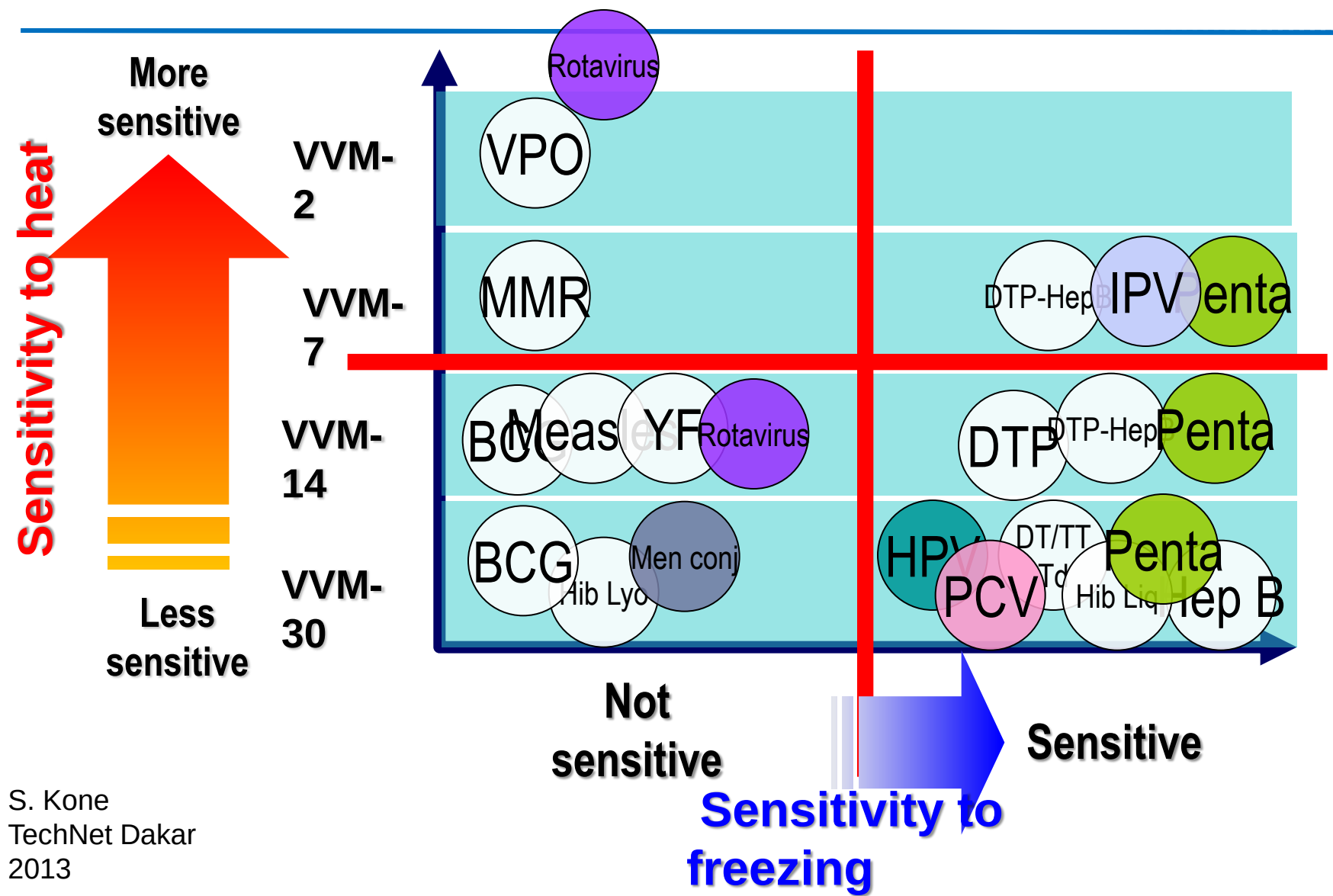
Key Benefits²

1. Assures that vaccine has not been heat-damaged at the time of administration
2. Reduces vaccine wastage by preventing the discard of usable vaccines
3. Enables vaccines with the shortest 'life' to be prioritized for distribution and use
4. Increases access to immunization for needy populations in difficult to reach areas
5. Assures that failures can be prevented and that wastage of vaccine due to failures of the cold chain is minimized

² From "The Key Role of VVM in Routine and Mass Immunization"

Mr. John S. Lloyd (PATH - Resident Advisor) October 2003

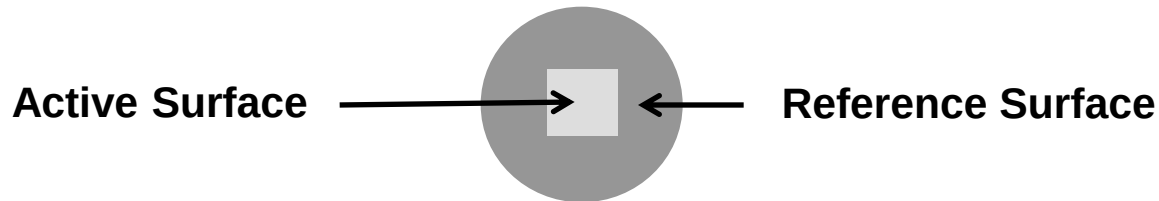
Diverging temperature sensitivity (2013)



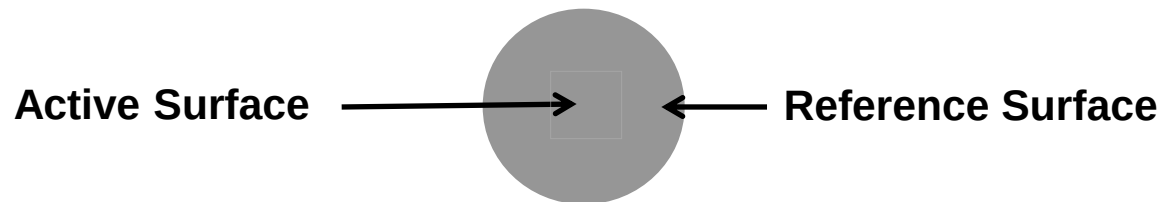
S. Kone
TechNet Dakar
2013

VVM Characteristics

- VVM is a WHO prequalified device



VVM BEFORE end point: Active Surface lighter than Reference Surface



VVM AT end point: Active Surface matches Reference Surface