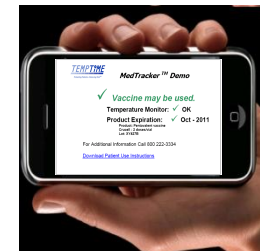


Innovations in Temperature Monitoring VVMs and Beyond



TEMPTIME



T. Prusik
27 October 2014

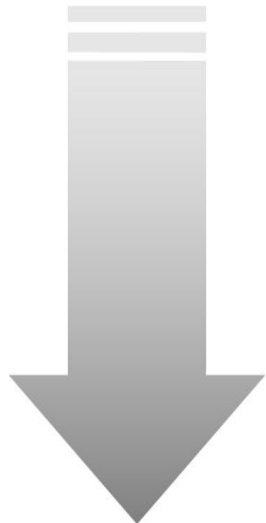
Agenda

- Vaccine Stability and VVM Selection
- Why should vaccine manufacturers use VVMs
- Innovations in the vaccine supply chain

Vaccine Temperature Sensitivity

Heat sensitivity

most sensitive



least sensitive

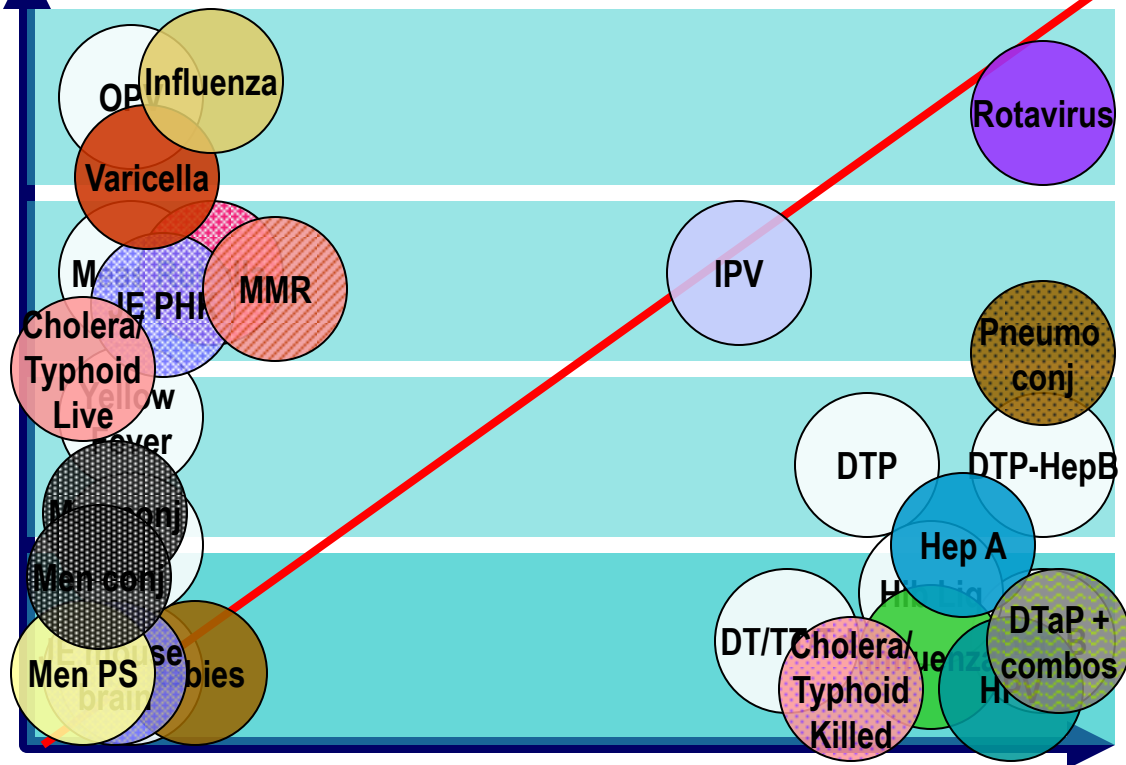
Days
at 37°C

2

7

14

30



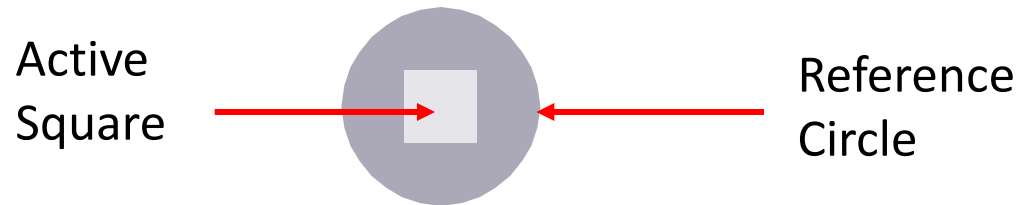
Freeze sensitivity

least sensitive



most sensitive

Monitor Cumulative Heat with HEATmarker 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 area is equal to the Reference Circle

The HEATmarker TTI Is Easy To Read

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

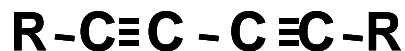
The Active Square matches or is darker than the Reference Circle.

DO NOT USE the vaccine.

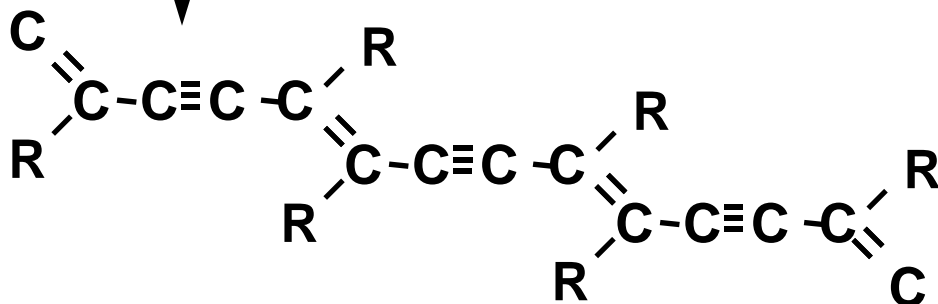
The Chemistry of the HEATmarker TTI

Polymerization Reaction

(Colorless)



Polymerization

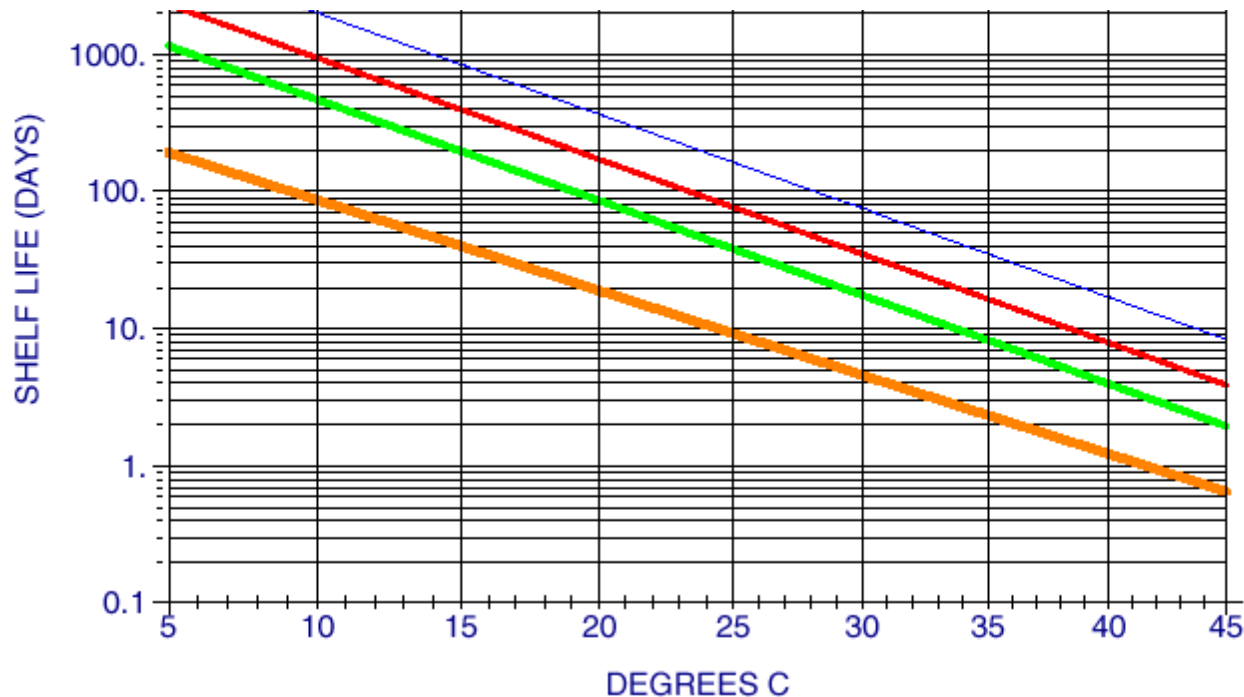


(Black)



- *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*

HEATmarker VVM Categories

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.



HEATmarker VVM for Use on Vaccines

<u>Pharmaceutical Product</u>	<u>Indication</u>	<u>Customer</u>	<u>Temptime Product</u>	<u>Value Delivered</u>
	<p>Children's Immunization Campaigns for a range of contagious diseases:</p> <ul style="list-style-type: none"> • BCG • Diphtheria • Tetanus • Pertussis • DTP • Hep B • HiB • Meningococcal A and C • Measles • Mumps, Pneumococcal • OPV • Rotavirus • Rubella • Tetanus Toxoid • Yellow Fever <p>Other Campaigns:</p> <ul style="list-style-type: none"> • HPV • IPV • Rabies • Typhoid 	<p>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, plus others</p>	 <p>VVM2, VVM7, VVM14, VVM30</p>	<ul style="list-style-type: none"> • Prevents immunization with heat damaged vaccines • Expands reach of immunization programs to remote populations • Increases immunization programs efficiency

WHO e-VVM Based Vaccine Management Course

ePELA extensio et progressio / authentic e-learning

e-VVM Based Vaccine Management Course

World Health Organization

The little big thing

00:29

HD :: vimeo

e-VVM based vaccine management course dates for 2014

- 27 January – 28 March 2014 (beta-course)
- 21 April – 20 June 2014
- 6 October – 5 December 2014

Introduction

PDF

Introduction Video

Learning Objectives

Programme

Document Library

Video Library

BACK

FORWARD

Mentors

Who said what

Credits

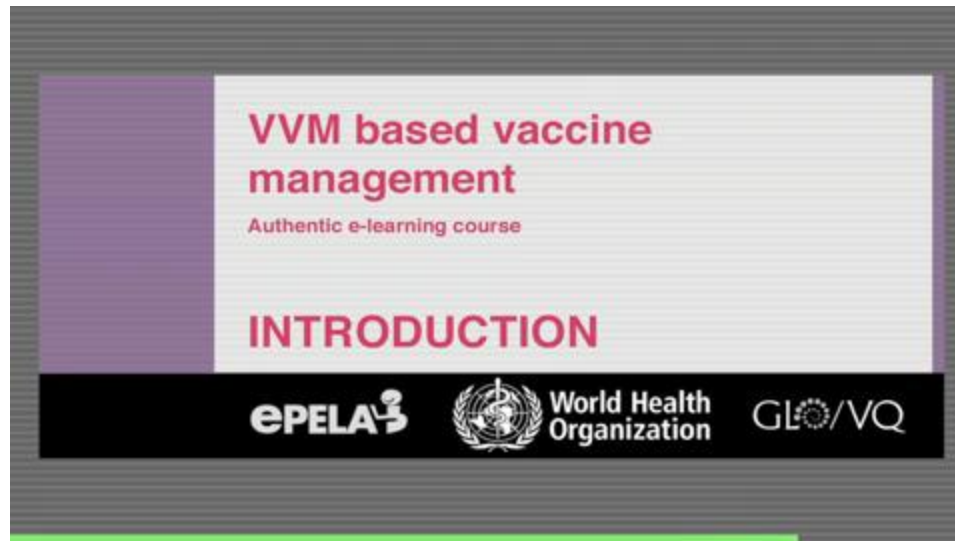
Apply online

Sponsors

Collaborators

http://www.epela.net/epela_web/

WHO e-VVM Based Vaccine Management Course



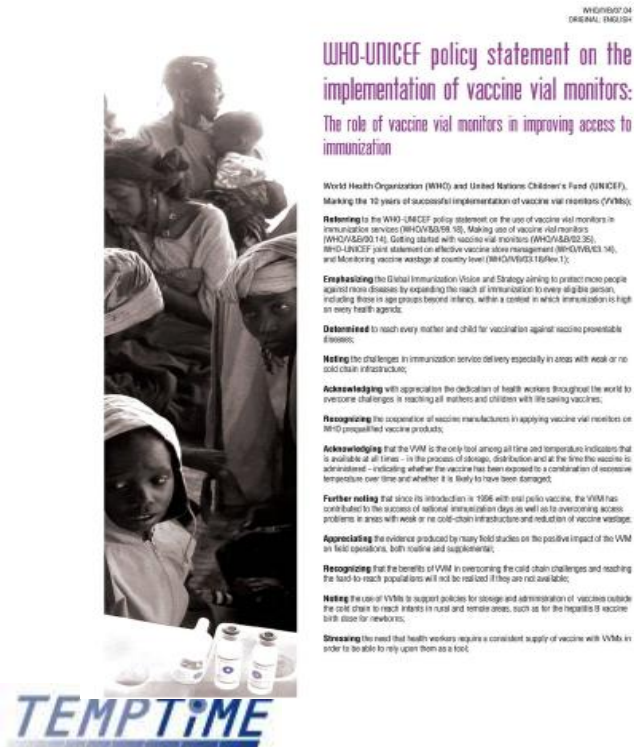
Selective vaccine use
Rotating stocks
Pinpointing cold chain problems
Increasing access
Preventing freezing
Reducing vaccine wastage
Signaling whether to use the vaccine for
subsequent session

The little big thing

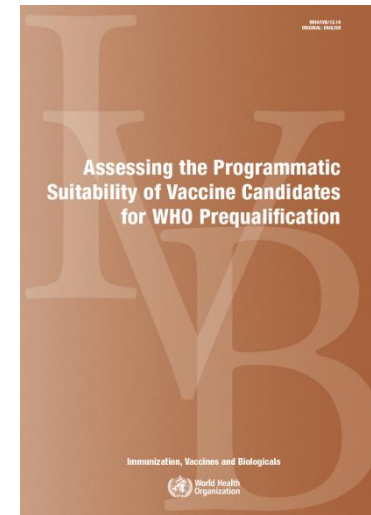


UNICEF/WHO Policies on Criticality of HEATmarkers (VVMs)

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	<p>Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below.</p> <p>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).</p> <p>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.</p>
----------------------------	--------------	---

Steps to VVM Implementation

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

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.*

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

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

http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.10_eng.pdf



WHO/BS/06.2049 - Final
ENGLISH ONLY

GUIDELINES ON STABILITY EVALUATION OF VACCINES

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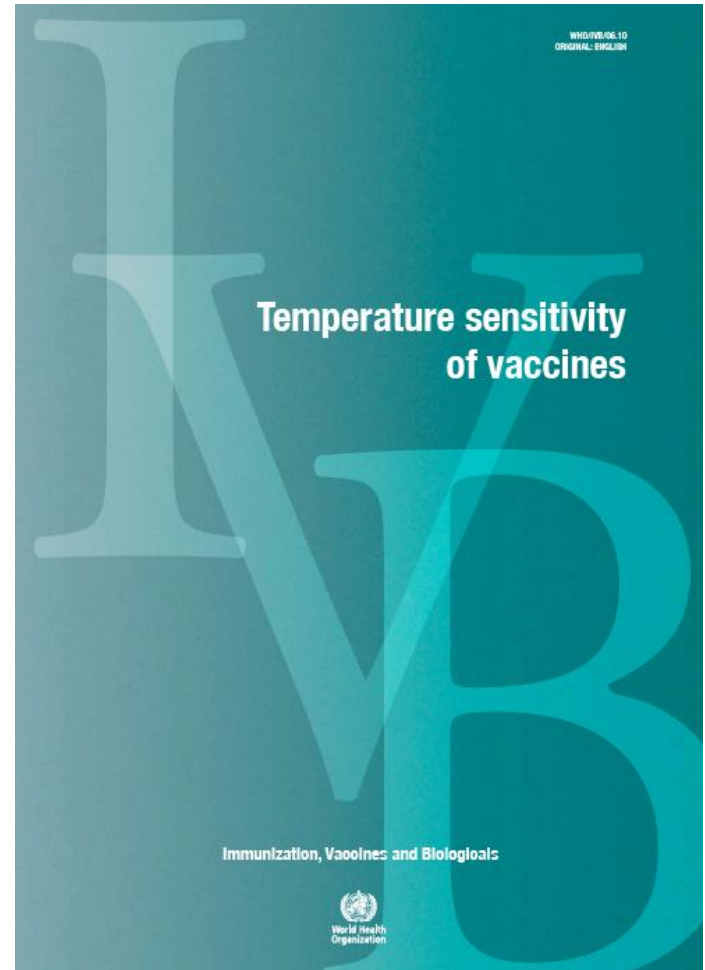
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Adopted by the 57th meeting of the WHO Expert Committee on Biological Standardization, 23-27 October 2006. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the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

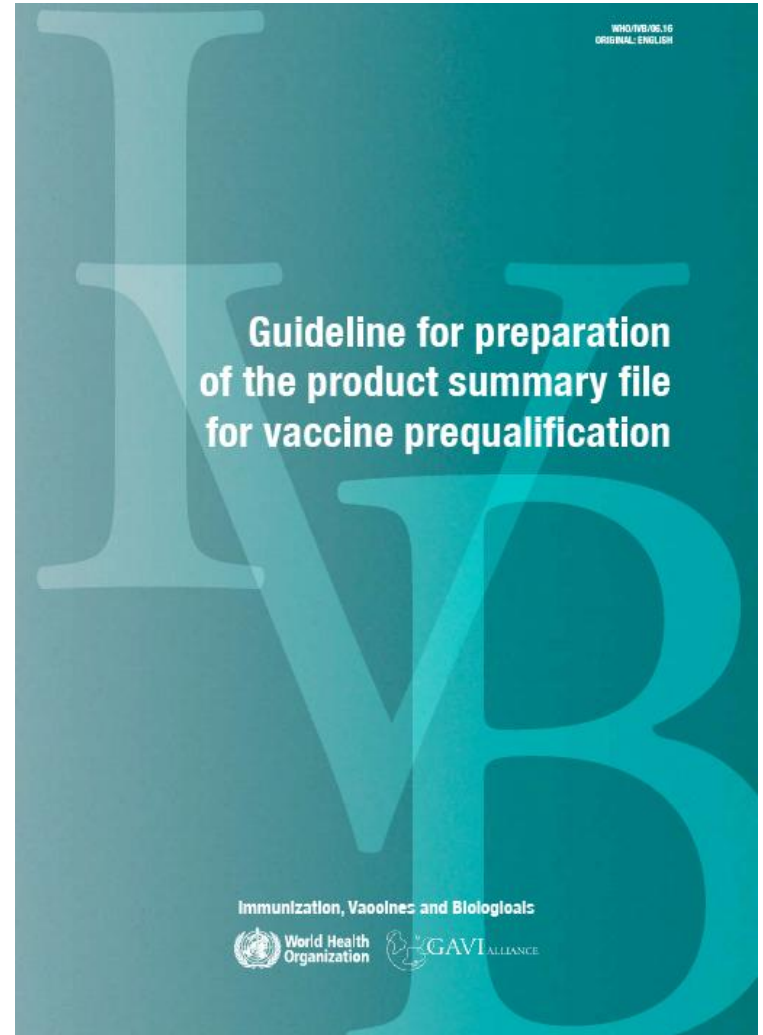


Guideline For the Preparation of the Product Summary File for Vaccine Prequalification⁴

- Chapter 7 in this Guideline provides specific requirements for inclusion in the product dossier submission regarding stability.
- Chapter 7.2 addresses accelerated stability testing of the final product to define the VVM category to be used with the specific vaccine:

“Tables of accelerated stability data are required to define the VVM category to be used with the specific vaccine (stability at 2 different temperatures are required and these are usually 2-8 C and 37 C or 45 C), However real time data establishes the expiry dating. Conclusions on stability and the claimed shelf life of the vaccine(s) should be presented.”

- Manufacturers are strongly encouraged to include 25 C as one of the accelerated test temperatures.



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.

Minimum Stability Data to Support Choice of VVM Category (except OPV)

Minimum Test Times at 25 C and 37 C

Test Temperature (C)	Test Times (days)
37	7, 14 and 30
25	45, 90 and 193

- These test times are coincident with the upper limit times in the VVM Performance Specification.
- These test times should be considered as the minimum requirement.
- Additional testing is encouraged.
- Tests should be continued until product failure, if possible.
 - For example, do not stop the test after 7 days at 37 C, continue testing at 14 days and 30 days.
 - Do not stop the test if a single assay is below the product specification.
- Some vaccine formulations are very stable towards heat exposure. Manufacturers should consider extending tests at 37 C to 45 and 60 days or longer as appropriate. Similarly extended test periods at 25 C should also be considered.

Selection of VVM Category

Example: Product A

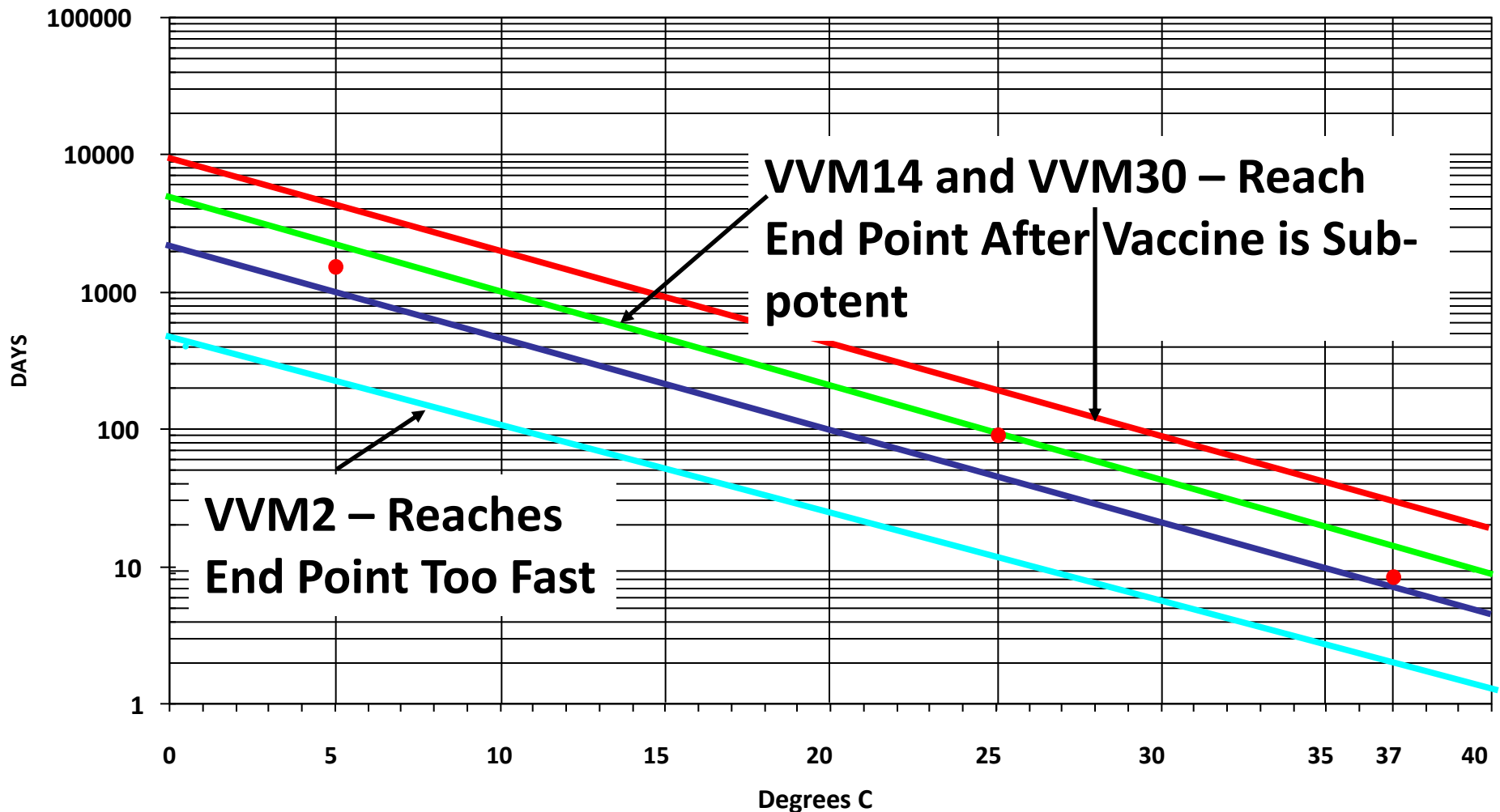
Step 1: Summarize stability data

- 2 to 8°C¹: 3+ years (1600 days)
- 25°C: 90 days
- 37°C: 8 days
- Expiry Date: 2 years

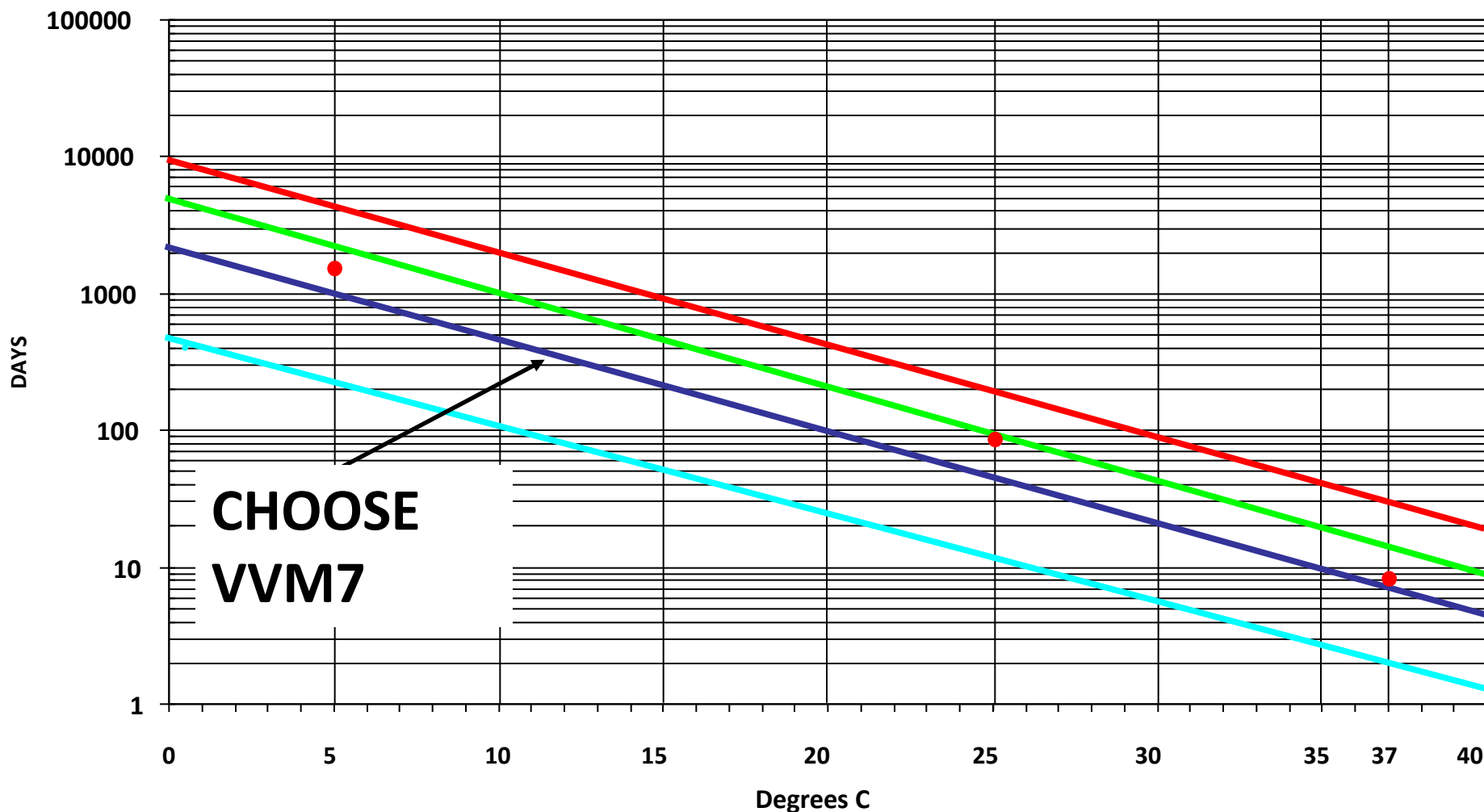
Step 2: Compare Stability Data with VVM Categories

¹2 to 8 C is treated as 5 C

Product A: VVM Choice and Rationale



Product A Stability Data and VVM Categories



Summary – Vaccine Stability and VVM Category

- VVM is a critical characteristic for WHO prequalification
- Sufficient stability data needs to be included in the Product Summary File to support the choice of the longest VVM category available
- Accelerated degradation studies must be carried out for sufficient duration to reach end of product life at the accelerated temperature
- Stability data and VVM category request submitted to WHO in Product Summary File
- WHO approves the VVM category for a particular vaccine
- Notification of VVM category is provided to manufacturer and Temptime

Why Should a Vaccine Manufacturer Implement VVM?

- VVM helps improve global health!
- VVM is good for business!
 - VVM is a critical characteristic for WHO prequalification
 - Case Study – Rotateq/Rotarix
 - VVM is has been adopted and is being introduced in countries outside of PQS requirement
 - Case Study – China
 - US consideration

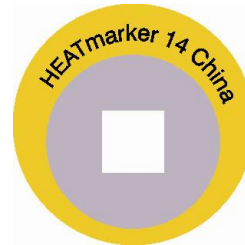
Case Study: Rotarix and RotaTeq Vaccines

A Cost Effectiveness and Capacity Analysis for the Introduction of Universal Rotavirus Vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines

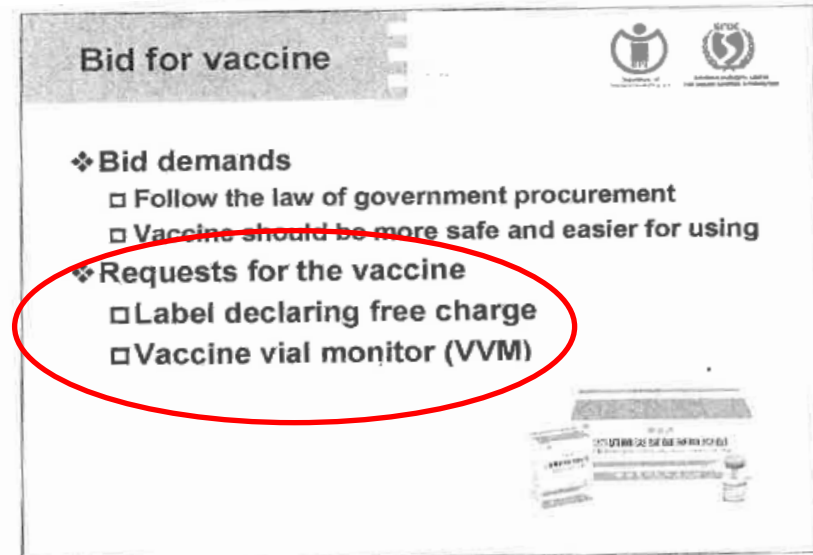
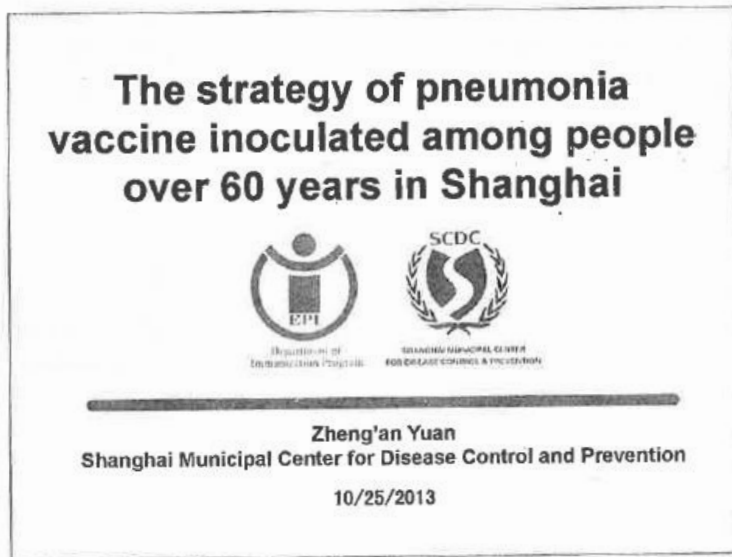
Albert Jan van Hoek¹, Mwanajuma Ngama^{2*}, Amina Ismail³, Jane Chuma², Samuel Cheburet⁴, David Mutonga³, Tatu Kamau⁵, D. James Nokes^{2,6}

- Conclusion:
 - Vaccination against rotavirus disease is cost-effective for Kenya irrespective of the vaccine.
 - Of the two vaccines Rotarix was the preferred choice due to
 - a better cost-effectiveness ratio
 - the requirement of fewer doses
 - less storage space
 - proven thermo-stability and
 - **presence of a vaccine vial monitor (VVM)**

Case Study: China



Shanghai CDC Implements HEATmarker® VVM on Pneumococcal Vaccine



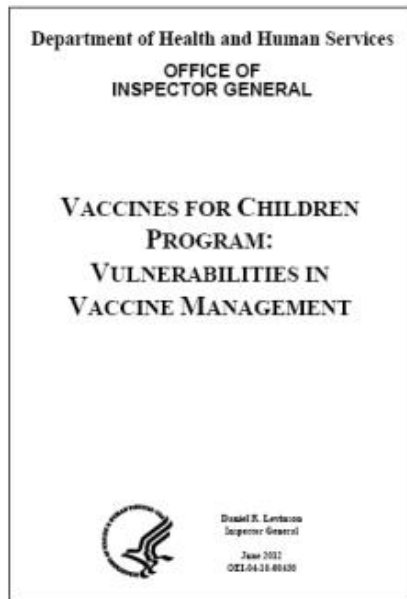
- Decision in October 2013 to implement VVM on pneumo
- Shanghai CDC extending the use to five vaccines

Beijing CDC Launches HEATmarker® VVM for 2014 Flu Vaccine Program



NCDC to launch a study covering 5 vaccines in three provinces

Case Study: Developments in US Policy for VVMs



Vulnerabilities in Vaccine Management¹ Office of Inspector General June 2012

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

Ice on box of
influenza vaccine



National Vaccine Advisory Committee – Minutes of September 2013 meeting to Assistant Secretary of Health

“Visual indicators of quality on the packaging may be further explored. The World Health Organization (WHO) already uses vaccine vial monitors in warm climates. Freeze threshold indicators could address the most common problem in U.S. clinics.”

Developments in US Policy for VVMs and FREEZEmarker



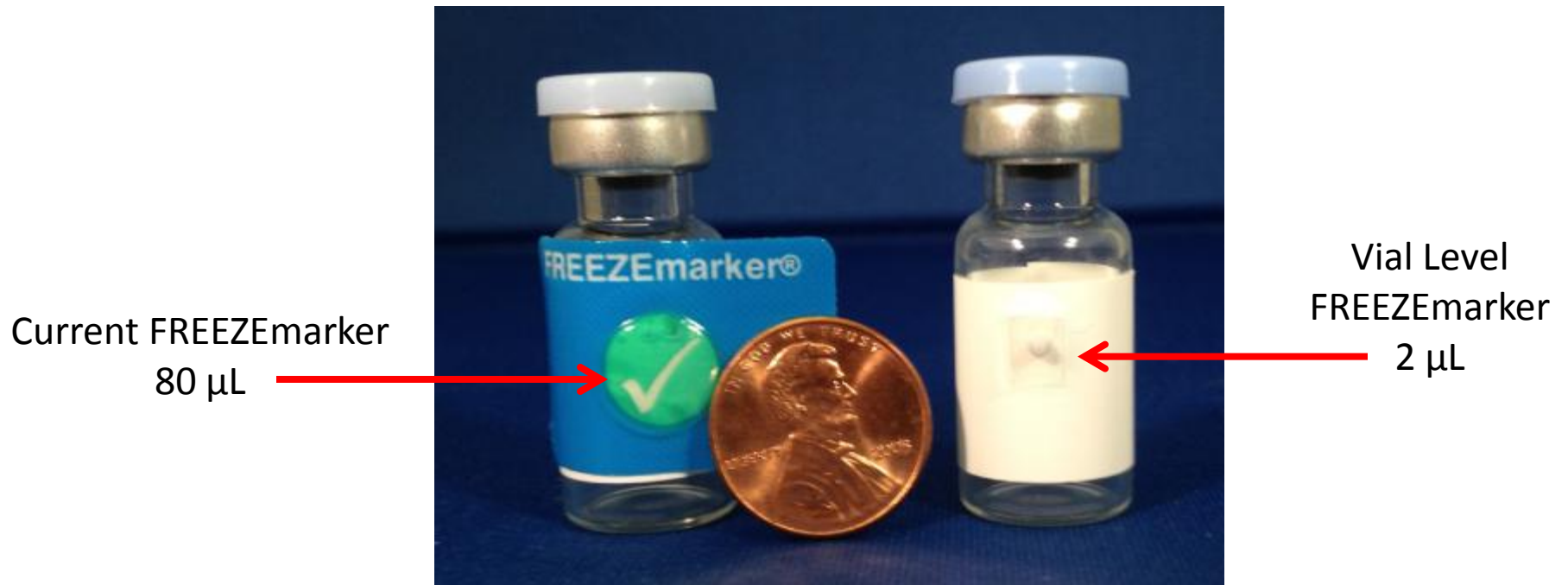
Audio from
September 2013
NVAC Meeting

National Vaccine Advisory Committee – February 2014 meeting

- National Vaccine Program Office (NVPO) is organizing Vaccine Storage and Handling Forum with VVMs and freeze indicators on agenda
- CDC and American Academy of Pediatrics (AAP) are supportive to participate in the forum
- NVPO contacted WHO to ask for representation and speak on VVM technology and value
- Temptime is asking for assistance to identify AAP members with VVM knowledge who could share their positive experience with VVM

Innovations

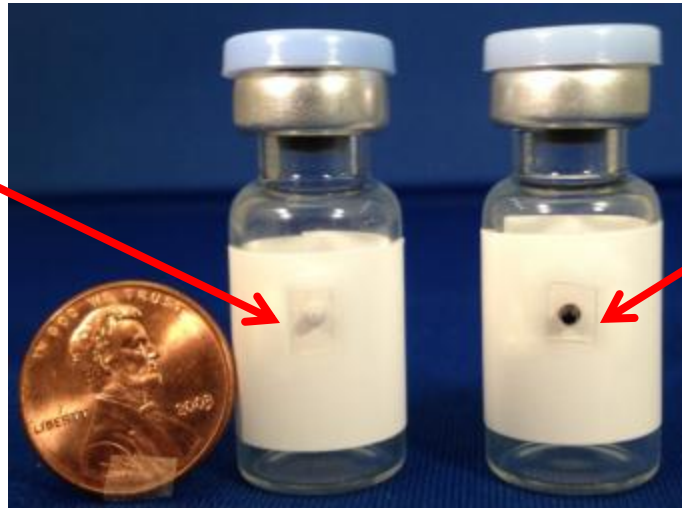
Vial Level Freeze Risk Indicator



The NEXT little big thing!



Before Freezing



After Freezing

- Unambiguous grey to black color change
- Clearly demonstrates that even 2 μ L volume is easily distinguished
- This is not a final design, simply proof of concept

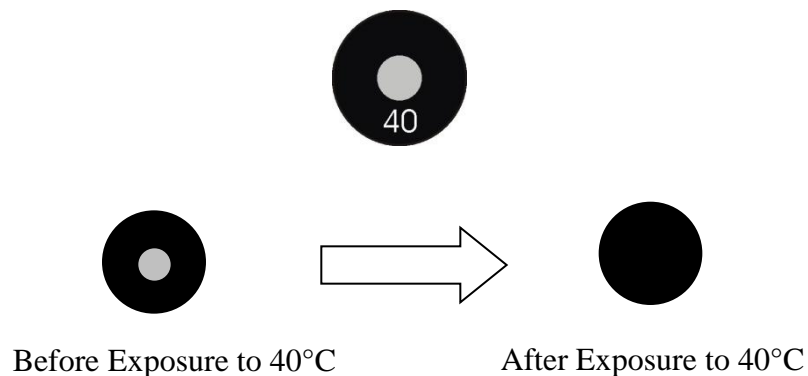
The Next Challenge – Controlled Temperature Chain (CTC)

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

- First pilot conducted on MenAfriVac in Banikoara, Benin in November 2012.
 - Over 155,000 people vaccinated using MenAfriVac in a CTC
 - VVM on each vial



- And Temptime's LIMITmarker™ in each vaccine carrier



New Product Concept – VVM+ VVM plus Peak Indicator

Temptime is BMGF GCE Grant Awardee



+



VVM

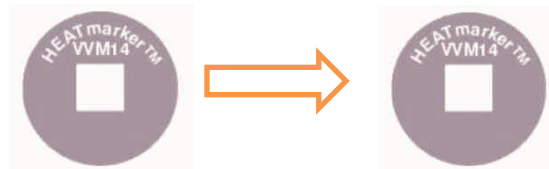
- VVM active square is translucent and the substrate color is seen through the monomer

Reactive Substrate

- Substrate develops color quickly at high temperature

Response after short exposure to 40°C

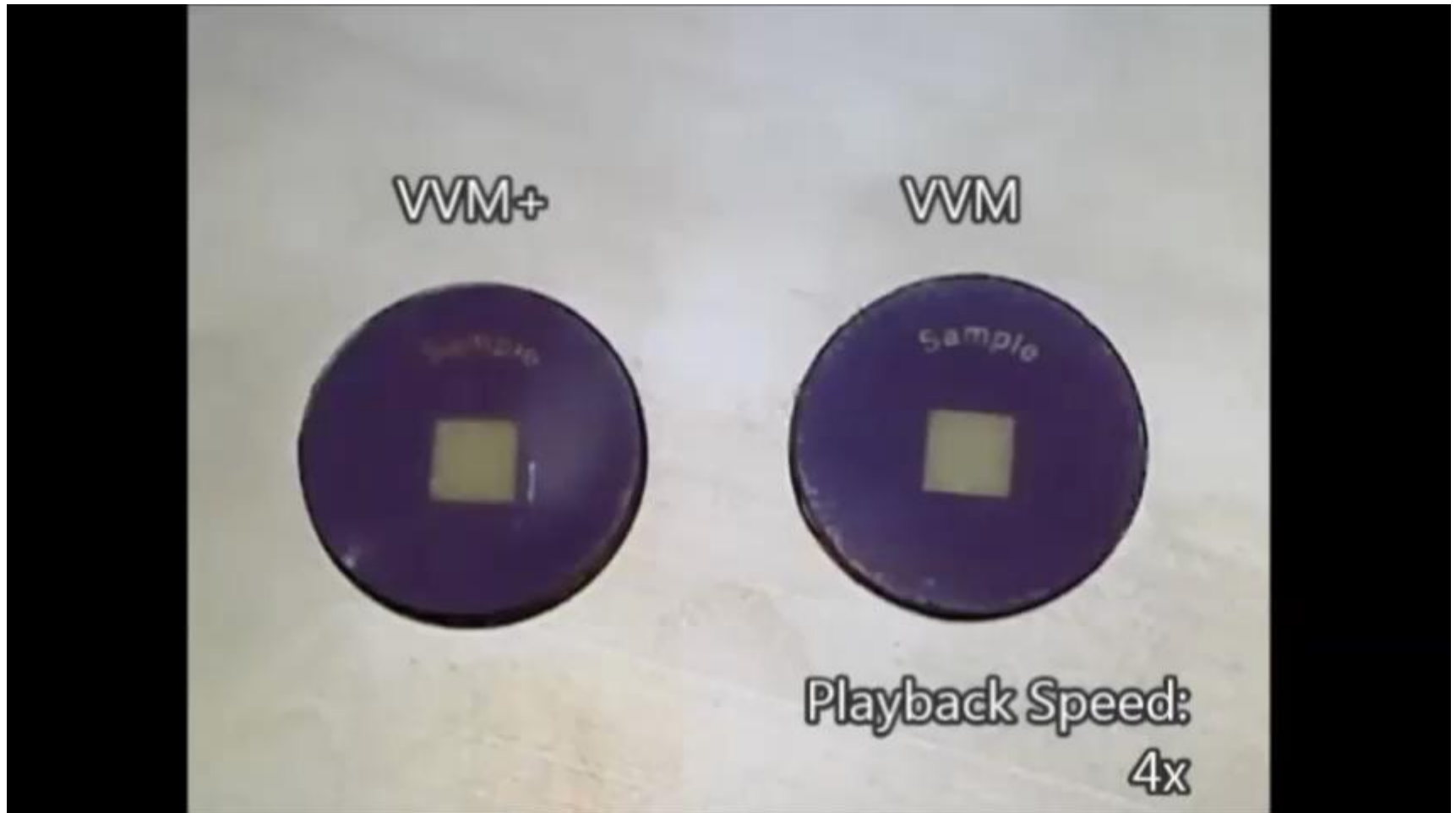
VVM



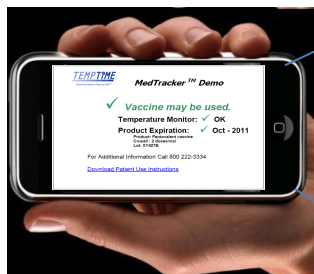
VVM+™



Comparison of VVM+ and VVM at 40°C



✓ MedTracker®



TEMPTIME
Protecting Patients • Reducing Risk™

MedTracker™ Demo

✓ **Vaccine may be used.**

Temperature Monitor: ✓ OK

Product Expiration: ✓ Oct - 2011

Product: Pentavalent vaccine
Cruell : 2 doses/vial
Lot: XY427B

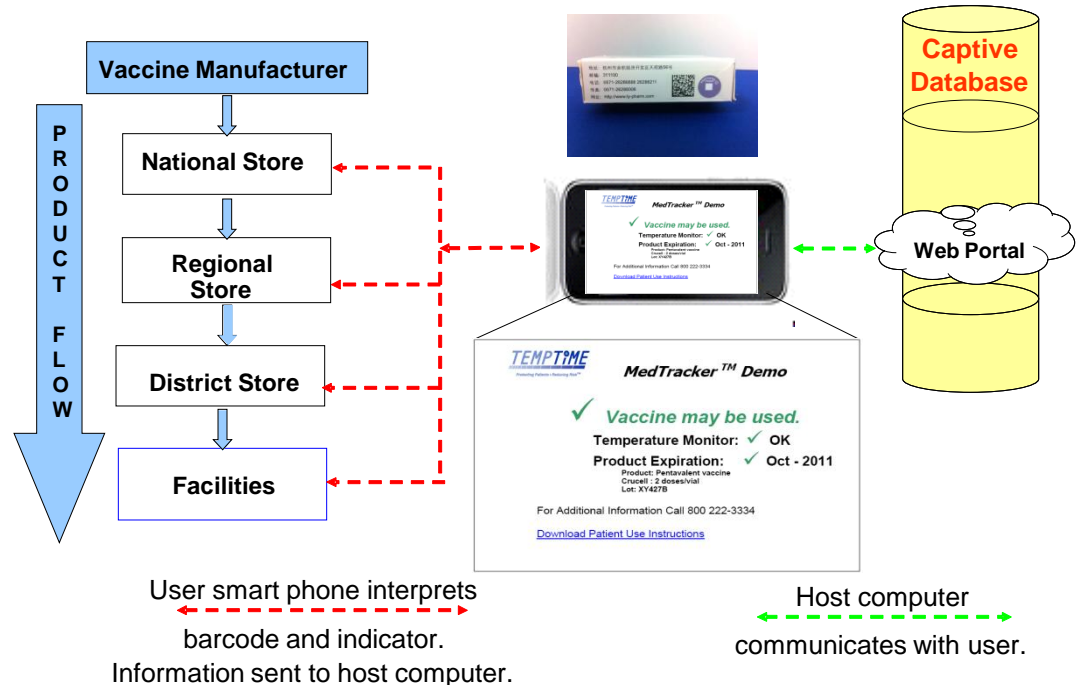
For Additional Information Call 800 222-3334

[Download Patient Use Instructions](#)

Typical Product and Information Flow



MedTracker - Vaccine Public Market Pilot



The Wall Street Journal news department was not involved in the creation of this content.

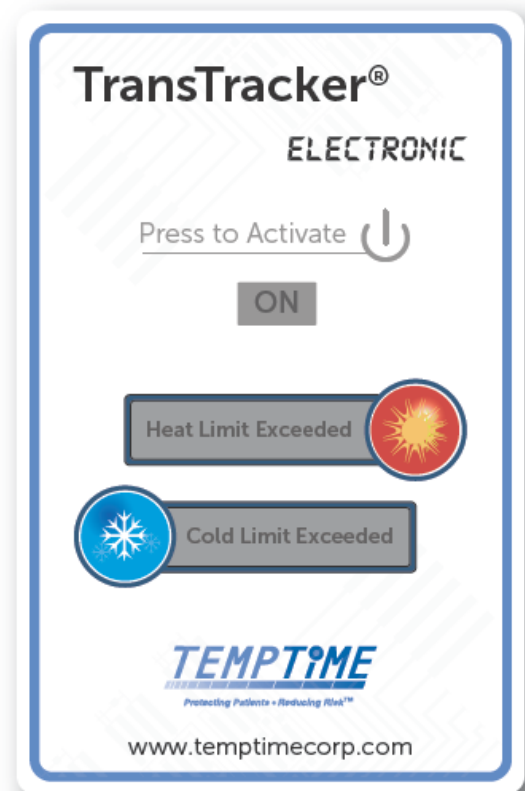
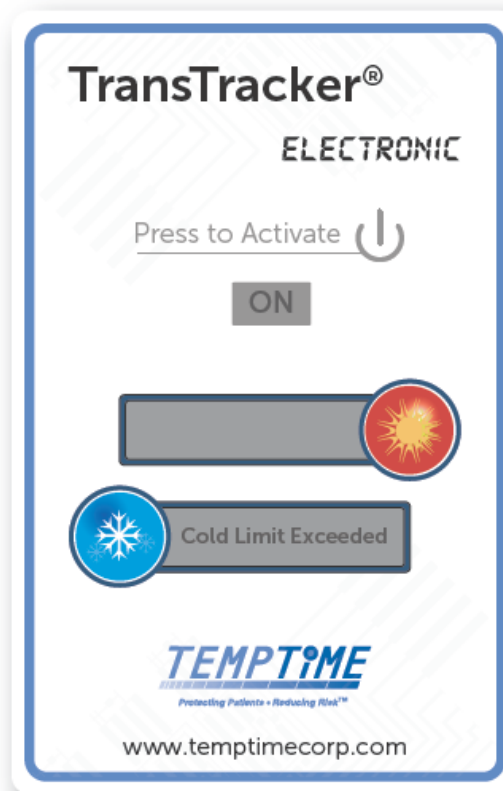
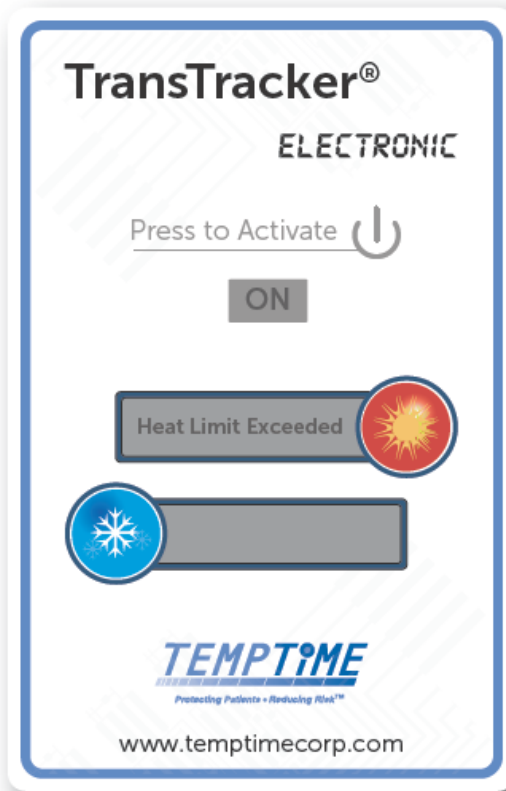
PRESS RELEASE | March 31, 2014, 6:05 a.m. ET

Thinfilm and Temptime Collaborate to Deliver Printed Electronic Temperature Indicators for Use in Distribution, Storage and Management of Sensitive Medical Products



- Printed Electronics Technology
- Credit Card Sized Device
- Indicates High or Low Excursion
- Irreversible & Disposable
- Lower Cost than Standard Electronics

Printed Electronics to Detect Temperature Excursions



Graphics and messaging TBD

Integrated wireless facility and transport monitoring solution

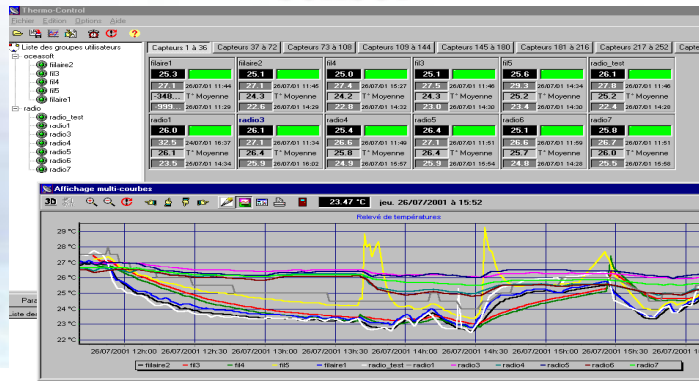
Cobalt wireless Datalogging solution from Oceansoft France
System Configuration



Cobalt radio Modules with
sensor



Cobalt Radio Receiver
and Repeater



Thermo software (server/ client based)

Integrated wireless facility and transport monitoring solution

Facility Monitoring Solution

- Wireless Datalogging System

SECTOR

- Pharmaceutical
- Food
- Laboratory
- Hospital

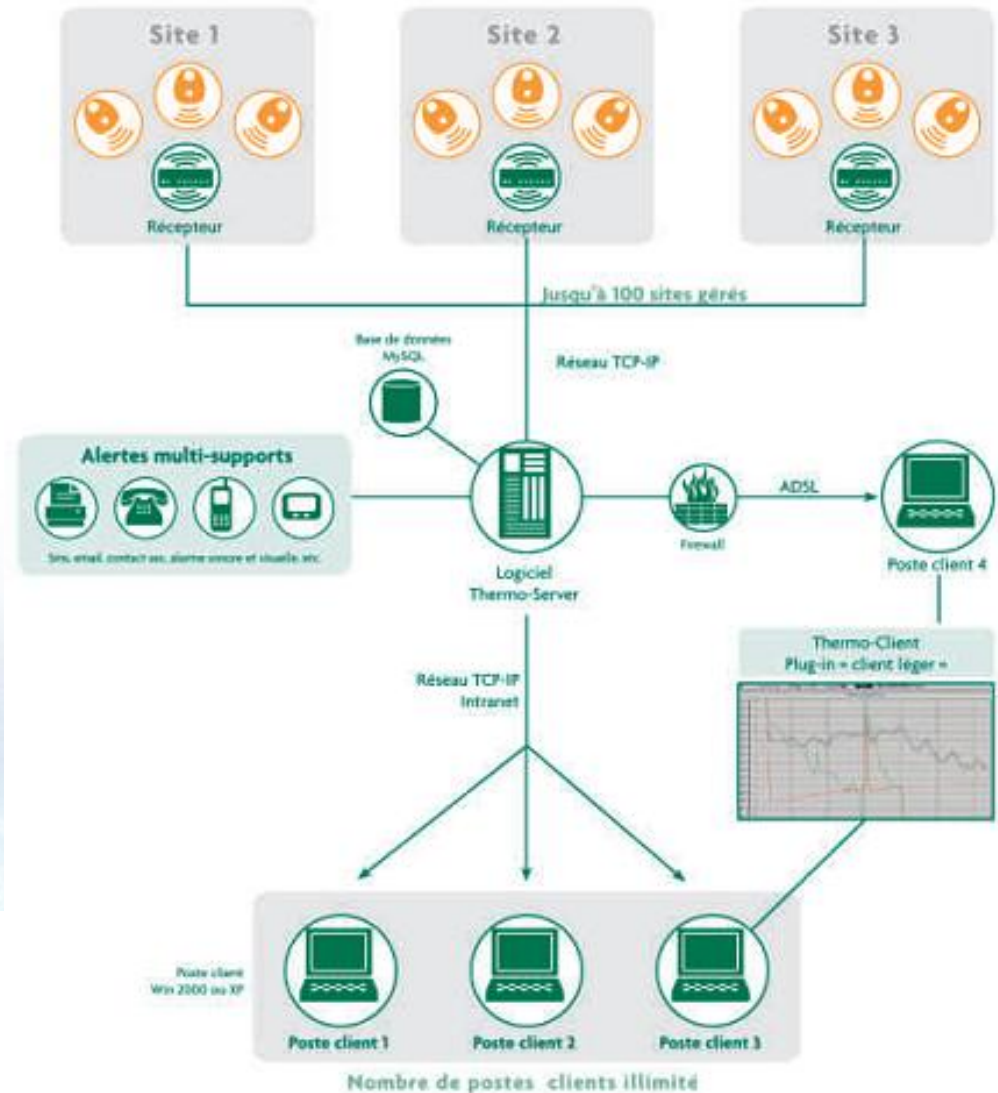
MONITORING

- Manufacturing Area
- Distribution Centers
- Transportation Vehicles
- Laboratory equipments

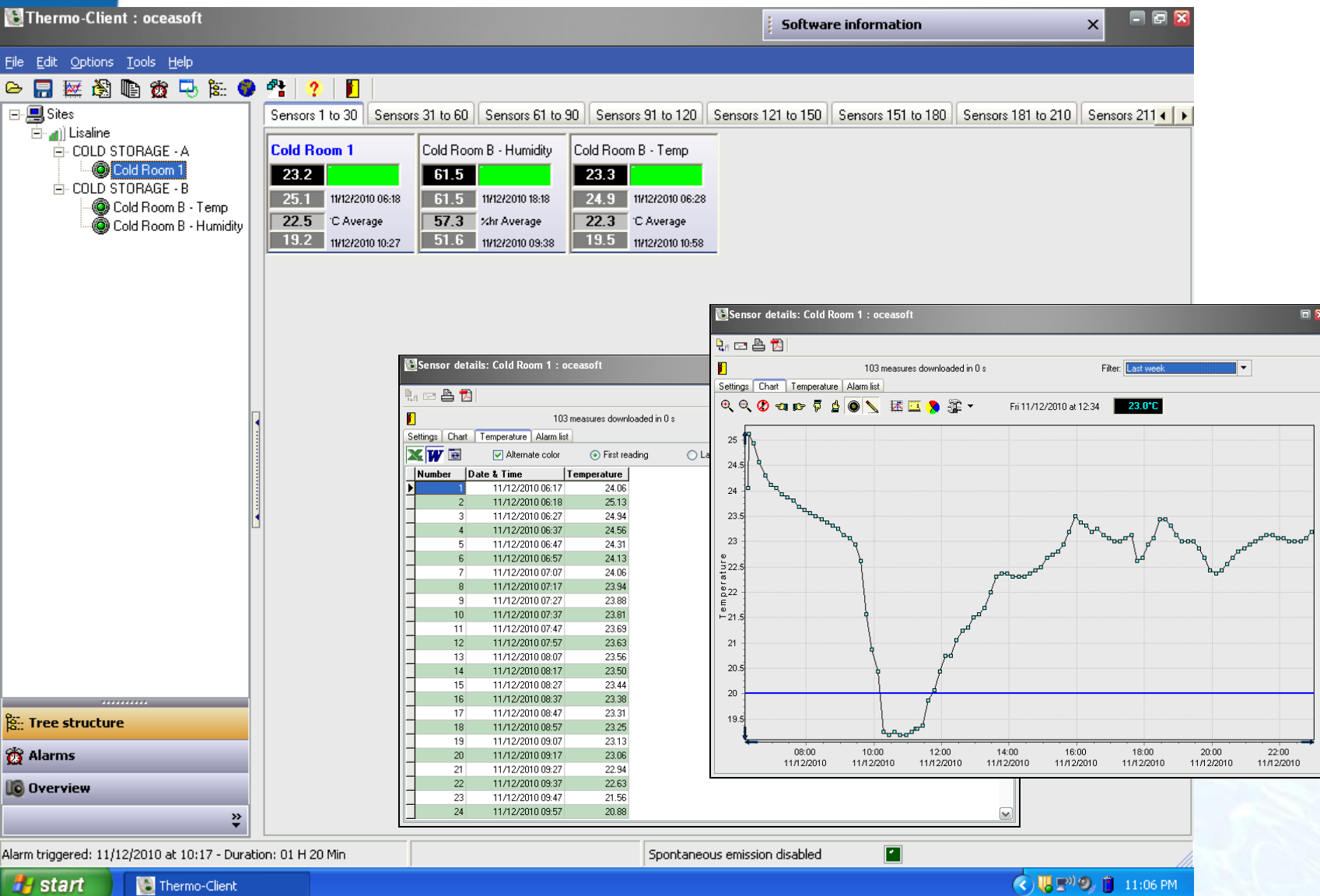


Integrated wireless facility and transport monitoring solution

Multiple location Real time Monitoring Solution



Cobalt – Real time monitoring snap view



Cobalt – Real time monitoring snap view

The screenshot displays the 'Sensor settings : oceasoftware' window. The left sidebar shows a tree view of sites: 'Lisaline' contains 'COLD STORAGE - A' (with 'Cold Room 1' as a sub-item) and 'COLD STORAGE - B' (with 'Cold Room B - Temp' as a sub-item). The main panel is divided into two tabs: 'Sensor parameters' and 'Alarm parameters'. The 'Sensor parameters' tab is active, showing four analog gauges for 'Transfer interval' and 'Measurement interval', each with 'Hours' and 'Minutes' digital readouts. Below the gauges, there are settings for 'Unit' (Temperature), 'Sensor' (Temperature), 'Mobile module' (unchecked), 'Use datalogging' (checked), and a 'Restart datalogging' button. A slider for 'Number of tries before "Error Absence" displayed' is set to 2. At the bottom, there is an 'Active' status indicator, a 'Sensor name' field (Cold Room B - Temp), and a 'Modify sensor name' button. The 'Alarm parameters' tab shows settings for 'Upper alarm' (28.0 °C), 'Pre-Alarm' (0.0 °C), and 'Temporization' (00:00). The 'Alarm parameters' tab also shows settings for 'Lower alarm' (20.0 °C), 'Pre-Alarm' (0.0 °C), and 'Temporization' (00:00). At the bottom of the window, there are buttons for 'Corrections', 'Load corrections', and 'Close'.

Sensor settings : oceasoftware

Add / Update wireless module | New group | Rename a group | Delete | Print settings

Sites

- Lisaline
 - COLD STORAGE - A
 - Cold Room 1
 - COLD STORAGE - B
 - Cold Room B - Temp
 - Cold Room B - Humid
 - Validation Cold Pack 1
 - Validation Cold Pack 2
 - Validation Cold Pack 3
 - Validation of Cold Pack
 - ZRC

Sensor parameters | Alarm parameters

Transfer interval

Hours: 01:00 Minutes: 00

Measurement interval

Hours: 00:10 Minutes: 00

Unit: Temperature

Sensor: Temperature

☐ Mobile module: Module used for transportation

☒ Use datalogging | Restart datalogging

Number of tries before "Error Absence" displayed: 0 2 4 6 8 10

☒ Active

Sensor name: Cold Room B - Temp | Modify sensor name

Corrections | Load corrections | Close

Alarm parameters

Upper alarm: 28.0 °C | On

Pre-Alarm: 0.0 °C | On

Temporization: 00:00 | On

Lower alarm: 20.0 °C | On

Pre-Alarm: 0.0 °C | On

Temporization: 00:00 | On

Corrections | Load corrections | Close

THANK YOU!