

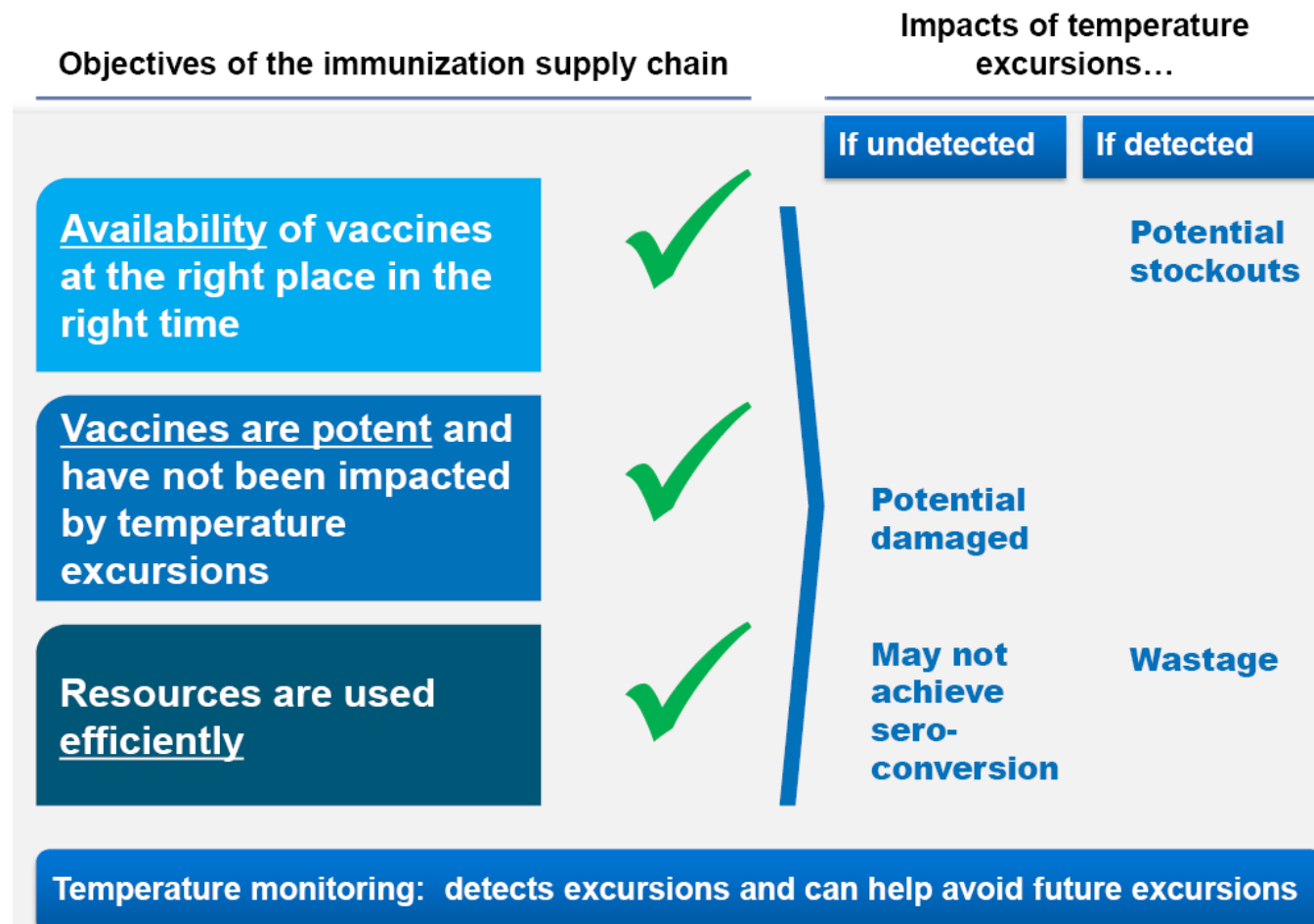
# Effective Monitoring of Vaccine Cold Chain

## GMP Aspects

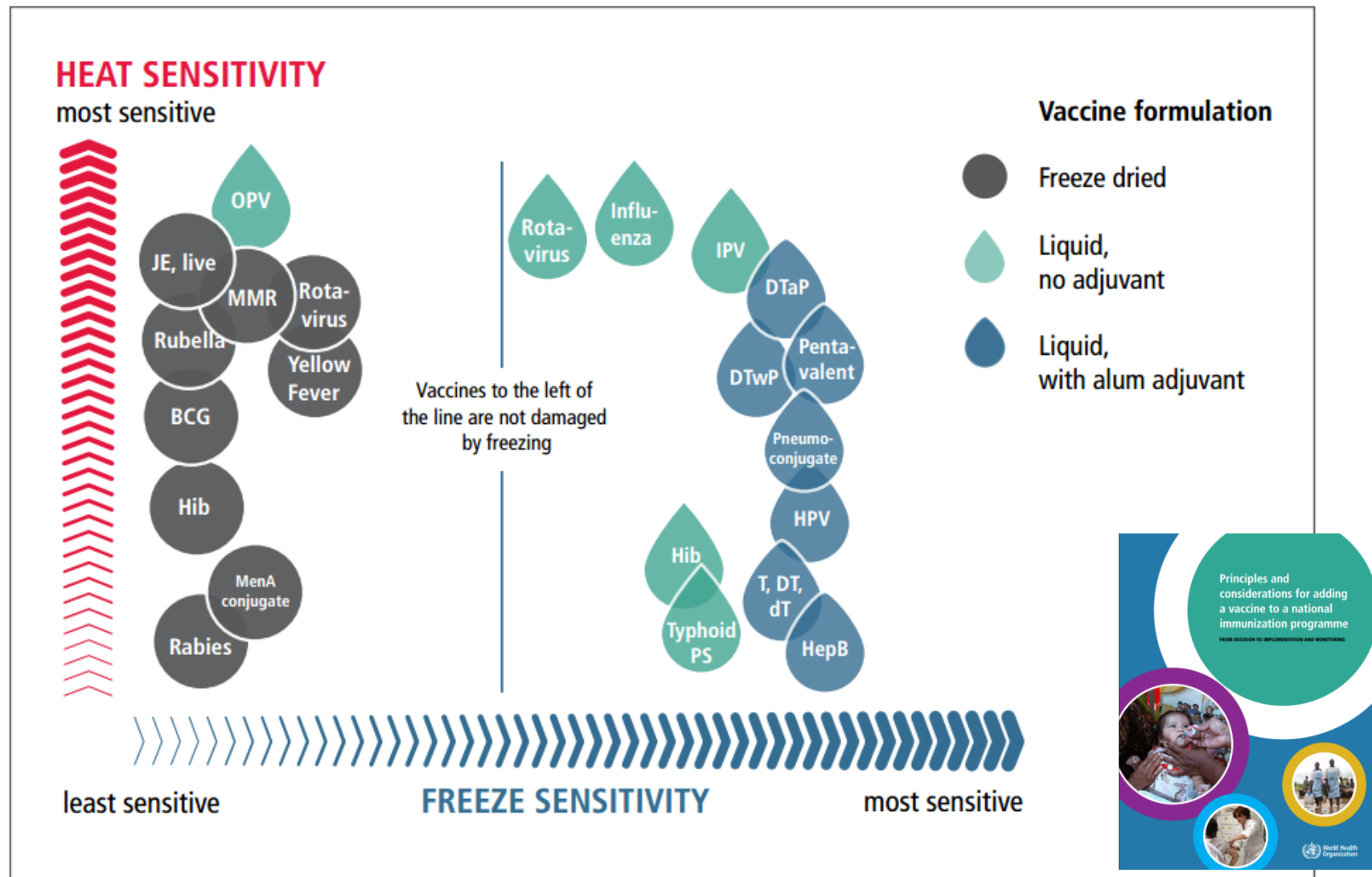


04 April 2017

# Why bother about temperature monitoring ?



# 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.

# Vaccine exposure to Heating & freezing

## - Current reality

Too hot  
“Easier to detect”



Health worker in Niger shows bottles with vaccine vial monitors. Source: WHO

### What do we know from the EVM Data Analysis

Over 90% of storekeepers and health workers know how to read VVMs.



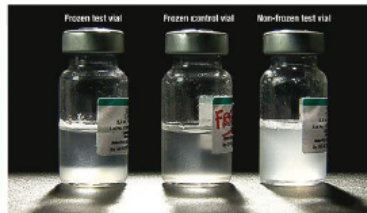
“What about excursions during weekends?”

Continuous temperature monitoring

Too cold  
“Harder to detect”



Example Freeze indicators



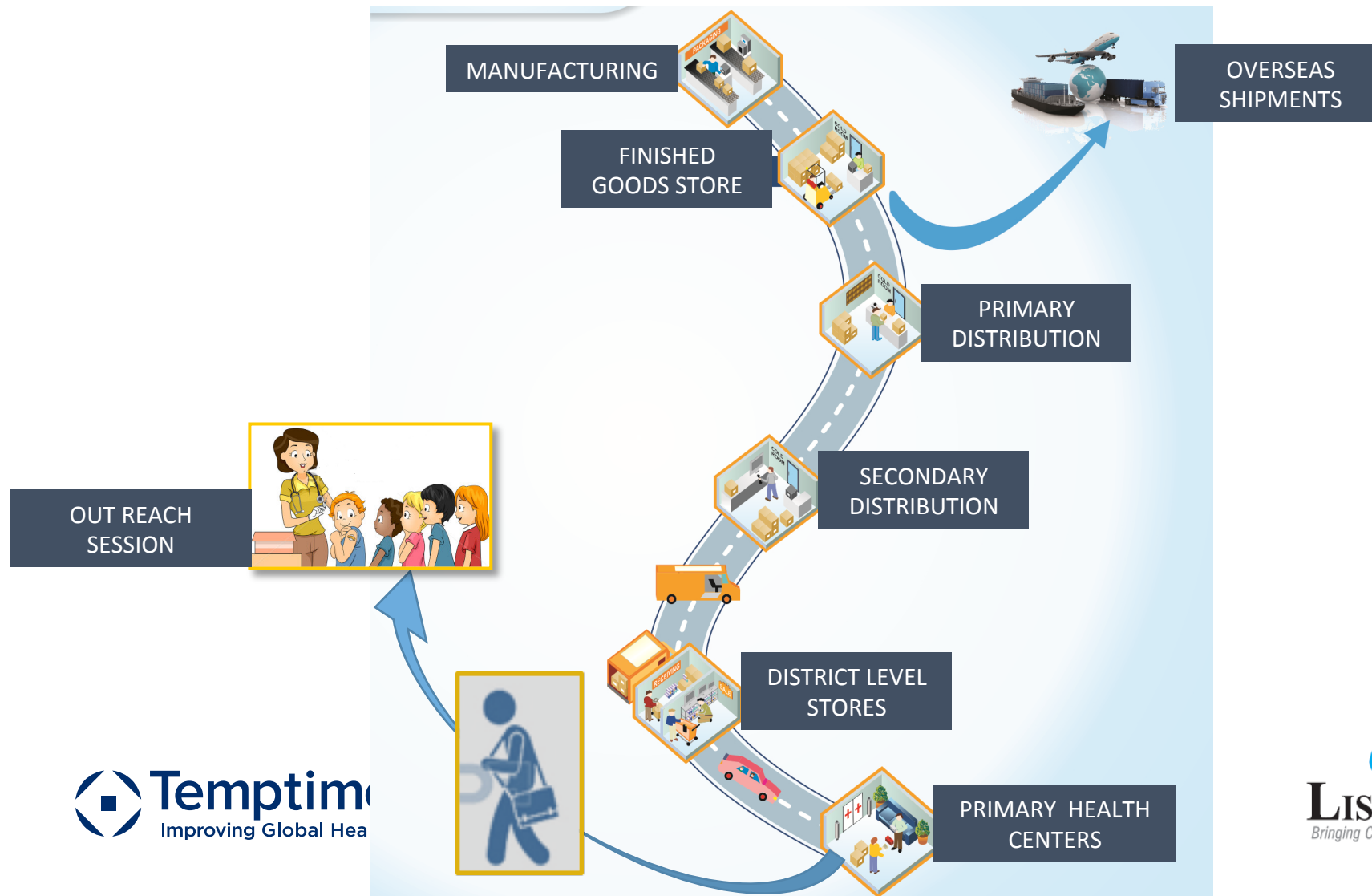
Shake test. Source WHO

Only 11 % of facilities pack freeze indicators with deliveries of freeze-sensitive vaccines

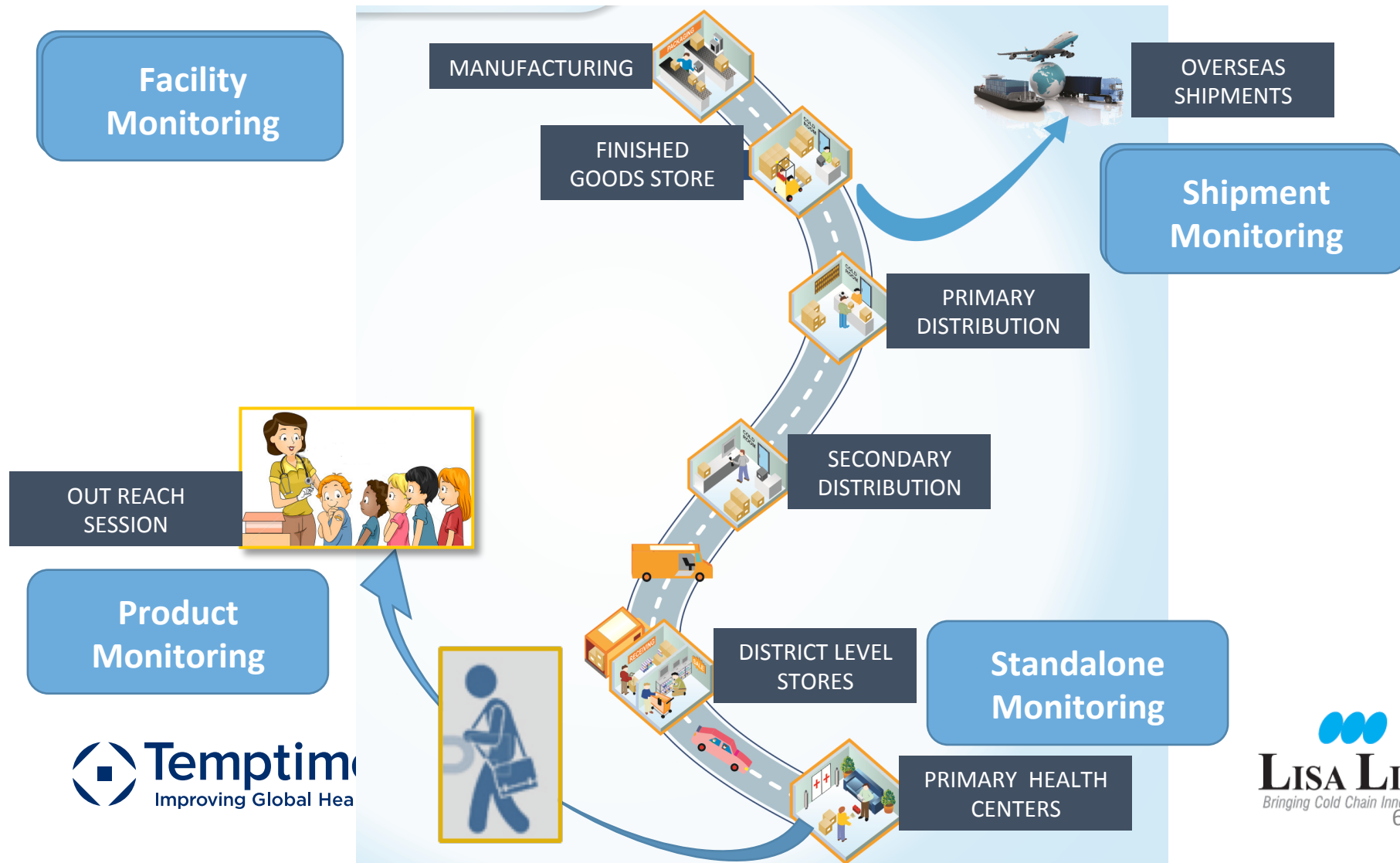




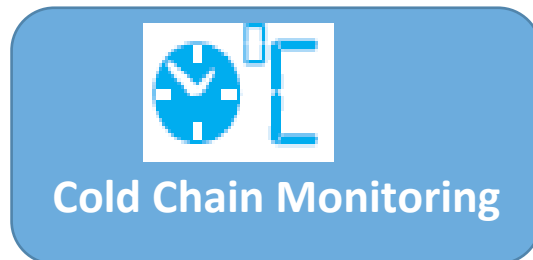
# Challenges in vaccine Cold Chain management



# Challenges in vaccine Cold Chain management



# Approach to effective vaccine Cold Chain management



Product  
Monitoring



With active  
cooling system



Facility  
Monitoring



With passive  
cooling system



Shipment  
Monitoring



Standalone  
Monitoring

# Guidelines for Vaccine Manufacturers

## Receipt, Storage and Use

### of HEATmarker® VVM

### GMP Aspects

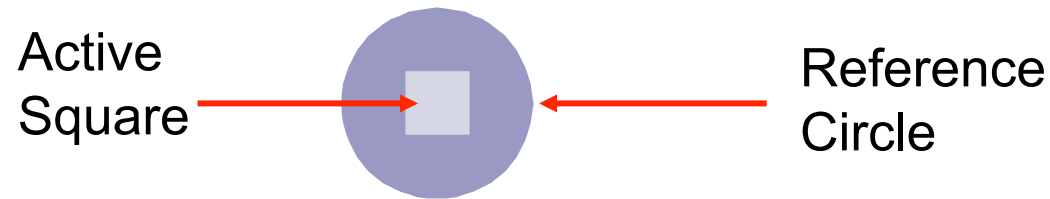
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04 April 2017

# VVM - Definition

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- A vaccine vial monitor (VVM) is a label containing a heat sensitive material which is placed on a vaccine vial at the time of manufacture to register cumulative heat exposure over time
- 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 VVM 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**



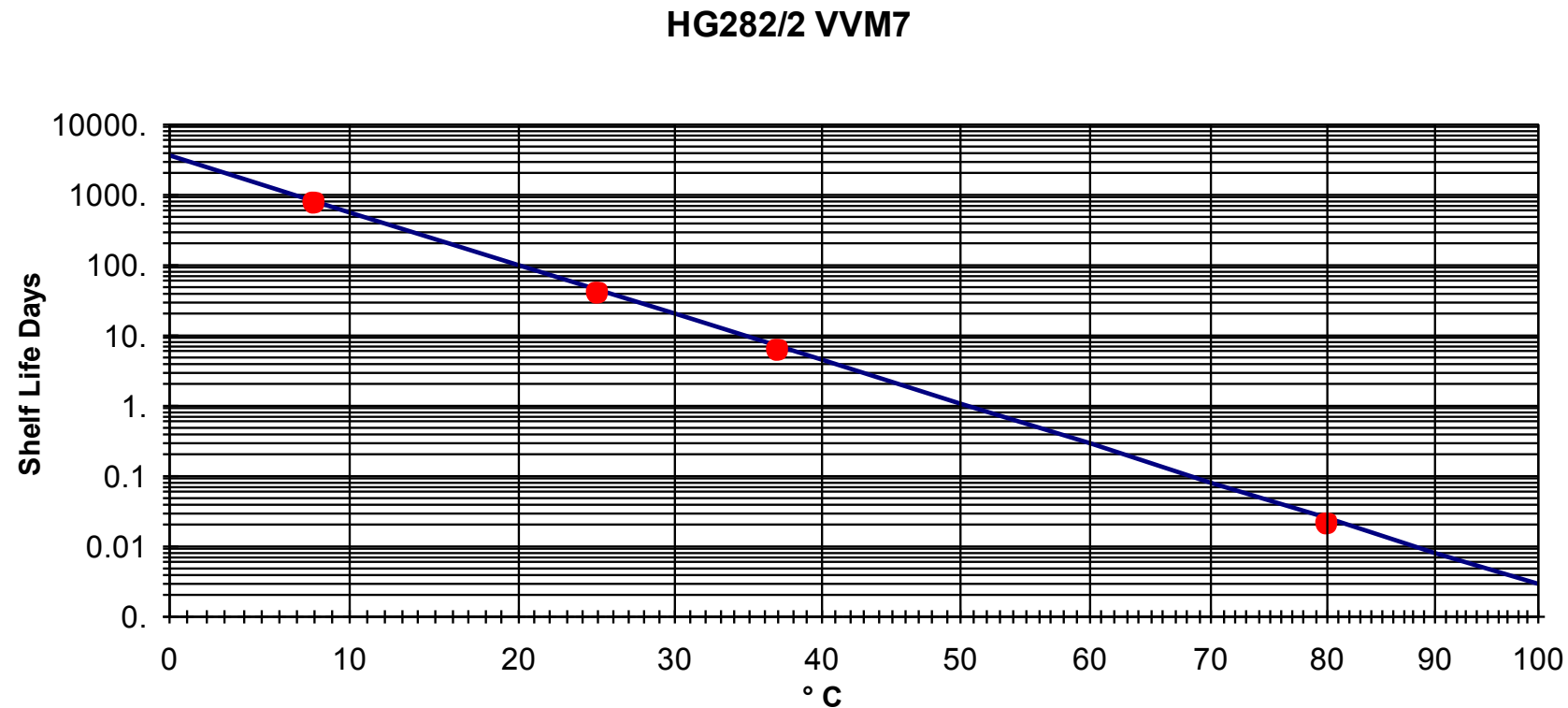
**DO NOT  
USE**



**DO NOT  
USE**

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

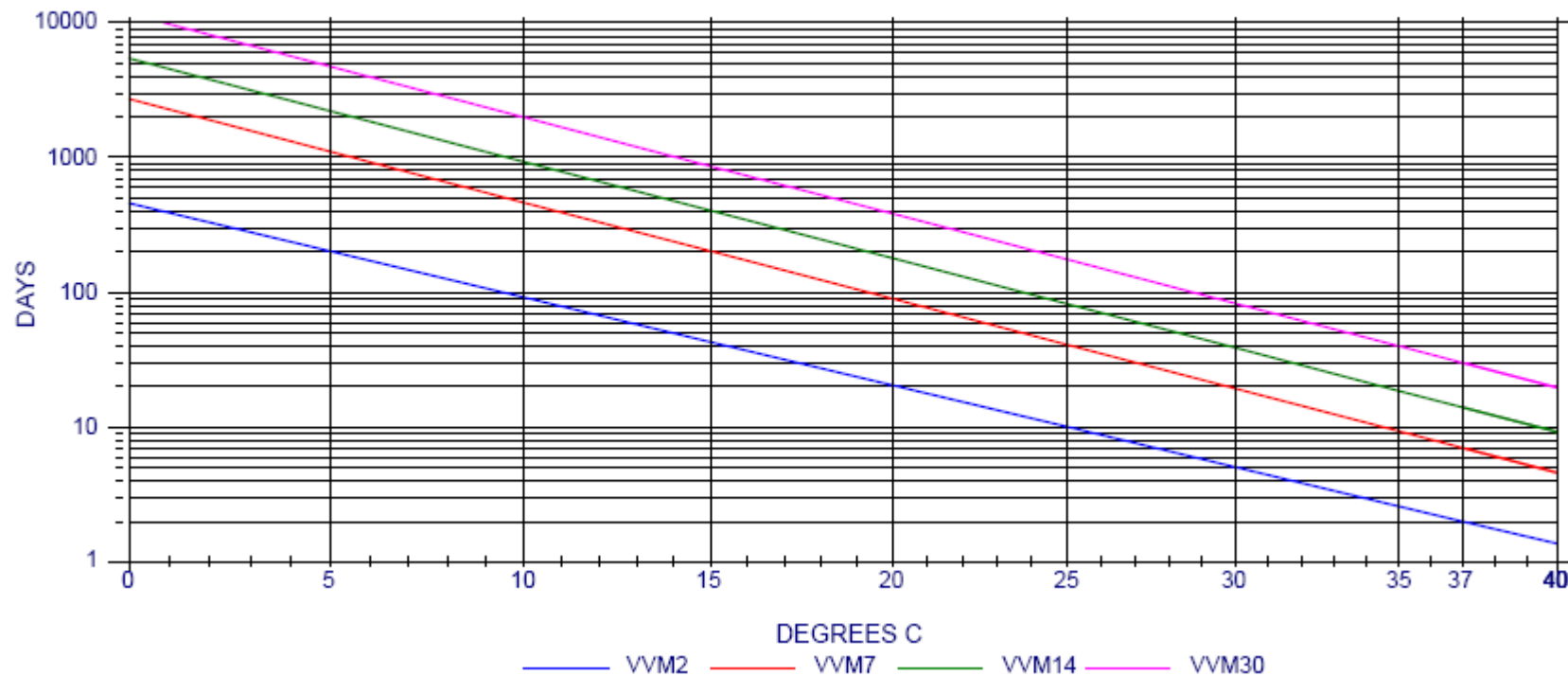
# VVMs have a well defined Arrhenius temperature relationship over time



● Time for VVM to reach end point

# Four WHO VVM categories



HEATmarker VVMs - Time to VVM Endpoint



VVM category chosen is correlated to vaccine stability

# HEATmarker VVM for use on vaccines

Over 650 million VVMs used last year

<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"> <li>• BCG</li> <li>• Diphtheria</li> <li>• Tetanus</li> <li>• Pertussis</li> <li>• DTP</li> <li>• Hep B</li> <li>• HiB</li> <li>• Meningococcal A and C</li> <li>• Measles</li> <li>• Mumps, Pneumococcal</li> <li>• OPV</li> <li>• Rotavirus</li> <li>• Rubella</li> <li>• Tetanus Toxoid</li> <li>• Yellow Fever</li> </ul> <p>Other Campaigns:</p> <ul style="list-style-type: none"> <li>• HPV</li> <li>• IPV</li> <li>• Rabies</li> <li>• Typhoid</li> </ul>	<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, Bio-Manguinos, plus others</p>	 <p>VVM2, VVM7, VVM14, VVM30</p>	<ul style="list-style-type: none"> <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>

# WHO e-VVM Based Vaccine Management Course

ePELA<sup>3</sup> extensio et progressio / authentic e-learning

e-VVM Based Vaccine Management Course

World Health Organization

The little big thing

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

00:29

HD :: vimeo

Introduction Video

Learning Objectives

Programme

Document Library

Video Library

BACK FORWARD



# Steps to HEATmarker VVM Implementation

---

1. Vaccine Manufacturer Submits Dossier to WHO for Prequalification
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

# Equipment Required at Vaccine Manufacturers

Frozen storage



Temperature monitoring and recording



Temperature controlled water bath for validation and control



Reflection densitometer for objective measurement of VVM color



Automatic label application equipment



# Receipt and Inbound Inspection

The receiving inspection process begins on the day the HEATmarker VVM's are delivered.

VVMs are normally shipped in an LD3 container with the VVMs packaged on a wooden pallet,



Alternatively, VVMs are sent in insulated shippers containing VVMs packaged with dry ice.

# Verification of Proper Transport Conditions

- Due to the sensitivity of the VVM, proper transport conditions are imperative
- Vaccine manufacturers need to be prepared to react immediately upon arrival to verify proper transport conditions and **move the VVM into frozen storage**

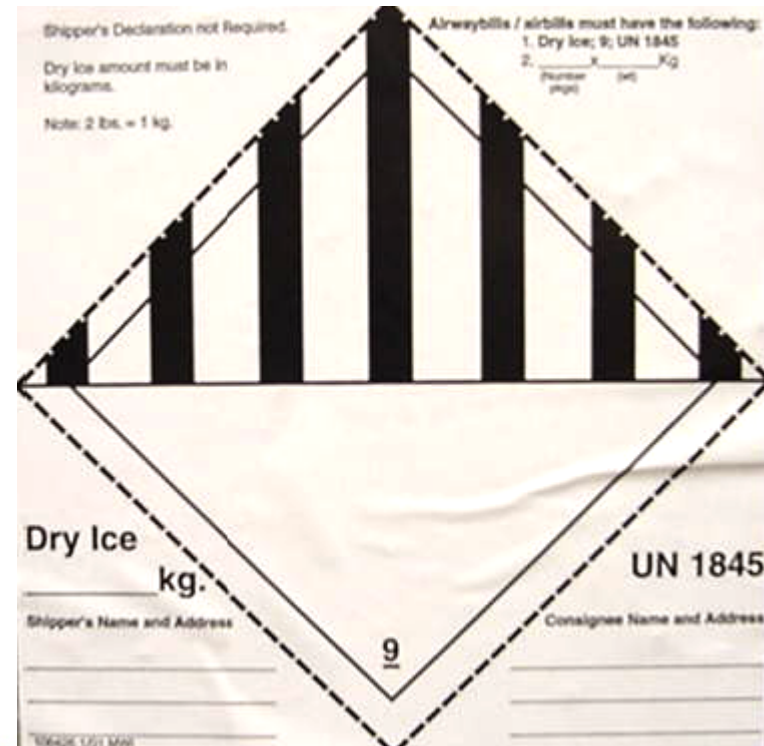




# Inspection to Verify Presence of Dry Ice – LD3

The first level of inspection of transport is the presence of dry ice. In addition to dry ice being placed in the LD3 container outside the insulated carton, select boxes of dry ice inside the carton contain dry ice only (no product). These boxes are marked with a black and white dry ice label. Proper safety procedures and equipment must be used when handling dry ice.

Dry Ice Label

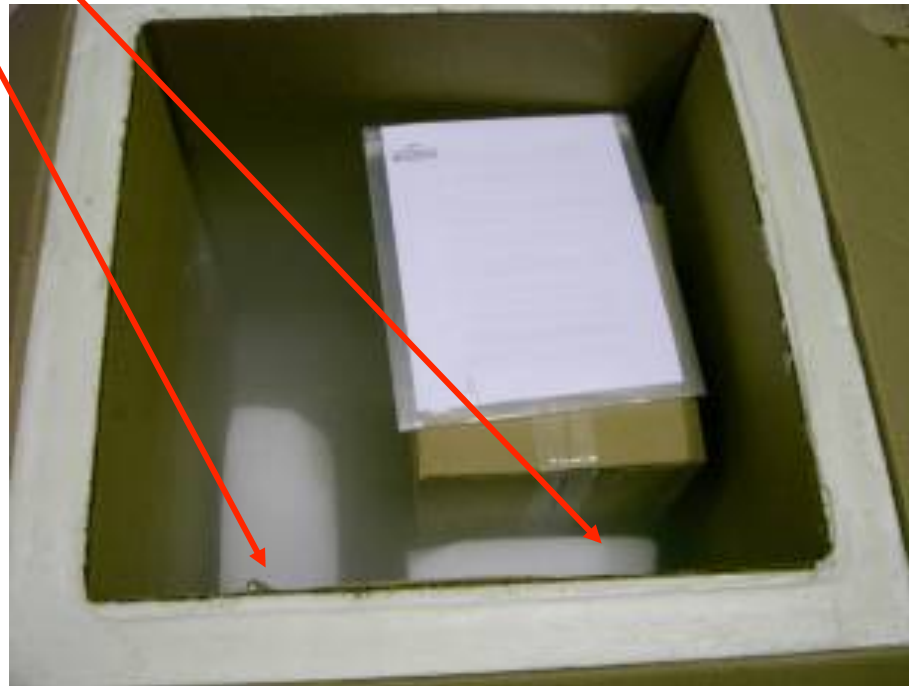




# Dry Ice in Insulated Shipper

---

Some dry ice should be present in the shipper when it is received.



# Verification of Any Physical Damage During Transport

---

- Complete inspection should be made within 24 hours after the arrival.
- Document any damage to the product with photos
- Contact the freight forwarding company immediately if damage is detected
- Notify TEMPTIME Corporation of any damage within 48 hours of delivery

SOPs for IQA must be developed

- Physical condition and VVM color

# Immediately Move Cartons of VVMs to Proper Frozen Storage

- **VVMs must be stored in the dark. VVMs can develop color changes very quickly when exposed to direct sunlight or indirect sunlight.**
  - Indoor lighting can also have an impact over time on the VVMs. Therefore VVMs should be stored in the absence of light.

VVM box should be sealed to prevent ice build-up and UV Light exposure



# Frozen Storage

- VVMs should be stored at or below  $-24^{\circ}\text{C}$  to minimize any measurable change in initial starting optical density.
  - Care should be taken when selecting a storage area within the freezer.
  - The VVMs should be kept away from the door so as to minimize temperature variations that can be as high as several degrees Celsius and cause premature color development.
  - Temperatures during frozen storage should be maintained and recorded.



## Storage Volume (depends on dot or full label)

- 10,000 VVMs per roll
- 20 rolls/carton (200,000 VVMs)
- Carton size: 23 x 25 x 41 cm

# Storage Conditions

**VVMs should be stored in packaging sufficient to avoid any deterioration of the physical properties of the VVMs.**

- For example, VVMs should be stored in sealed plastic bags to avoid condensation. VVMs should be stored in a closed carton to avoid physical damage and other appropriate steps should be taken to avoid deterioration.



VVM rolls should remain in sealed plastic bags while in frozen storage

VVM box should be sealed to prevent ice build-up and UV Light exposure



SOPs for frozen storage must be developed

- Temperature, physical condition and in the dark



# Control of VVM End Point at 37°C

- VVMs are released by lot
- A Certificate of Analysis is included each lot
- Each received lot should be sampled and tested according to the established procedure should be sampled and tested at 37°C and color of VVM measured with densitometer



SOPs for sampling, control test and release must be developed

# Example Certificate of Analysis

SAMPLE			
TEMPTIME Corporation			
CERTIFICATE OF ANALYSIS: Time-Temperature Indicators			
Lot Number:	NG019/1	TEMPTIME Part Number:	
Date of Manufacture:	19-Jan-2004	Customer:	
Quantity Approved:	1,449,470	Customer Part Number:	
TTIs Tested:	1452		
Limit Calculations and Optical Density (OD) Readings as Described in Testing Protocol P023C (January 23, 2002) approved by WHO on March 25, 2002 in conformance with WHO Specifications of March 25, 2002			
TTI Type:	VVM2	Test Time:	1.75 days
Test Temperature:	37.0°C ± 0.2	Upper OD Limit:	0.05
Lower OD Limit:	0.06		
ANALYSIS	REQUIREMENT	TEST RESULTS	STATUS
1. Average starting value of OD(Ref - Ind)	≥ 0.25 OD ± 0.02	0.00	Conforming
2. Percent above upper OD limit	≤ 5%	0.0%	Conforming
3. Percent below lower OD limit	≤ 5%	0.0%	Conforming
4. Average temperature of water bath	37.0°C ± 0.2	36.9°	Conforming
5. Layout, text, and dimensions correct	Yes	Pass	Conforming
6. Distribution of OD values			
<p>TTI Measurements at 37.0°C ± 0.2 NG019/1</p> <p>Percent of TTIs</p> <p>OD(Ref - Ind) after 1.75 days</p>			
This lot conforms to specifications and is released.			
Document prepared by:		Date:	
Document approved by:		Date:	
QCLF TTI Certificate of Analysis Rev 1			

WHO has approved Temptime Corporation's Testing protocol #P023C "Protocol for Testing and releasing a lot of HEATmarker VVMs at 37 degrees C"

Acceptance criteria for the lot are shown on the CoA.

SOPs for sampling, control test and release must be developed

# In Process Inspection & Use

- Prior to application on vaccine products, the VVMs should be inspected to verify that there has been no change in Optical Density during storage. Measure the starting initial reflectance density to verify the continuing conformance of the VVM to the acceptance criteria.
- Remove only the necessary quantity of rolls of VVMs from the freezer vault for some hours of use.
- Store the VVMs in a freezer or at least a refrigerator in or near the labeling room for in-use storage of VVMs.
- The VVMs are sensitive to light and should be properly protected from light during the labeling process.
- The roll number on each roll of VVMs provides traceability. It is important to record the roll numbers used during production.

SOPs for need to be developed for final inspection, application environment and record keeping

# Application of VVM to Vial

- VVMs can be applied manually or by automatic label application
  - Chengdu Institute of Biological Products applied 10 million VVMs manually during two years
  - Studies by Chengdu showed no difference in adhesion between manual or automatic application
- No specific VVM required temperature/humidity control of environment during label application by any manufacturer
  - VVMs are normally applied during final labeling process
  - Some manufacturers have validated cold storage in final labeling area
  - Excessive exposure to light should be avoided
- Adhesion of VVM dot to vial cap must be verified for the appropriate storage and distribution conditions of the vaccine



# Case Study 1

## **Situation:**

All vaccines with VVM 7 full labels arrive in country from manufacturer with somewhat darkened VVM

## **Root cause investigation:**

Storage temperature of finished Labeled vaccines at vaccine manufacturer for few months at temperature close to upper limit of refrigerated temperature

## **GMP deviations:**

Vaccines stored near door of walk-in cold room (actual for this case study); improper mapping of cold room ; labeled vaccine with VVM 7 was stored for > 6 months in such conditions.



# Case Study 2

## **Situation:**

Vaccine stored in country at any stage of supply chain in vaccines stores ( WIC) were found with somewhat darker VVMs

## **Root cause investigation:**

Improper refrigerated storage temperature at vaccine storage centers

## **GMP deviations:**

VVMs stored near door of walk-in cold room; improper temperature mapping of WIC, loss of electricity for significant time without power pack up no real time temperature monitoring with active alarm system





## Case Study 2

### **Guidelines for handling Field complaint of VVM color change :**

On many occasions , during vaccine supply chain the color of VVM changes color considerably due to unintended temperature excursions.

Such observations are brought by cold chain officers to UIP team  
Based on nature of the complaint MOH UIP team contacts Lisaline as field support agents of Temptime Corporation in India to visit and investigate the VVM color change.

Lisaline technical person visits the site and collects sample of Vials with VVMs. The VVM readings are taken using densitometer. The report is prepared and shared with MOH UIP team with estimated balance shelf life of VVM based on the OD readings.

MOH UIP team takes the decision about the stock at the site based on the report.



# Case Study 3

## Situation:

Vaccine from **new** supplier with VVMs applied to cap: VVMs coming off vial during vaccine distribution



## Root cause investigation:




























Improper cap to assure VVM attachment while in supply chain. Cap surface being rough with raised letters.

## GMP deviation:

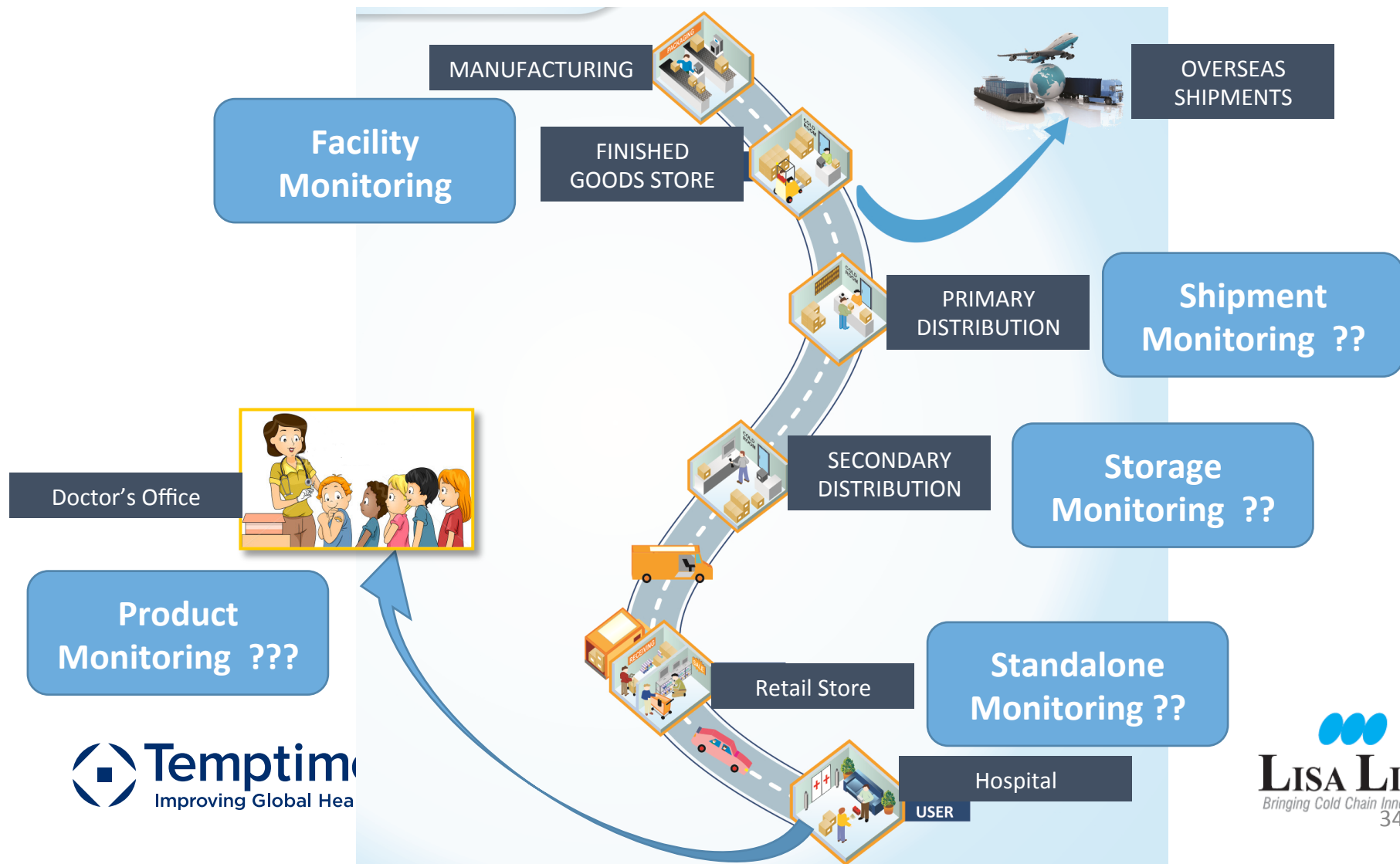
Insufficient qualification of VVM adhesion to cap

Manufacturer switched cap supplier and did not qualify the new cap

## Examples and main use of WHO recommended temperature monitoring devices for storage and transportation of vaccines

Device	Int. transport	Primary store	In-country transport	Intermediate store	In-country transport	Service level
Electronic temperature monitor with LCD screen						
Vaccine cold chain monitor						
Vaccine vial monitor						
Freeze indicator						
Multi-channel computerized temperature recording sys.						
Electronic refrigerator temperature logger						
Downloadable electronic temperature data logger						

# Challenges in Private vaccine Cold Chain management



# Vaccine Crisis' Can Happen Anywhere

## National Vaccine Scandal in China Becomes Source of Frustration and Outrage

By [Leo Timm](#), [Epoch Times](#) | March 23, 2016

Last Updated: March 28, 2016 6:34 pm



## 900 Southern Ocean Children May Have Received Improperly Refrigerated Vaccines

by [Patricia A. Miller](#), [patch.com](#)

January 9, 2017 09:06 PM

The state has filed a complaint with the state Board of Medical Examiners against a Manahawkin physician who may have vaccinated 900 children with improperly refrigerated vaccine, according to the state Department of Health.

The vaccines the children received include measles, mumps, rubella, chickenpox, hepatitis A & B, rotavirus, DTaP/Tdap, Hib, pneumococcal, polio, meningococcal and HPV, the health department said.

# Key Reasons for expanding into Private Market

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- Adopt the international standard of care for vaccines established by WHO and adopted by the Indian MOH for all publically procured vaccines
- Visibly show to healthcare professionals and parents that vaccines distributed in private market have been handled according to policy
- Increase the parents confidence in vaccination and give them a same value of vaccine as offered for vaccine in pubic distribution
- Provide an easy to use and understand tool that makes temperature management at the point of vaccination less risky and more effective
- Extend the surveillance of quality from the manufacturers site to the point of vaccination with a proven and effective tool
- Identify vaccine not handled properly before administering to the child



# VVM Extension into China Private Market

## 热标签

### 疫苗温度监测指示标签 (简称VVM)



正方形的颜色比圆圈的颜色浅——如果未过期，  
**可以使用**该疫苗。



正方形的颜色与圆圈相同或比圆圈更深——  
**不要使用**该疫苗\*。

### 疫苗温度监测指示标签的常见问题解答

**什么是VVM?**  
VVM是一种含有热敏材料的标签。黏贴在疫苗瓶上，用来自动指示疫苗随时间的推移而形成的累积热效应。

**VVM的工作原理**  
在时间和温度的共同作用下，VVM内部的正方形区域的颜色会逐渐不可逆地变深。

- 温度越低，颜色变化得越慢。
- 温度越高，颜色变化得越快。

**VVM会经历几个阶段?**  
VVM只有两个阶段。“可以使用”阶段——此阶段，正方形的颜色比圆圈的颜色浅。“不可使用”阶段——此阶段，正方形的颜色与圆圈相同或比圆圈更深。

**VVM的重要意义**  
VVM是一种指示疫苗是否随时间的推移而累积受热过多的工具。VVM也用来标示疫苗是否可能已损坏。VVM可以明确地提示保健工作者，疫苗是否已受热过度。

\*世界卫生组织 (WHO) 文献《了解疫苗温度监测指示标签：户外使用的问题和解答》[www.who.int/medicines](http://www.who.int/medicines)

**用智能手机扫描此二维码，查看热标签VVM在儿童疫苗免疫项目上的应用信息。**



**联络方式:**  
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# Beijing CDC Launches HEATmarker® VVM



- Beijing CDC requiring VVM on all private vaccines



# VVM Training and Education

- Temptime collaborated with Beijing CDC to organize VVM training sessions for healthcare practitioners (vaccinating doctors and nurses)
- 1,200 HCP participants
- Keynote presenter was Dr. Zheng from National CDC



# Vaccine Manufacturer's Ability to Comply with VVM

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- All of the multi-national vaccine companies (MNC) are complying with the VVM requirement coming from WHO, UNICEF, Chinese CDC and MOH from various countries
- All of the vaccine manufacturers, both those domestic and MNC, have the capability and expertise to apply the VVM in their facilities
- By asking to implement VVMs for all the vaccines manufactured and distributed in India irrespective of the type of markets will result in:
  - A uniform quality standard for all children receiving vaccines – either purchased by the government or coming from the private vaccine market
  - Providing a powerful tool that identifies and can prevent the administration of potentially heat damaged vaccines to children



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# Best contribution that we can do for the lives of the children



# Just D◻ it!

# Other Core Technologies offered by Temptime

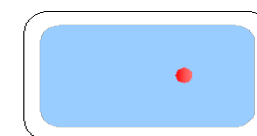
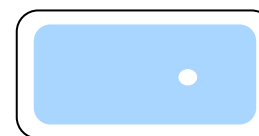
- **HEATmarker® Time-Temperature Indicator (TTI)**

A single-use indicator that shows whether there has been cumulative temperature exposure above a predetermined profile.



- **TH-F™ - Threshold Indicators**

A single-use threshold indicator that signals whether there has been a temperature exposure above a predetermined temperature for a short period of time.



- **TransTracker™D DEGmarker**

Single-use Instantaneous Threshold Heat Indicator signals heat excursion over risky temperature within seconds



- **FREEZEmarker® Freeze Indicator**

The TempTime Freeze Indicator is a single-use indicator that signals when there has been exposure to temperatures below 0°C.





# What is a FREEZEmarker® ?

- It is a indicator on a card.
- Response Temperatures:  $0 \pm 1^{\circ}\text{C}$
- Response Time : within 30 minutes
- Easy to Read
- Irreversible , Single use
- Reliable and Accurate
  - No False Positives
  - Continuous Monitoring
  - Quick Visual Response to Temperature Drops
- No Activation required
- Produced Under GMP Quality System for Medical Devices
- No Hazardous Waste , Environmentally Friendly



**Before Freezing**

*Green background is visible*



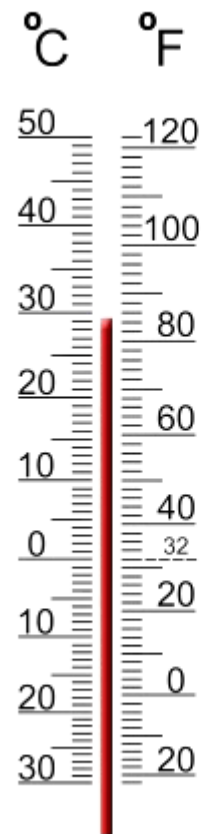
**After Freezing**

*Opaque appearance*



# How FREEZEmarker<sup>®</sup> works ?

---



# How to read the FREEZEmarker® ?



✓ Ok to Use

If the tickmark is clearly seen on FREEZEmarker indicator then the vaccine placed in the vaccine carrier has not been frozen and can be used



✗ FROZEN. Not OK to use

If the tickmark is not seen clearly on FREEZEmarker indicator then the vaccine placed in the vaccine carrier may be frozen. Do not use the vaccine & report the incident to the officer.

# How FREEZEmarker® can be used for monitoring freezing ?



Freeze monitoring at primary box level



Freeze monitoring during shipment / out reach

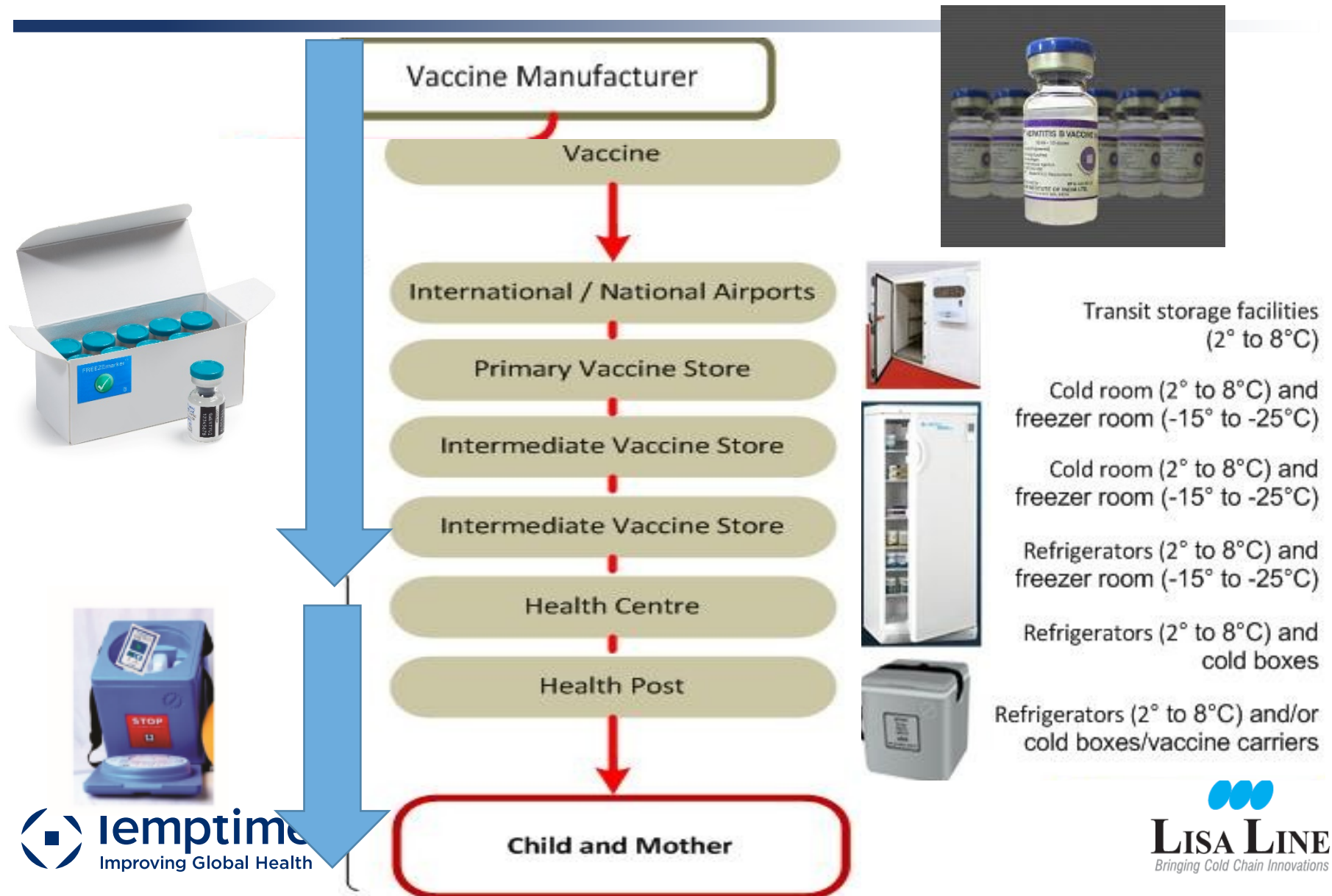


Before Freezing  
Event



After Freezing  
Event

# How FREEZEmarker® can be used for monitoring freezing ?





# Monitoring of freezing during Outreach in MP



- During Routine Immunization & State vaccination drive the vaccines are issued to the health workers.
- Throughout the day the health worker is travelling for vaccination & has to maintain the cold chain.
- As part of Multi Dose Vial guidelines Vaccine vials are transported to & from cold chain points to vaccination sites in vaccine carriers .
- Ice packs are used but leads to risk of freezing if not conditioned.
- VVM exist to monitor heat exposure till vaccination.
- Now FREEZEmarker is being used to monitor freezing event during outreach





# Conclusion

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## **Product Monitoring :**

The color changing Temperature Indicators are being used as effective tools for product level monitoring

## **Advantages of Temperature Indicators :**

Economical

Ability to monitor up to single unit level through out supply chain

Precise and reliable

Ease of application using standard labelling machinery

Ease of reading and interpretation with minimum requirement of training

Enables stake holders to take decision

Enhances the confidence

---

# THANK YOU!!