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# ***Sharing Experiences of HEATmarker<sup>®</sup> Vaccine Vial Monitor for WHO PQ***



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## **DCVMN-Medigen workshop on Global Registration and Supply Shortages from 6th to 10th March 2017, Taipei**

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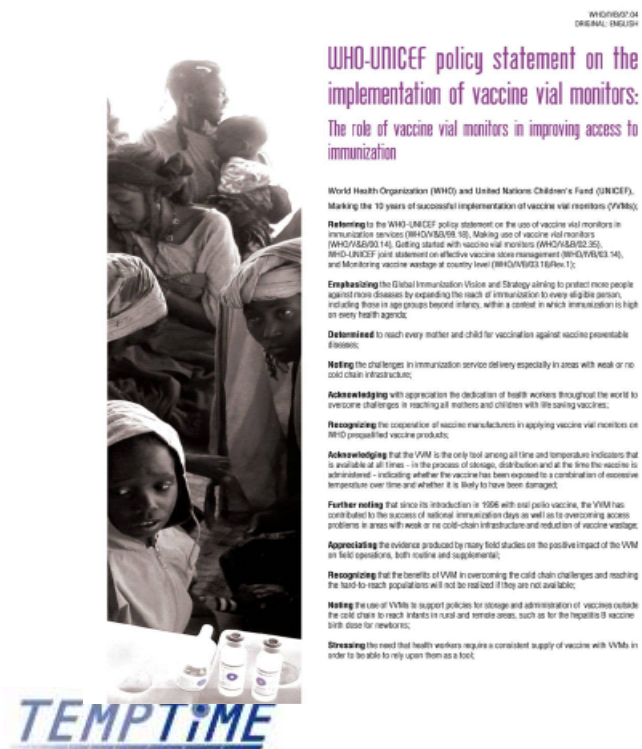
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北京市朝阳区建国路79号华贸中心写字楼2座9楼 951邮编100025;  
9F, Tower 2, China Central Place, No.79 Jianguo Road, Chaoyang District,  
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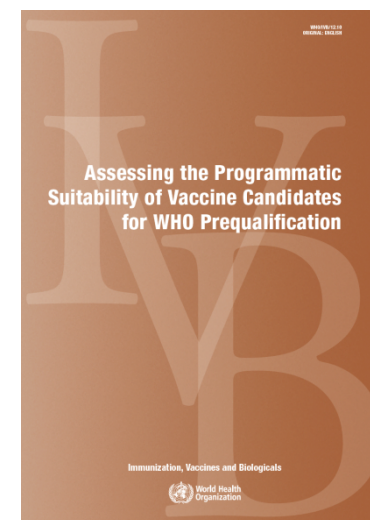
莫里斯平原,新泽西州,美国'116 American Rd Morris Plains, NJ 07950

# 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



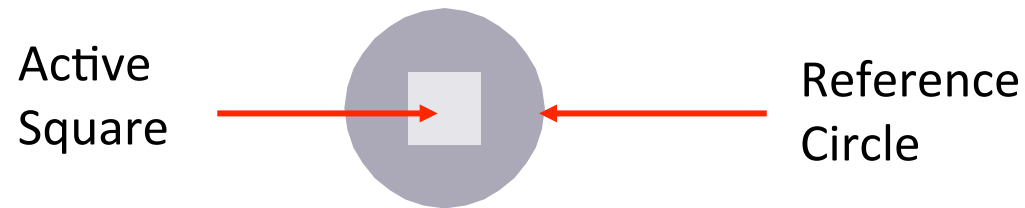
## 2012 WHO Includes VVMs As Critical Characteristic for Vaccine Prequalification



|                            |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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&amp;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> |
|----------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

# Monitor Cumulative Heat with HEATmarker VVM

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- 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



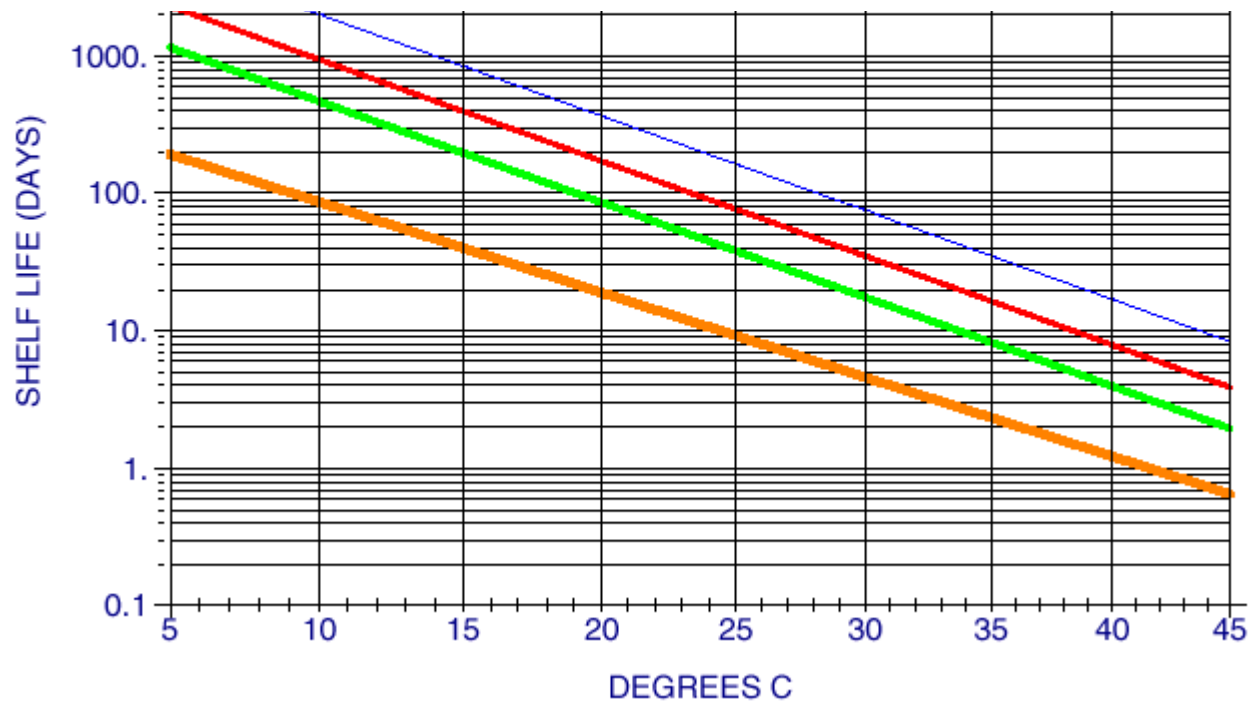
DO NOT  
USE

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

DO NOT USE the vaccine.

# 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.



— 30 days @ 37°C — 14 days @ 37°C — 7 days @ 37°C — 2 days @ 37°C

# 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"> <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, 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> |
|                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                 |                                                                                                                     |                                                                                                                                                                                                                                    |

# Steps to VVM Implementation

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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

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- 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 Vaccines<sup>1</sup>

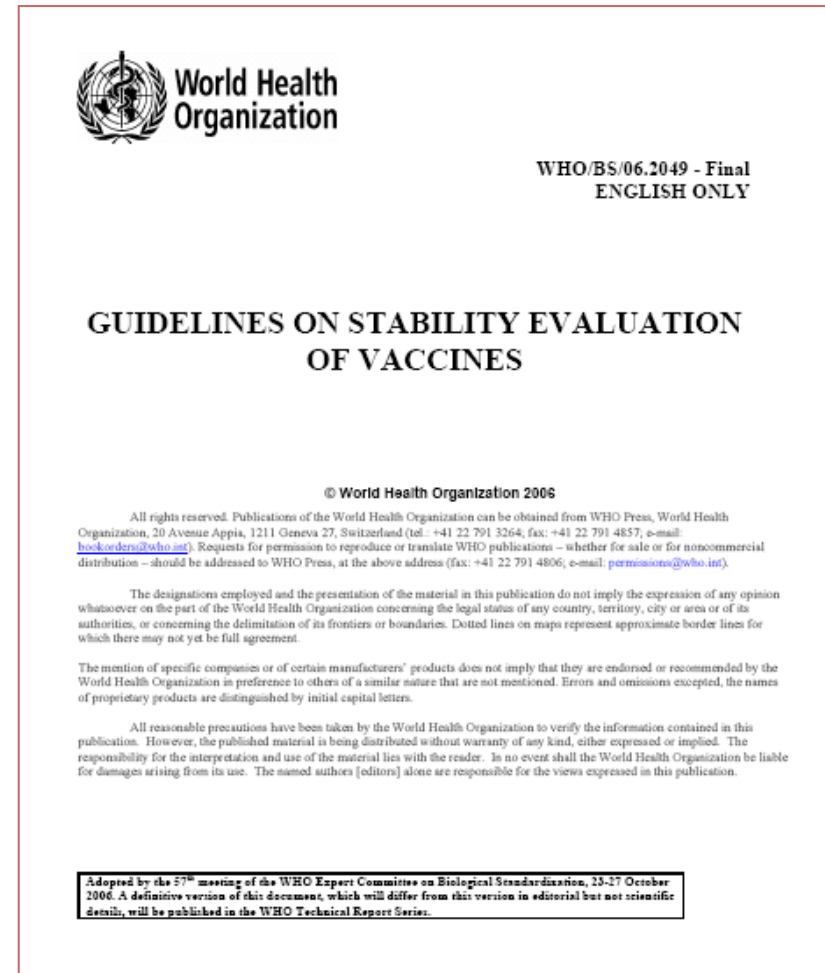
The temperature sensitivity of vaccine characteristics, particularly potency, has a major impact on the success of global immunization programmes. WHO has acknowledged the importance of clearly defining the stability characteristics of a vaccine.

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.”<sup>2</sup>

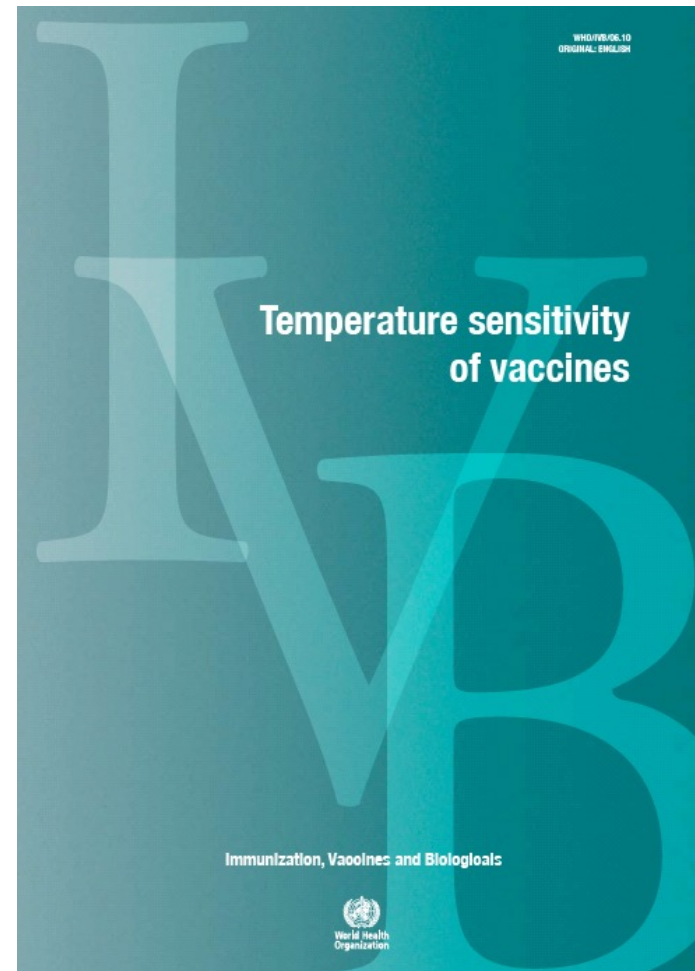
<sup>1</sup> [http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%2020BS%202049.Stability.final.09\\_Nov\\_06.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%2020BS%202049.Stability.final.09_Nov_06.pdf)

<sup>2</sup> WHO *Temperature Sensitivity of Vaccines (WHO/IVB/06.10)* [http://whqlibdoc.who.int/hq/2006/WHO\\_IVB\\_06.10\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.10_eng.pdf)



# WHO Temperature Sensitivity of Vaccines<sup>3</sup>

- 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.

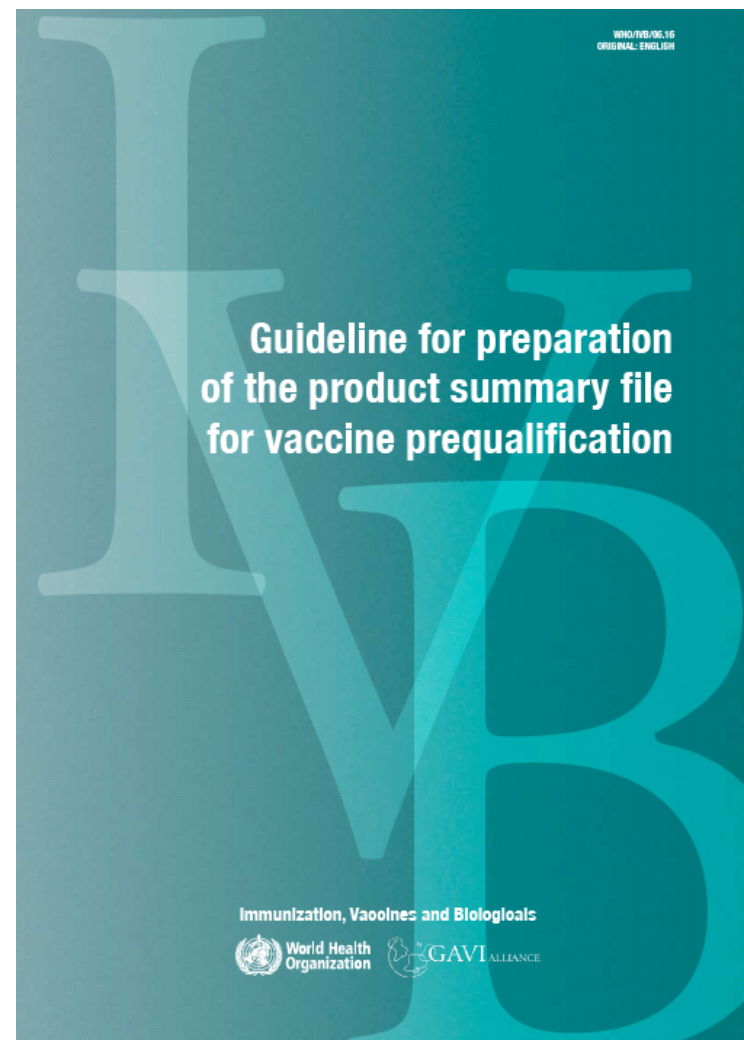


# Guideline For the Preparation of the Product Summary File for Vaccine Prequalification<sup>4</sup>

- 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)<sup>5</sup>

## 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.

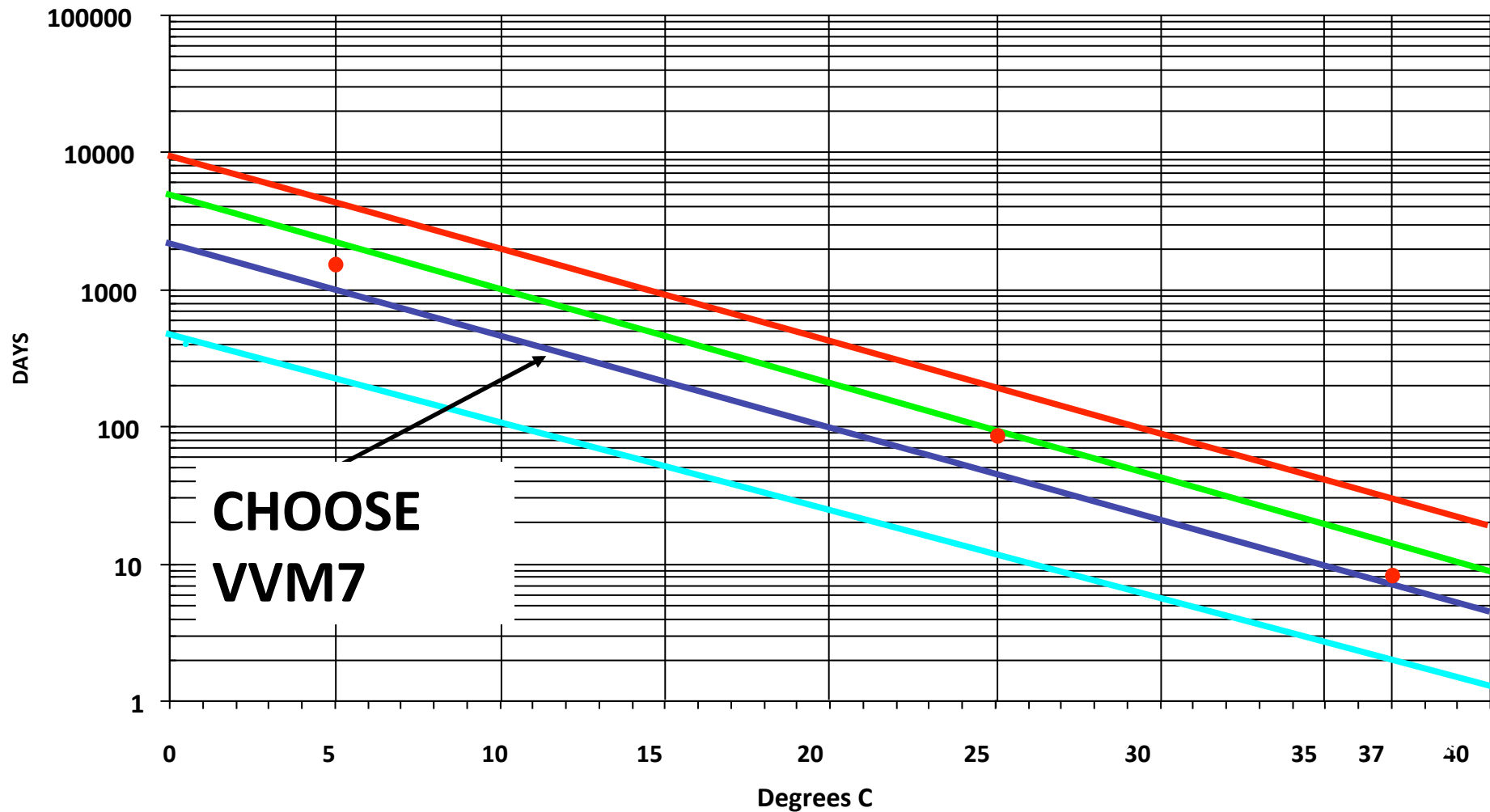
# Minimum Stability Data to Support Choice of VVM Category (except OPV)

## 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.

# Product A Stability Data and VVM Categories



# Summary – Vaccine Stability and VVM Category

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- 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

# 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.

SOPs for IQA must be developed

- Physical condition and VVM color

# Frozen Storage

- **VVMs should be stored at or below -24°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

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

# 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

# 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 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



# Location of VVM on Vaccine<sup>5</sup>

The location of the VVM on the vial depends upon whether the vaccine must be discarded at the end of the immunization session in which it is opened, or whether any remaining contents in an opened vial can be retained for use in subsequent sessions. The following cases apply:

- **For multi-dose vials containing a vaccine that can be used in subsequent sessions:**

Regardless of the vaccine presentation (liquid, freeze-dried or two vial combinations of liquid and freeze-dried), the VVM must be permanently attached to the label of the vaccine vial and must remain readily observable before, during, and after use, until the entire contents of the vial have been used.

- **For vaccines that must be discarded at the end of the session or within 6 hours, whichever comes first:**

The VVM must be attached to the vaccine vial or ampoule and must remain readily observable until the vial or ampoule is opened, but not observable after opening. In order to achieve this requirement, the VVM must be located on the flip-off top of a vial or on the neck of an ampoule.

On a product by product basis, WHO will advise both the vaccine and the VVM manufacturer where the VVM is to be located.

Locating the VVM on the bottom of a vial or ampoule is never acceptable – it must always be in a visible location.

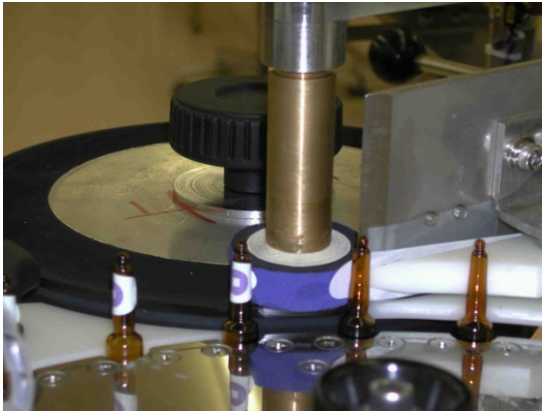
TEMPTIME



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## *Automatic Application of VVMs*

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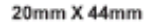
Japan BCG



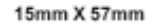
Serum Institute of India



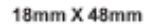
Kartoglu - WHO



Double Size



Double Size



### Double Size



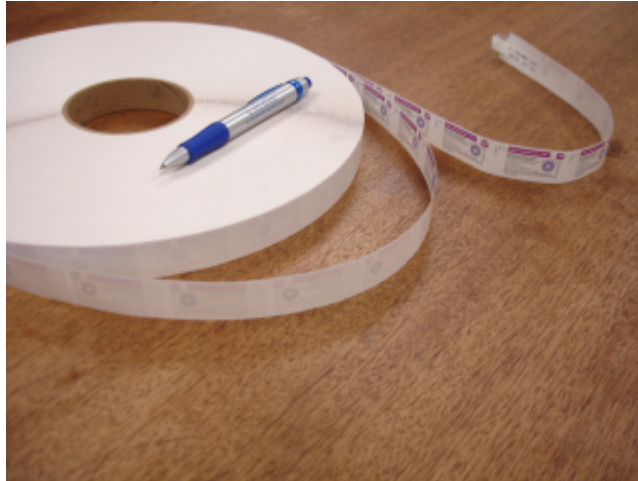
10 mm



# VVMs are Supplied on Rolls

## 10,000 VVMs/roll

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**Full Label VVM**



**VVM Dot**

# 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





- YouTube Link to Serum Institute of India Video



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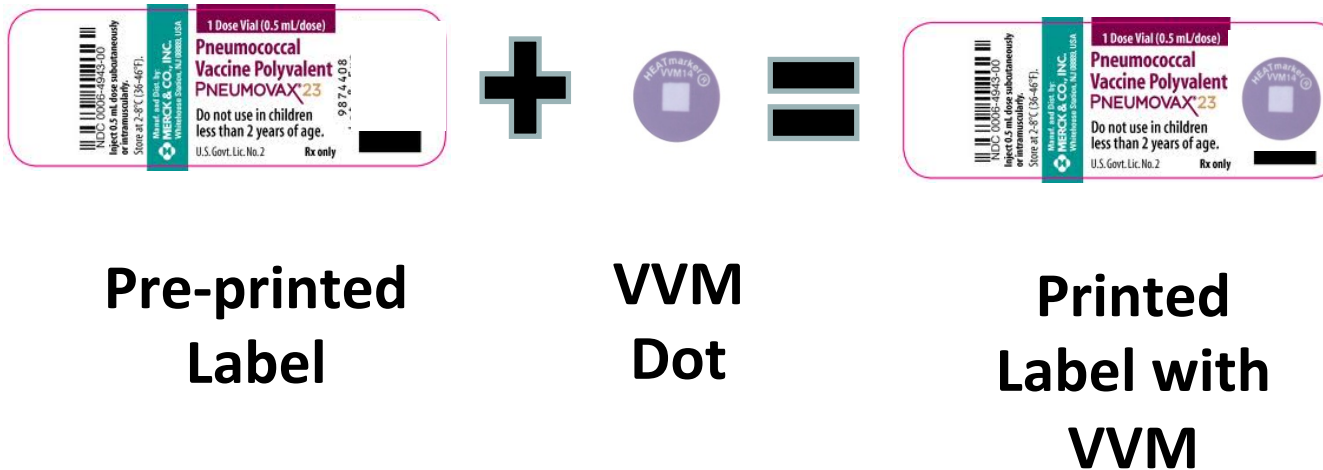
# Application of Full Label VVM to Vial

- VVM applied with existing equipment
- Speeds over 400/minute in routine operation



# VVM Application on Printed Label

The vaccine manufacturer can decide to apply the VVM dot onto the common label (printed locally) at his facility before the vial labeling.



# VVM Application on Printed Label

## 2 Step Process



CruceII

1) VVM dot is applied to pre-printed common label with no VVM



TEMPTIME



CruceII

2) Common label with VVM is applied to vaccine vial



# Automatic Label Application Equipment Suppliers

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Several companies that are familiar with VVM application are:

- Accraply (Barry-Wehmiller Group)
- Bausch & Strobel
- Herma (Labelworx)
- Neri
- Maharshi Udyog and
- PharmaPack

# 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)
- 2<sup>nd</sup> 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

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- 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

- Thanks!