What is a VVM?
Vaccine Vial Monitor (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**

Square darkens with cumulative heat exposure
Two doses of vaccine are ready to be administered

- Lyophilized vaccine and diluent
- Both products within expiry date
- Both products look OK
- No issues identified in transport and handling

Would you administer these vaccines?
What about now?
Monitor Cumulative Heat with HEATmarker VVM

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Chemistry of the TTI: Solid-State Polymerization

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

(Colorless)

\[
\begin{align*}
R - C\equiv C - C\equiv C - R \\
R - C\equiv C - C\equiv C - R \\
R - C\equiv C - C\equiv C - R
\end{align*}
\]

(Highly colored)

\[
\begin{align*}
C - C\equiv C - C\equiv C - C\equiv C - C - C\equiv C - C - C - C - C - C - R \\
C - C\equiv C - C\equiv C - C - C - C - C - C - R
\end{align*}
\]

- The solid monomer particles are formulated into an ink and printed.
- The chemistry can be printed in any shape or format.
- The color developed through polymerization is from light blue/purple to dark blue/purple.
- Covering the printed indicator with an orange film does not alter the polymerization process.
Vaccine Vial Monitor (VVM) – Faster color change at higher temperatures

**Slower color development at lower temperature**

Before heat exposure

**Faster color development at higher temperature**

After heat exposure
The HEATmarker Is Easy To Read

The Active Square is **lighter** than the Reference Circle.

*If the expiry date is not passed, **USE** the vaccine.*

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

**DO NOT USE** the vaccine.
The Arrhenius Equation

HEATmarker TTs contain a heat-sensitive material that integrates cumulative heat exposure over time that:

- Is based on a chemical reaction (polymerization) following the Arrhenius equation

\[ k = A_0 e^{-\left(\frac{E_a}{RT}\right)} \]

- Darkens, irreversibly, with time and temperature (cumulative) and faster when the temperature increases
- HEATmarker is a Mean Kinetic Temperature (MKT) indicator
VVMs have a well defined Arrhenius temperature relationship over time.
Four WHO VVM categories

VVM category chosen is correlated to vaccine stability
Two New VVM Categories Added in 2018

VVM11 – more closely monitors the shelf life of new vaccines
VVM250 – extends the capability to monitor room temperature stable vaccines
VVM Response is Correlated with Vaccine Stability

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.

- VVM should reach endpoint before vaccine potency drops below efficacy requirements
- Dossier with these stability data supports VVM7
- For WHO prequalified vaccines, WHO makes decision on VVM category and sends letter to vaccine manufacturer and Temptime
- For other applications, vaccine manufacturer makes VVM category decision
# HEATmarker VVM for Use on Vaccines

<table>
<thead>
<tr>
<th>Pharmaceutical Product</th>
<th>Indication</th>
<th>Customer</th>
<th>Temptime Product</th>
<th>Value Delivered</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Children’s Immunization Campaigns for a range of contagious diseases:</td>
<td>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</td>
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<tr>
<td></td>
<td>• BCG</td>
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<td>• Prevents immunization with heat damaged vaccines</td>
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<td></td>
<td>• Diphtheria</td>
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<td>• Expands reach of immunization programs to remote populations</td>
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<td></td>
<td>• Tetanus</td>
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<td>• Increases immunization programs efficiency</td>
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<td>• Pertussis</td>
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<td>• Hep B</td>
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<td>VVM2 VVM7 VVM14 VVM11 VVM250</td>
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<td></td>
<td>• HiB</td>
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<td>• Meningococcal A and C</td>
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<td>• Measles</td>
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<td>• Mumps, Pneumococcal</td>
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<td>• OPV</td>
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<td>• Rotavirus</td>
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<td>• Rubella</td>
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<td>• Tetanus Toxoid</td>
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<td>• Yellow Fever</td>
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<td><strong>Newer Vaccines:</strong></td>
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<td>• Rabies</td>
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<td>• Typhoid</td>
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VVM follows the vaccine from time of manufacture to time of use
VVM follows the vaccine from time of manufacture to time of use.
VVM follows the vaccine from time of manufacture to time of use

No matter how the vaccine got there!!
Value of VVM in Immunization
Value of VVM in Global Immunization Programs

Vaccine Vial Monitors – helping save lives!

Time temperature indicator known as vaccine vial monitor (VVM) absolutely vital to eradication effort, allowing health workers to know vaccine has not been exposed to excessive heat.
Improving vaccine effectiveness.

D. Kristensen
Example: Pinpoint Cold Chain Problem and Identify Heat Damaged Vaccine – India

- Inspection of VVMs on JE vaccine in outlying district was at the endpoint
- The local health officials conducted an investigation and found that the 450,000 doses of JE vaccine were stored in a walk-in refrigerated storage facility at the Government Medical Store Depot outside of Delhi that had experienced power interruptions for an unknown amount of time, and the back-up generator failed to function properly
- VVMs avoided administration of vaccine exposed to excessive heat due to equipment failures and identified equipment problems
Enabling vaccine outreach.
Expanding vaccine coverage.
Example: Improving Access to Immunization in Remote Areas of China

Objective: To evaluate the feasibility and effectiveness of a village-based, out-of-cold-chain strategy for improving the on-time administration (within 24 hours) of the HB vaccine birth dose in remote areas of China, especially among children born at home.

Strategy possible because of use of VVM.
Conclusions of Study in China

- Village health workers using an out-of-cold-chain immunization strategy can improve the on-time administration of the hepatitis B birth dose among home-born infants.

- Simple tools such as VVMs, AD syringes, and Uniject can ensure vaccine quality and injection safety when vaccines are administered by village health workers.

- Taking vaccine out of the cold chain could potentially decrease the risk of vaccine damage due to inadvertent freezing (this study did not follow up on the children who were given potentially frozen vaccine).
Facilitating stock management.
Preventing vaccine wastage.
Yogyakarta earthquake 2006.
Example: Reduce Wastage of Vaccine
Earthquake in Yogyakarta, Indonesia

- OPV
- DTP-HepB
- Measles
- DT
- TT
- HepB
- BCG

VVM at endpoint
Saved Vaccine
No VVM

Damaged the infrastructure, including the cold store facilities at the district and health centers.

Electricity was out for several days and generators were either not used or not functioning.

Vaccine in 5 districts and more than 50 health centers was saved from being discarded prematurely (wasted) due to the presence of the VVM on the vials.
Impact of VVM

Over the last 10 years\textsuperscript{1}, it is estimated that VVMs have:

- Saved developing country immunization programs $140$ million in vaccines that are no longer discarded due to suspected heat exposure.
- Facilitated the delivery of 1.46 billion doses of vaccine through outreach.
- Averted 100,824 deaths from potential heat exposed vaccine and avert 57,725 deaths by extending vaccine delivery.

\textsuperscript{1} PATH 2013
Helping to save lives!

D. Kristensen
PATH

Save The Children UK