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**Dr. Sushil Kumar Sharma**
LIG 56, Pkt-1, Sector-A9,
Dda Flats, Narela, Delhi, India

**Yatendra Sharma**
Young Professional,
Ministry of Youth
Affairs and Sports, India

**Dr. Ekta Sharma**
Assistant Professor (Sr. Scale),
Textiles and Apparel Designing,
Ethelind School of Home
Science, SHIATS, Allahabad,
Uttar Pradesh, India

**Saurabh Kumar**
B.P.ED Student, Department of
Physical Education,
Kurukshetra University,
Thanesar, Kurukshetra,
Haryana, India

**Correspondence**
**Dr. Sushil Kumar Sharma**
LIG 56, Pkt-1, Sector-A9,
Dda Flats, Narela, Delhi, India

# Vaccine vial monitors (VVMs): Applications and challenges

**Dr. Sushil Kumar Sharma, Yatendra Sharma, Dr. Ekta Sharma and Saurabh Kumar**

**Abstract**
VVM is the only tool among all time temperature indicators that is available at any time in the process of distribution and at the time a vaccine is administered indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates to health workers whether a vaccine can be used. VVMs have also become an invaluable tool to increase coverage through increased access in hard-to-reach communities and in areas with very weak and no cold chain infrastructure. There is consensus that VVMs play an extremely valuable role in improving the quality of immunization efforts throughout the world. In recent years vaccine manufacturers raised some questions and concerns about issues impeding VVM implementation. UNICEF Supply Division facilitated further feedback on these issues through a specific letter on the general terms and conditions governing VVM procurement. In addition to regular contact with vaccine manufacturers, WHO, in coordination with UNICEF, began visiting vaccine manufacturers on a one-on-one basis to discuss VVM implementation issues in detail. The issues are categorized as follow: Validation issues, Cold Chain & Logistics issues, Regulatory issues, Programme issues, and Commercial issues etc.

**Keywords:** Vaccine vial monitors

## Introduction
The historical information on the introduction of new VVMs for other vaccines is as follows, and this explains how vaccine manufacturers were involved in the process as well as the reasons for selecting only four categories of VVMs rather than individual product specific designs. VVM concept conceived by WHO. Starting in the late 1970s, PATH worked with the World Health Organization (WHO) and a variety of technology developers to find a way to track the heat exposure of individual vaccine vials. In the early 1980s we teamed up with the Temptime Corporation, to develop VVMs. Many donors provided financial support to the project, especially the US Agency for International Development. In 1996, VVMs became commercially available for oral polio vaccine, adding only a few cents to the price of each vial. Today, WHO requires that all vaccines purchased through the United Nations Children's Fund (UNICEF) use VVMs. And together, WHO and UNICEF have urged other groups that procure vaccines including donor agencies, international organizations, and country leaders to make sure VVMs are required in all of their vaccine purchase agreements and donations. PATH and WHO have also developed and tested training materials for health workers that help them learn how to handle vaccines and use VVMs effectively.

In the years since introduction, the VVM has demonstrated its value again and again. In one example, electricity went out at health facilities in Yogyakarta, Indonesia, for several days during an earthquake. Vaccine vial monitors showed that most vaccines were undamaged, despite the heat, saving 50,000 doses of vaccine that otherwise would have been thrown away.

Success with Cold Chain Monitors at higher levels of the cold chain prompted interest in a vial indicator to extend monitoring to the periphery. Product development on a VVM for measles vaccine began at PATH using a PTS (p-toluenesulfonate) chemical licensed with permission from Allied Corporation.

Over the next 2-3 decades, it's estimated that VVMs will allow workers to recognize and replace more than 200 million doses of damaged vaccine and to confidently deliver more than a billion more doses in remote settings—saving lives and reducing illness for countless people. In addition, thanks to the presence of the VVMs on vaccines, WHO revised its policies to allow open vials of liquid vaccine to be used for more than a single day. UNICEF and WHO

estimate that the use of VVMs on basic vaccines saves the global health community more than $14 million each year by preventing undamaged vaccines from being discarded.

1. There are two main benefits of using vaccine vial monitors:
2. Vaccine vial monitors reduce wastage of good vaccine.

Vaccine vial monitors ensure that only good vaccine is used on our children. Health workers can see at a glance whether the vaccine has been protected from heat sufficiently to be used. Previously, there was no way to see if vaccine had been exposed to too much heat. Consequently, vaccine which could no longer provide protection against disease was sometimes used while, in other cases, good vaccine was thrown away following minor cold chain failures.

Storekeepers and vaccinators can determine which vials of usable vaccine have been exposed to more heat than others. Vials with monitors which show more heat exposure should be used before vials with less heat exposure. In this way, health workers and storekeepers can minimize the number of vials which have to be rejected. This will also decrease the wastage of vaccine.

VVMs are a simple but effective system adapted from a similar labeling scheme used to guard refrigerated food during transport. The adaptation was an uncomplicated idea but a difficult reality. To date, only a single provider, Temptime, has perfected the technology to work on vaccines.

**Fig 1:** Vaccine Vial Monitors


The tribulations did not end once the technology was mastered, however. It took more than three decades to turn this idea into a common practice in developing countries where adding even a penny's worth of difference to the price of vaccines was a burden they hesitated to bear. The price of the vial monitors was small, but still it was a price increase and, thus, a burden to overcome.

If it were not for the prolonged and consistent push by organizations like the World Health Organization (WHO), PATH, the United States Agency for International Development (USAID), the Global Alliance for Vaccines and Immunization (GAVI), United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention among others, the tiny label would have become stuck to a pricing hurdle. By adding the simple procurement specification requiring the VVMs, low-resource countries, where vaccines are the most at risk, now benefit from its simple but urgent warning.

The simplicity of the label belies the difficulty in its development. The adaptation from existing cold chain (or temperature-controlled supply chain) labeling technologies used for refrigerated foods proved far more challenging than anticipated. Even Temptime, the sole producer of VVMs for vaccines today, abandoned earlier developmental attempts. PATH interceded and made a compelling humanitarian case for the product, and Temptime renewed its efforts until the product eventually was developed. To date, no other producer has been able to achieve the same success, although several are still trying.

**The Challenges associated with applications, logistics, Implementations and regulatory of VVM:**

Even with the advances in VVM technology and the spread of advantages the technology seems to present, consistent use of the product has been difficult to ensure.

While VVMs are increasingly supplied on vaccines purchased for the international market through UNICEF, they are not yet available on many of the vaccines produced in developing countries for domestic markets, the exceptions being India, Indonesia and Pakistan.

Vaccine procurement for developing and emerging countries is becoming increasingly decentralized, meaning that a variety of purchasers must include VVMs in their tender specifications to ensure consistent availability to immunization programs. In 2007, WHO and UNICEF released a policy statement encouraging member states, donors and nongovernmental organizations procuring vaccines to include VVMs in their specifications. Continued work to strengthen procurement at the country level, e.g., through interagency coordinating committees, will be necessary to ensure vaccine quality and availability of vaccines with VVMs.

Although PAHO supported a number of field trials with early VVM prototypes, it has never required VVMs on products purchased through the PAHO revolving fund, citing lack of cold chain difficulties in its region and unwillingness of consumers or purchasers to pay the slight price increases for products with VVMs. Vaccine suppliers complained that they had to supply vaccine with VVMs for UNICEF and without

for PAHO, but eventually most complied with the UNICEF requirement.

One repeated difficulty has been the inability of the UNICEF supply system to consistently send the same brands of vaccines to countries or to notify WHO with regard to which countries would receive vaccines with VVMs. WHO was, therefore, unable to target early training efforts to countries that would definitely receive the VVMs. For many years, countries received supplies of vaccines both with and without VVMs and, therefore, could not rely on VVM use as a routine management tool. This situation is improving as more vaccine suppliers have integrated VVMs into their products.

**Regulatory Considerations**

When OPV VVMs were implemented, WHO did reassessment visits to manufacturers and various regulatory authorities, discussed the VVM issue and provided a VVM information packet. Regulatory authorities have been aware of VVMs since 1996. The need for regulatory oversight has not come up as an issue with OPV VVMs, but now some concerns have been raised. Therefore WHO has decided to accelerate contacts with regulatory authorities including those related to the suppliers of large quantities of vaccine to the UN system. The findings can be summarized in Table 1.

**Table 1:** Regulatory considerations on VVM implementation on all vaccines, responses from National Regulatory Authorities

| Region | Country | Position |
|---|---|---|
| Asia | India | Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport. |
| | Indonesia | Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport. |
| Europe | Belgium | No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation. |
| | France | No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation. |
| | EMEA | Awaiting response |
| America | USA | If the vaccine is not licensed for US distribution, the exportation must comply with the regulatory requirements described in Sections 801 and 802 of the Food, Drug and Cosmetic Act (21 CFR 381 and 382) which refer to export provisions. If specific vaccine as labeled is licensed for distribution in the US, manufacturers need a supplement to their license application. The exact situation of vaccine for UN market needs further clarification with USFDA. USFDA advises US manufacturers implementing VVMs to contact the agency directly. |

Validation is a process that provides assurance for the user that the monitoring device has been tested by assessing measurement accuracy and measurement responsiveness. The device's measurement accuracy and measurement responsiveness need to be defined. Validation should include the defined range over which performance is expected. These attributes of validation have not been addressed. In real life the product will not be at consistent temperature and temperature spikes may occur. The Justification from manufacturer that the VVM reaction is a predictable reaction and any scenario can be mathematically calculated. The validation is focused on standard temperatures. It should be clarified in details with stability data.

**Table 2:** Processes and validation/quality control (QC) tests needs to be performed during VVM implementation

| Step | Description of the process | Validation and/or QC tests |
|---|---|---|
| Manufacturer's request and approval of VVM type by WHO | Manufacturer's request to LifeLines | |
| | WHO review of stability data | Manufacturers have to validate their stability tests |
| | WHO approval of VVM type based on stability data (communicated to both the manufacturer and LifeLines) | |
| Validation of VVM reactivity by the manufacturer | Vaccine manufacturer procures necessary equipment (water bath tanks, densitometer and special thermometers, etc.) | |
| | Conduct initial validation test | Initial validation test conducted at vaccine manufacturer's facility |
| Determination of VVM position on the vial and approval of the artwork | Vaccine manufacturer provides artwork | |
| | LifeLines confirms that artwork is satisfactory | |
| | For special applications, validation tests are performed for application (better adhesion, etc.) | Application validation tests conducted at vaccine manufacturer's facility |
| VVM printing/slitting | Prepare ink base and run pilot press (LifeLines) | |
| | Conduct accelerated tests for the ink base | Testing of ink base |
| | Run actual printing | |
| | Take samples from each master roll for kinetic tests | Kinetic test |
| | Take master rolls for slitting | |
| | Visual check and samples taken for homogeneity test | Visual check and homogeneity test |
| | Goods to freezer | |
| | Conduct lot release test | Testing VVM reactivity |
| | Ready for shipment | |
| Packaging and shipment | Give sequential numbers and pack in corrugated boxes | |
| | Make necessary booking for shipment | |

| | | |
|---|---|---|
| | Inform customer and advise on arrival | |
| VVM application on vial | Vaccine manufacturer to check the time temperature indicator which is placed on shipping carton, and measure colour of sample indicator | |
| | Conduct lot acceptance test using LifeLines Lot Release Protocol and recommended Sampling Plan | Acceptance tests (by vaccine manufacturer on arrival) using LifeLines Lot Release Protocol and recommended Sampling Plan |
| | Place goods in freezer | |
| | Apply VVM to label and/or vial | |
| | Store at specified temperatures asrequired by type of vaccine | |

In 2009, vaccine manufacturers raised some questions and concerns about issues impeding VVM implementation. UNICEF Supply Division facilitated further feedback on these issues through a specific letter on the general terms and conditions governing VVM procurement. WHO responded to all these questions on 28 August 2001. In addition to regular contact with vaccine manufacturers, WHO, in coordination with UNICEF, began visiting vaccine manufacturers on a one-on-one basis to discuss VVM implementation issues in detail. WHO compiled a list of all questions and prepard a Question & Answer (Q&A) document which was sent to all parties invited to this meeting and included in the meeting file.

The questions were categorized as follows:

**Validation issues**

1. The shelf life of the VVM is less than the shelf life of the vaccine.
2. Will WHO conduct correlation studies for VVMs and vaccine potency for all vaccines?
3. Can the VVM consistently reflect the true stability of each vaccine?
4. What data exist to show how the VVM is validated?
5. Is there some typical specification for VVM adhesion?
6. Chemical temperature indicators produce a high percentage of false readings...

**Logistics issues**

1. Concerns about introducing a different labeling system for a portion of their production.
2. How to maintain the logistics of import and inventory control?
3. Different multi-lingual, multi-production and multi-packed quantities.
4. Additional capital expenditures to implement VVMs.
5. Does the current GMP requirement prohibit pre-printed labels or require an on-line printer with a blank roll?

**Regulatory issues**

1. Does VVM attachment to the vaccine vial need to be approved by the national regulatory authority?
2. Who is legally and financially responsible when a vial or shipment is rejected because the status of the VVM(s) indicates excessive heat exposure?
3. Does the manufacturer's obligation cease at the time that the shipment is acceptedin country?

**Commercial issues**

1. LifeLines is the sole supplier of VVMs, there is no other competitor.
2. Why doesn't the LifeLines warranty mirror the minimum shelf life required of the vaccine suppliers (18 months from the date of shipment from the vaccine supplier)?
3. Why does LifeLines have a +/-10% tolerance on the quantity of VVMs delivered?
4. Why does a minimum VVM order quantity have to be set? Below graph explains the need to control temperature during testing in water baths. Slight differences in temperature dramatically affect results of VVMs.

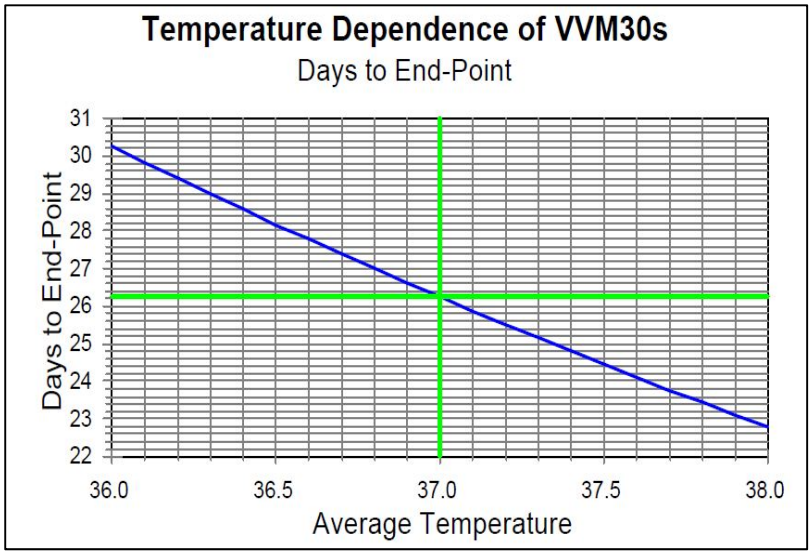


**Fig 2**: Temperature dependence of VVM30s (days to end point) Temptime Inc.

Over the last 10 years 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 death from potential heat exposed vaccine and avert 57,725 death by extending vaccine delivery. (Source: PATH 2013)

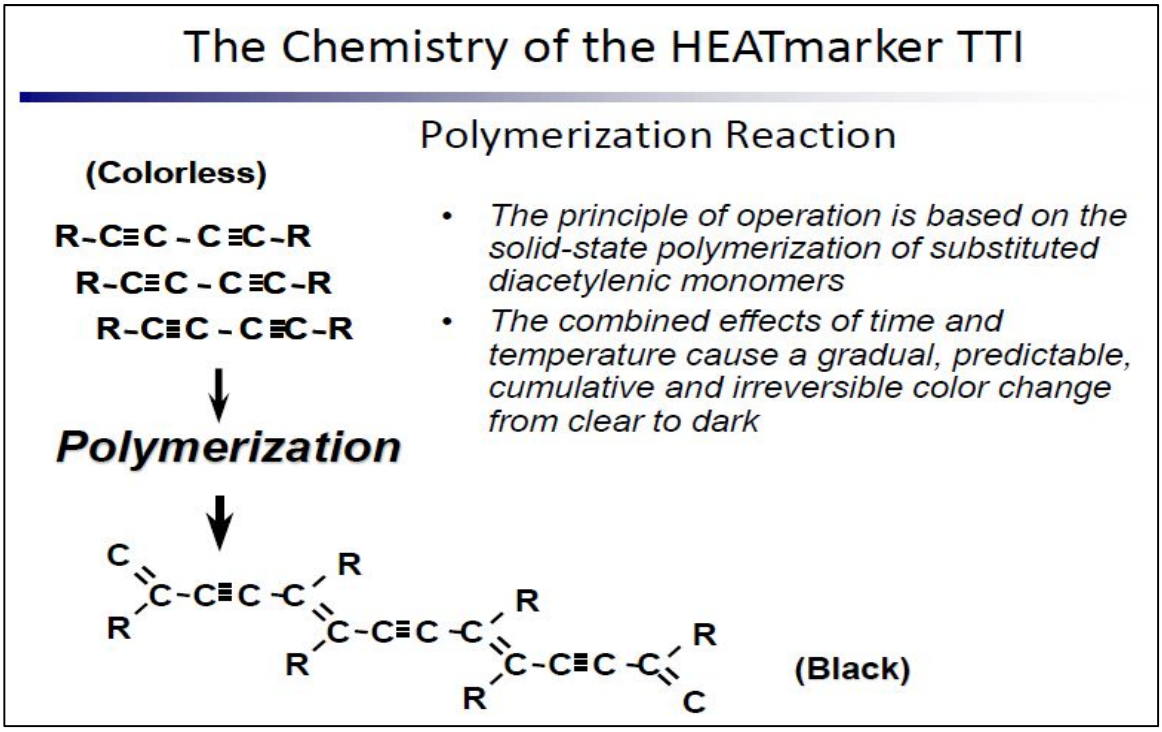


**Fig 3:** The Chemistry of Vaccine Vial Monitors

**Table 4**: Relationship between facility type and cold chain compliance scores

| Health System Nomenclature (India) | WHO Cold Chain Nomenclature | n | Compliance Score (%) | Significance |
|---|---|---|---|---|
| Central Vaccine Store | Intermediate Level-1 | 01 | 100 | NA |
| District Hospital | Intermediate Level-2 | 01 | 88 | NA |
| Primary Health Centre/Community Health Centre | Health Centre Level | 22 | 77[a] | P<0.05 |
| Sub-health Centre | Health Post Level | 28 | 48[a] | |

[a]Statistically Significant

**Conclusion:** As seen in Table 4, a total of 52 facilities were evaluated. This included one central vaccine store, one district hospital, 22 primary/community health centers, and 28 sub-health centers. The mean cold chain compliance score obtained across the health centers in this district was 60%. The range of compliance scores was 0–100%.

Survey results demonstrate that as distance from the district hospital increases, there is a concomitant difficulty in maintaining the cold chain. Our data point to the difficulty in reaching rural communities with adequate immunizations. This is consistent with work conducted by Datar et al. These authors reported that as distance from larger health centers increased, immunization coverage decreased.

Section 381 refers to general procedures for exported products. 382 deals specifically with exported products that are not approved. However, on both sections, further advice is needed from the FDA. The issue of the USFDA will be very important to understand. If WHO advises that UNICEF should take on the liability of the vaccine under export provisions, then buyers would make sure that appropriate regulatory processes are taking place. UNICEF could not accept that.

Another issue of concern is power supply at the primary/community health centers in this rural district. Electrical power or an alternative source of energy is crucial to the maintenance of the cold chain, and our data indicate 90% of all primary/community health centers reporting frequent power failures (5–10 hours) during summer months. This is compounded by the fact that only 45% of these primary/community health centers have a power generator that can help maintain the cold chain. Given these findings, feasibility and potential of solar technology in rural India to improve health infrastructure and, in turn, the cold chain need to be assessed.

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