Implementation of VVM at a Vaccine Manufacturer
Part 2
Steps to VVM Implementation Part 2

1. WHO process
2. Receipt, Control and Storage of VVMs
3. Calibration of X-Rite 500 Series Spectrodensitometer
4. VVM Acceptance Testing
5. Application of VVM to Vials
Spectrodensitometer Daily Calibration and Annual Maintenance Program

• X-Rite 500 series spectrodensitometers are used to measure VVM active and reference surfaces
• Since the size of VVM is very small, specially-fabricated, very small apertures (2 mm) are required in the spectrodensitometer used for VVM
• Spectrodensitometers must be purchased from and serviced by Temptime to assure proper measurement capability
• Temptime pays for calibration by the spectrodensitometer manufacturer when required (every two years)
• Vaccine manufacturer is responsible for shipping charges
• Temptime provides notification when calibration is due and can also provide a “loaner” unit while the densitometer is out for calibration
VVM Acceptance Testing

- Vaccine manufacturers are responsible to develop SOPs related to VVM consistent with their quality system requirements
- SOPs for receiving, inspecting, storing and releasing of a lot of VVMs must be developed
- Some manufacturers rely solely on the Certificate of Analysis provided with a lot to support their release process
- Other manufacturers perform additional tests and verifications, including the 37°C water bath test as routine or on random lots
- These processes should suit the vaccine manufacturers’ quality system and risk management practices
VVM Acceptance Testing - 37°C Water Bath
Helpful Tips for Acceptance Testing Available

VVM Acceptance Testing: Helpful Tips for Vaccine Manufacturers

Temptime understands that acceptance testing of VVMs is a critical part of many of our customers' quality systems. We are providing this list of helpful tips so we can share the benefits of our experience and expertise in testing VVMs. Temptime's test methods are based on the World Health Organization PQS Specifications E6/WHO/2 and E6/WHO/2. This list of tips is not a replacement for the specification but is additional information that will help our customers test VVMs in a consistent and compliant way.

- **Spectrodenstometer**: Temptime Corporation strongly recommends the use of an X-Rite 500 Series spectrophotometer with special modifications made to the target by Temptime that allow the spectrodenstometer to be used effectively with VVMs. Temptime also provides the service and calibration of our customers' spectrodenstometers.

- **Optical Density Measurement**: Place VVMs with the release liner still attached on white card stock when measuring. The active indicator surface and label substrate are somewhat translucent, which allows the color of the testing surface before the indicator to affect the densitometer reading. White card stock eliminates this potential source of error. Temptime recommends using white, letter-size, 65 to 110 lbs. card stock with Cyan Optical Density ≤ 0.05 as measured with an X-Rite 500 Series Spectrophotometer.

The VVM consists of two parts, the Active Square, also called the Active Indicator or I, and the Reference Ring, also called the Ring or R. Measure the Optical Density of the VVMs by taking two optical density measurements from different points within the Active Square and two measurements from the Reference Ring; one on the bottom and another 90 degrees away from the first measurement. Refer to the diagram below.

![Diagram of VVM Measurement Targets](image1)

**Figure 1. VVM Dot Measurement Targets**

![Diagram of VVM Measurement Targets](image2)

**Figure 2. VVM Full Label Measurement Targets**
Examples of Full Label VVM and VVM Dot

Full Label VVM - VVM Printed as Part of Vial Label

- Sanofi Pasteur
  - 20mm X 44mm
  - Double Size

- GlaxoSmithKline
  - 15mm X 57mm
  - Double Size

- P.T. Bio Farma
  - 18mm X 48mm
  - Double Size

VVM Dot

- 10 mm
VVMs are Supplied on Rolls 10,000 VVMs/roll

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

Kartoglu - WHO
VVM Dot Application to Cap of Vial or Neck of Ampoule

VVMs Dots are normally applied to the cap of the vial

YouTube Link to Serum Institute of India Video
http://www.youtube.com/watch?v=ytpS1SB_qGY

VVM Dot rectangles are applied to the neck of ampoules
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

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

2) Common label with VVM is applied to vaccine vial
Automatic Label Application Equipment Suppliers

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^{nd} 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

• 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
Thank you!!!