Heat and Freeze Sensitivity of Vaccines

DCVMN Workshop
"Vaccine quality management systems for manufacturing excellence"

Michael Rush, MBA
Executive Director - Global Health Policy

October 24-25, 2013
30 Good Distribution Practices
World-Wide Regulations & Guidelines

- **Initial focus – “cold chain”**
  - Track-and-Trace/Serialization

- **New terminology – Supply Chain Integrity**

- **Covers entire process: GLP, GCP, GDP**

- **Expanded to include**
  - Supply chain temperature management
  - Import/export compliance/security
Studies Supporting Product Licensure

1. Studies supporting product licensure include:
   - Long term stability of bulk intermediate
   - Long term stability of final container product
   - Accelerated stability at conditions of handling, excursion, and use
   - Release and manufacturing models
   - Clinical support of specifications

Approaches to Stability Assessment

- Currently stability data are usually analyzed using a “single point” model, wherein any individual data point on a stability study must meet end expiry specifications
  - This has also been called the “compliance model”

---

Approaches to Stability Assessment (cont.)

- Use of statistical models is scientifically correct, is recognized by the WHO Guidance, and represents the future of stability analysis
  - This has also been called the “comprehensive model”, or the “estimation model” or the “statistical model”

Adapted from T.L. Schofield, *Biologicals* 37 (2009) 387-396
Vaccine categories and characteristics

- Viral vaccines
  - Live attenuated
    - Generally heat sensitive
    - Usually can be frozen
    - (Protect from light)
  - Killed or purified protein
    - Normally very stable at 37 °C
    - If adjuvanted may be sensitive to freezing
Vaccine categories
and characteristics

• Bacterial vaccines
  – Live attenuated
    • Usually sensitive to heat
    • Generally lyophilized, so can be frozen
  – Killed or purified protein
    • Normally very stable
    • If adjuvanted, will be freeze-sensitive
  – Polysaccharide
    • Fairly stable and if lyophilized, can be frozen
  – Polysaccharide conjugate
    • Stability depends on possibility of hydrolysis of conjugate
    • Lyophilized products can be frozen; if liquid, probably not
Vaccine Temperature Sensitivity

Heat sensitivity vs. Freeze sensitivity

Days at 37°C

Most sensitive

Least sensitive

Freeze sensitivity

Most sensitive

Freeze sensitivity

Vaccines:
- OPV
- DTP
- Hep B
- Yellow Fever
- DTP-HepB
- Hib Lyo
- Hib Liq
- Rubella
- JE PHK
- Rotavirus
- IPV
- Hep A
- HPV
- Cholera/Typhoid Live
- DTaP + combos
- Cholera/Typhoid Killed
- Pneumo conj
- Men PS
- Men conj
- JE mouse brain
- Men PS
- Men conj

Note: This chart represents the sensitivity of vaccines to temperature changes. The x-axis indicates heat sensitivity, while the y-axis represents freeze sensitivity. Each vaccine is plotted according to its sensitivity profile.
Accelerated Stability Studies for WHO Prequalification

- **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.
## Characteristics that Define Vaccine Suitability

<table>
<thead>
<tr>
<th>Type of characteristic</th>
<th>Compliance</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory</td>
<td>- Pre-qualification process proceeds</td>
<td>- Rejection of application for prequalification evaluation.</td>
</tr>
<tr>
<td>Critical</td>
<td>- Pre-qualification process proceeds</td>
<td>- Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
</tr>
<tr>
<td>Unique and innovative</td>
<td>Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for pre-qualification evaluation.</td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>Pre-qualification evaluation proceeds</td>
<td></td>
</tr>
</tbody>
</table>
UNICEF/WHO Policies on Criticality of 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

<table>
<thead>
<tr>
<th>Vaccine vial monitor (VVM)</th>
<th>All vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below. 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/I/0707.048). 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.</td>
<td></td>
</tr>
</tbody>
</table>
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.”

1 http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049_Stability.final.09_Nov_06.pdf

2 WHO Temperature Sensitivity of Vaccines (WHO/IVB/06.10)
WHO Temperature Sensitivity of Vaccines

● 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.

3 http://www.who.int/vaccines-documents/DocsPDF06/847.pdf
VVM Characteristics

- VVM is a WHO prequalified device

VVM BEFORE end point: Active Surface lighter than Reference Surface

VVM AT end point: Active Surface matches Reference Surface
VVM Reaction Rates

<table>
<thead>
<tr>
<th>Category (Vaccines)</th>
<th>No. of days to end point at +37°C</th>
<th>No. of days to end point at +25°C</th>
<th>Time to end point at +5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVM 30: High Stability</td>
<td>30</td>
<td>193</td>
<td>&gt; 4 years</td>
</tr>
<tr>
<td>VVM 14: Medium Stability</td>
<td>14</td>
<td>90</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>VVM 7: Moderate Stability</td>
<td>7</td>
<td>45</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td>VVM 2: Least Stable</td>
<td>2</td>
<td>N/A*</td>
<td>225 days</td>
</tr>
</tbody>
</table>

- 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.

5 http://www.who.int/immunization_standards/vaccine_quality/who_pqs_e06_in05_1.pdf
Arrhenius Graph of VVM Categories
Based on Upper Limits at 25°C and 37°C
Selection of VVM Category
Example: Product A

Step 1: Summarize stability data
- 2 to 8ºC\(^1\): 3 years (1095 days)
- 25ºC: 45 days
- 37ºC: 7 days
- Expiry Date: 2 years

Step 2: Compare Stability Data with VVM Categories

\(^1\)2 to 8ºC is treated as 5ºC
Product A Stability Data and VVM Categories

CHOOSE VVM7
Product A - VVM Choice and Rationale

VVM14 and VVM30 – Reach End Point After Vaccine is Sub-potent

VVM2 – Reaches End Point Too Fast
Selection of VVM Category

Example: Product B

Step 1: Summarize stability data

- 2 to 8°C\(^1\): 1600 days
- 25°C: 150 days
- 37°C: 21 days
- Expiry Date: 2 years

Step 2: Compare Stability Data with VVM Categories

\(^1\)2 to 8°C is treated as 5°C
Product B Stability Data and VVM Categories

Product Expiry Date is 730 days

VVM will show if excessive heat exposure has occurred prior to Expiry Date

CHOOSE VVM14
Thank You

Obrigado
Gracias

Thank You