Heat Stable Oral Rotavirus Vaccine

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We are working with a pre-approved oral rotavirus vaccine

- Licensed in the US in 2006, WHO pre-qualified in 2010

- Licensed in >110 countries and ~119 million doses distributed worldwide as of June 2014

- Demonstrated safety profile and efficacy in low and high income countries as three dose vaccine

- Liquid, oral live pentavalent vaccine, containing five human-bovine reassortants
  - Four G serotypes (G1, G2, G3, G4) representing 80% of the G strains worldwide
  - One P serotype representing >75% of the P strains circulating worldwide
We adopted a unique approach to optimizing rotavirus vaccine

| 1 | Thermostability         | 2 | Ease-of-administration | 3 | Affordability          | 4 | Package size           |
|   |                         |   |                        |   |                        |   |                        |
|   | • Target: 4 months or more at 37/45°C |   | • Delivery systems that will be less expensive, easy to use and generate less waste |   | • Program level cost of administration • Cost of antigen / dose |   | • Target: Current EPI vaccines |

However, bulk antigen, viral titers, route of administration and dosing regimen remain unchanged

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From several vaccine stabilization approaches, we chose one established and one emerging technology.
Each approach has unique attributes to create vaccine dry powders

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Spray Drying</th>
<th>Freeze drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermostability</td>
<td>&gt; 120 days @ 40°C</td>
<td>&gt; 120 days at 37/45°C</td>
</tr>
<tr>
<td>Reconstitution required</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ready to fill powder</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Footprint</td>
<td>a) Dual Chamber Pouch: ~15 cc / 1 dose, ~5 cc /10 dose</td>
<td>a) Vial + Syringe + Adapter: 256cc monodose, 156 cc/ 10 dose b) Dual Chamber Pouch: ~15 cc/1 dose, ~5 cc /10 dose</td>
</tr>
<tr>
<td>Scalability/ Process cost</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Worldwide Manufacturing Options</td>
<td>Few</td>
<td>High</td>
</tr>
<tr>
<td>Speed to Market</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Process cost/dose</td>
<td>≤ Rs. 3</td>
<td>~ Rs. 4</td>
</tr>
</tbody>
</table>
Our freeze dried and spray dried processes are robust with low/no process loss.

Freeze Drying Process Loss

Spray Drying Process Loss
Pentavalent RVV is stable for at least 120 days at 37°C in a freeze dried lead formulation.

**Stability Results of Freeze Dried RVV at 37°C**

Confirmed in 3 independent manufacturing batches.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Potency Change (Log_{10} month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>-0.04</td>
</tr>
<tr>
<td>G2</td>
<td>-0.02</td>
</tr>
<tr>
<td>G3</td>
<td>0.00</td>
</tr>
<tr>
<td>G4</td>
<td>-0.01</td>
</tr>
<tr>
<td>P1</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

Freeze dried virus detected using RT-PCR assay. No process loss observed. All values statistically same as Zero.
Stability Results of Freeze Dried RVV at 45°C

Pentavalent RVV is stable for at least 90 days at 45°C in a freeze dried lead formulation

Freeze dried virus detected using RT-PCR assay. No process loss observed.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Potency Change (Log_{10}/ month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>-0.04</td>
</tr>
<tr>
<td>G2</td>
<td>-0.07</td>
</tr>
<tr>
<td>G3</td>
<td>-0.04</td>
</tr>
<tr>
<td>G4</td>
<td>-0.08</td>
</tr>
<tr>
<td>P1</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

All values statistically same as Zero
Stability Results of Spray Dried RVV at 40°C

Confirmation in additional independent batches ongoing

RVV Serotype G1 is stable for at least 36 weeks at 40°C in a Spray dried formulations

Spray dried lead formulation supports stability to RVV serotypes for at least 24 weeks at 40°C

Spray dried virus detected using FFA assay key points confirmed by RT-PCR assay.
Arrhenius kinetics demonstrate a vaccine shelf life of up to 33 months at 37° and 16 months at 45° C
India uses a 5 tier storage and distribution system wherein 12 month vaccine stability could be effective.

Source: UNICEF – National Cold Chain Assessment, India
A key component of our optimization is the choice of primary container/closure

<table>
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<tr>
<th>2-4 components</th>
<th>Single component</th>
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**Vaccine Presentation**
- Lyophilized or Spray-dried Powder in Sachets
- In situ Blister Lyophilized Tablets in Blister Packs
- Lyophilized or Spray-dried Powder Sachets with Luer-Lok adapter
- Lyophilized Cake in Vials with adapter for reconstitution

**Diluent/Buffer Presentation**
- Diluent/Buffer in Vial supplied with graduated disposable dropper
- Diluent / Buffer in Syringe

### Advantages

<table>
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<tr>
<th>2-4 components</th>
<th>Single component</th>
</tr>
</thead>
</table>

- **Advantages**
  - Low footprint in cold chain
  - Cheap, standardized packaging

### Disadvantages

- **Disadvantages**
  - Relatively complex logistics for separate components
  - Reconstitution

### Advantages

- Some devices cheap
- Simple logistics for single component
- Reconstitution
- Low footprint

### Disadvantages

- Few manuf. Options
- New concept for vaccines
Our Low Cost, Mono-Dose, Container Closure

Spray Dried/Milled Lyophilized Powder and Diluent in a two component pack

‘Packaged in a single component/ready to use format’ thereby meeting PSPQ – Critical characteristic
Thermostable Rotavirus Vaccine Program: Clinical/Device Development Strategy

Pre Clinical Tox.

Phase I Adults, Toddlers, Infants (~20-30 each)

Phase II Infants (~800-1000)

Phase III (if needed) Infants (~7000-8000)

Bulk Freeze Drying

Milling & Blending

Final Container Alignment

Licensure

Go / No-Go
≥ VVM 60
Potency Loss < Log[0.5]

Go / No-Go
AE, SAEs ≤ Comparator
Serum IgA ≥ Comparator

Go / No-Go
AE, SAEs ≤ Comparator
Serum IgA ≥ Comparator

Go / No-Go
AE, SAEs ≤ Comparator
Pouch URS Spec
PCT, Ph-I observations

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Summary: Thermostable RVV program

- Hilleman Laboratories has demonstrated longitudinal stability for five serotypes constituting RVV
- Pilot Scale-up completed with identification of critical process parameters
- Preclinical Tox.
  - protocol design completed
  - Preclinical lots manufacturing and tox study completion under planning
- Dual chamber frangible pouch design completed and prototypes are under testing
- Phase I trial initiation by 2015