Performing Comprehensive Risk Assessments for Live Virus Vaccine Manufacturing

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The information contained in this presentation is intended solely to provide general guidance on issues of interest to members of ABSA.
GSK Vaccines

- 1.4 billion vaccine doses
- Over 30 marketed vaccines available worldwide
- Over 20 vaccines in clinical development
- 11,206 employees worldwide
- Over 1,600 passionate scientists
- £4.3 billion sales (+15% compared to 2009)
A Proud Legacy

The Marietta Site - 130 Years of Vaccine Manufacturing

1882 – 1905: Lancaster County Vaccine Farms
• Smallpox

1905 – 1916: H.M. Alexander & Company
• Licensure by US Government
• Rabies, Tetanus, Diphtheria

1916 – 1943: Gilliland Labs
• Typhoid, Cholera

1943 – 2004: Wyeth
• Crucial Role in Nationwide Polio Trials
• Formally Recognized for Role in Smallpox
• Polio, Adenovirus, Antivenin, Influenza, Rotavirus, Pertussis, Various Pharmaceuticals, CAIV-T

SEP2005 – Present: GSK Vaccines
Objectives

- Introduced Measles, Mumps, Rubella vaccine at manufacturing site
- First live vaccine at site, need to assess biorisk
  - Engineering changes, if needed, require long lead time.
  - Vaccination strategy based on risk to product and risk to people.
  - Training & communication plan
  - Biosecurity
  - Environmental Permitting.
Did you know…

- Measles is a highly infectious disease spread by respiratory droplets.

- Mumps is a virus that effects mainly children and can be spread through the air, or direct contact with saliva or discharges from the nose.

- Rubella, although a mild disease, can cause devastating damage to unborn babies including deafness, heart defects and lesions of the brain, liver, lungs and bone marrow.
Secondary Manufacturing for Vaccines

- Measles, Mumps, Rubella vaccine is attenuated live virus vaccine for immunization against measles, mumps and rubella disease.

- Sterile lyophilized mixed preparation containing 3 strains of virus

- Secondary manufacturing
  - formulating, filling, lyophilizing and performing manual visual inspection

- Primary manufacturing occurs off site. Each of the three antigens is shipped to the site frozen.
Process Flow

Primary Manufacturing → Warehouse → Formulation

Filling → Lyophilization → Warehouse

MVI → Warehouse → Shipping
Formulation
Filling
Lyophilization
Manual Visual Inspection
All three attenuated strains are classified as: **BSL1**

The US Advisory Committee on Immunizations Practices (ACIP) has recommended severely immunocompromised individuals not be exposed to live virus vaccines, as there can be a risk of severe complications.
Biorisk - Medical

- There are no known cases of infection of a person with a positive antibody titer.

- The risk from exposure to the live vaccine virus to a healthy employee is the same as being given the vaccine.
Recommended Methods

- Establish cross functional teams:
  - Site Leadership and Process
    Subject Matter Experts, e.g.,
  - Warehouse
  - Formulation/Filling
  - Lyophilization
  - Manual Visual Inspection (MVI)
  - Waste
  - Medical

- Leverage engineering tool, Failure Modes Effects Analysis (FMEA), to map the process on-site.

- Collaborate with Company internal resources and ABSA members
Establish Criteria for Risk Assessment

- For the purposes of rating likelihood, evaluate the probability that a failure mode would occur.

- Not evaluate the probability that an exposure might occur, assume if the failure does occur then an exposure does occur.

- For the purposes of rating consequence, assume worst case: e.g., the individual exposed is an immuno-compromised person without a positive titer for Measles, Mumps, or Rubella.

- For all ratings assume the current controls in place unless they were specifically stated as not in place.
<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
<th>Bio-risk</th>
<th>Score</th>
<th>Category</th>
<th>Risk Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Risk</td>
<td>No mechanism to transfer to humans</td>
<td>0</td>
<td>Not possible</td>
<td>Incident probability is zero.</td>
</tr>
<tr>
<td>1</td>
<td>Theoretical Risk</td>
<td>A theoretical risk exists to an immunocompromised person with no titer.</td>
<td>1</td>
<td>Rare</td>
<td>Incident unlikely ever to happen</td>
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<td></td>
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<td>2</td>
<td>Unlikely</td>
<td>Incident foreseeable but probability very low</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Incident might be seen once during working life (40 year period)</td>
</tr>
<tr>
<td>3</td>
<td>Possible</td>
<td></td>
<td>4</td>
<td>Likely</td>
<td>Incident may have occurred in past</td>
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<tr>
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<td></td>
<td></td>
<td>Expect to see several incidents during working life (40 year period)</td>
</tr>
<tr>
<td>5</td>
<td>Almost Certain</td>
<td></td>
<td>0</td>
<td>Not possible</td>
<td>Incident probability is zero.</td>
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**Biorisk rating scale**

This scale was modified to reflect the risk associated with MMR. Any future Biorisk FMEA must use a scale which reflects the risks associated with those vaccines.
Conduct Risk Assessments

- Meet with process experts and draft steps in the process for moving vaccine through the site from initial warehouse receipt to outbound shipping.
- Complete initial training on the FMEA
- Create a flowpath associated with the steps from above and the initial FMEA form.
- Present the Biorisk rating scales for "consequence and likelihood".
- Meet with process experts to rate the likelihood (probability) that an individual failure mode would occur at each step.
- Meet with the medical officer and core team to discuss and rate the consequence of exposure for personnel and product.
- Sort and prioritize items by risk priority number.
- Meet with core group to review the FMEA and make recommendations.
### Risk Assessment / FMEA

<table>
<thead>
<tr>
<th>Item or Process Step</th>
<th>Type of Exposure</th>
<th>Consequence</th>
<th>Potential Causes</th>
<th>Control</th>
<th>Current Controls</th>
<th>Preventive Controls</th>
<th>Risk Priority Number (RPN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt in Building 21 at -45C and SB7 containers of 10L, 5L, or 1L plastic bottles - Packed in dry ice - batches are mixed lots of containers and mixed lots of M, M or R - Bottles are double-wrapped prior to shipment and should be contaminant free - Receipts quarterly</td>
<td>Product exposure</td>
<td>Not sealed by sender</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Do not require</td>
</tr>
<tr>
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<td>Product exposure</td>
<td>Forklift damage to shipping container</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Either move by pallet jack or unpack on dock</td>
<td>Worker exposure</td>
<td>Damaged by handling</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>Require gloves</td>
</tr>
<tr>
<td>Either move by pallet jack or unpack on dock</td>
<td>Worker exposure</td>
<td>Damaged by handling</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Do not require</td>
</tr>
<tr>
<td>(NOT a bio exposure risk) Move product into a chest freezer farm on</td>
<td>Elevator failure - product</td>
<td>Worker death or</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Risk Analysis
Outputs

- Vaccination strategy based on risk assessment conclusions
- Internal training and communication plan for First Responders e.g., Fire, EMS
- Biosecurity plan
- Environmental permitting requirements
Thank-you for your attention.