Performing Comprehensive Risk Assessments for Live Virus Vaccine Manufacturing

24Oct2012

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GlaxoSmithKline Vaccines

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

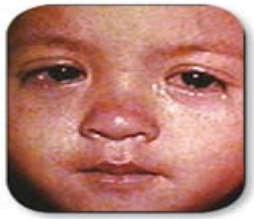
SEP2005 – Present: GSK Vaccines

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.

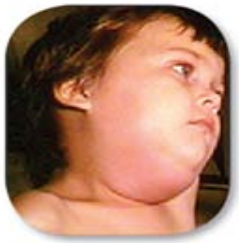
Did you know…

- Measles is a highly infectious disease spread by respiratory droplets



Measles

- 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.



Mumps

- 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.

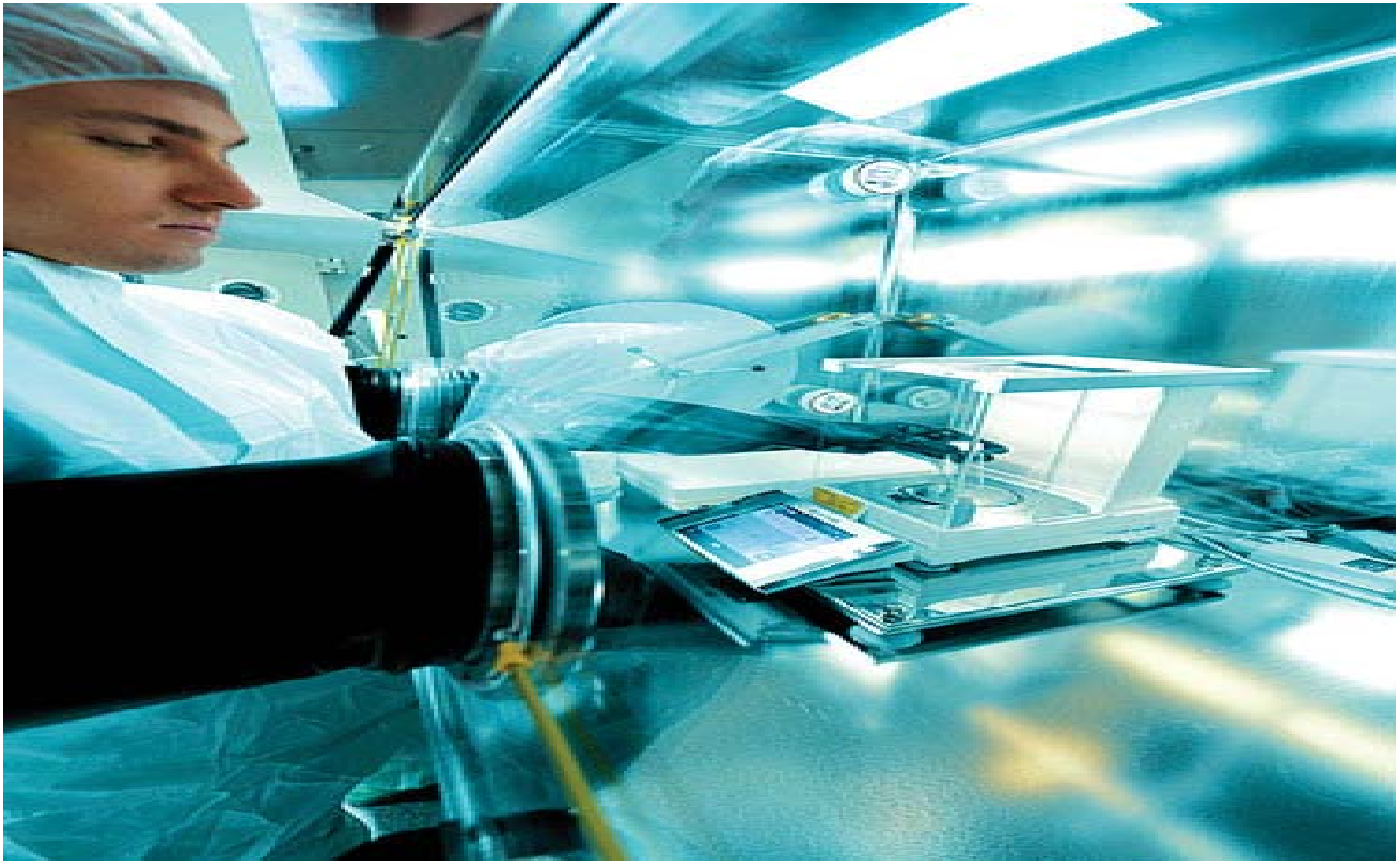
Rubella

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

Formulation



Filling

Lyophilization

Manual Visual Inspection

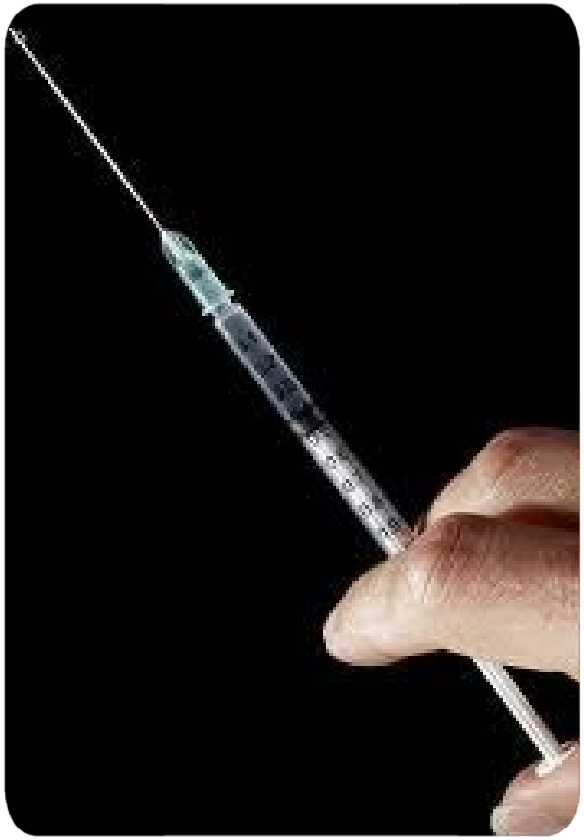
Biorisk

All three attenuated strains are classified as: **BSL1**

The US Advisory Committee on Immunizations Practices (ACIP) has recommended severely immuno-compromised 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.

Method for prioritising Health and Safety and Environmental Risks

Potential Consequences (Severity) (0-1)			Likelihood (0–5)		
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.					
Score	**Category**	**Bio-risk**	**Score**	**Category**	
0	**No Risk**	No mechanism to transfer to humans No mechanism to cause illness in humans.	**0**	**Not possible**	Incident probability is zero.
1	**Theoretical Risk**	A theroetical risk exists to an immunocompromised person with no titer.	**1**	**Rare**	Incident unlikely ever to happen Probability of incident close to zero
			2	**Unlikely**	Incident foreseeable but probability very low Incident might be seen once during working life (40 year period)
			3	**Possible**	Incident may have occurred in past Expect to see several incidents during working life (40 year period)
			4	**Likely**	Expect at least one incident per year Personnel would not be surprised by incident
			5	**Almost Certain**	Incidents occur frequently Expect significant number of incidents each year

Biorisk rating scale

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

RISK ANALYSIS										
Item or Process Step	...vation	Exposure Mode	Type of exposure	Consequence	Potential Causes	...elihood	Current Controls	Detection Rating with current controls	Risk Priority # (RPN)	
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	**VH**	Containers /bags not sealed	Product exposure	0	Not sealed by sender	0			0	Do not require
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	**VH**	Containers /bags not sealed	worker exposure	1	Forklift damage to shipping container	5	0		5	Require gloves
Either move by pallet jack or unpack on dock	**VH**	Container damaged	worker exposure	1	Damaged by handling	4		1	4	Require gloves
Either move by pallet jack or unpack on dock	**VH**	Container damaged	Product exposure	0	Damaged by handling	0		1	0	Do not require
(NOT a bio exposure risk) Move product into a chest freezer farm on	...	Elevator failure - product	worker death or	...	**asphyxiation from dry**	...		...	...	

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.