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Biosafety and Biosecurity in Vaccine Manufacturing Facilities, Principles and Practices

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Contents of presentation

- Definition
- Biosafety & Biosecurity considerations and principles
- Biosafety levels and Risk Groups
- Elements of Biosafety program
- GMP and Biosafety, Synergies and conflicts
- Biosecurity program and issues.
- Conclusion
Laboratory biosafety (working safely) describes containment principles, technologies and practices implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release. (Laboratory biosafety manual, 3rd edition, 2004)

Laboratory biosecurity (keeping the work safe) describes the protection, control and accountability for valuable biological materials (VBM) within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release. (Biorisk management: laboratory biosecurity guidance, 2006)
Laboratory biosecurity as a complement to laboratory biosafety

- Laboratory biosafety and biosecurity mitigate different risks, but they share a common goal: keeping valuable biological materials safely and securely inside the areas where they are used and stored.
- Good laboratory biosafety and biosecurity practices reinforce and strengthen GLP and GMP
Why biosafety practice in the Facility

Protection of:
- Personnel
- “products”
- co-workers
- lab support personnel
- environment
When is it Relevant to Consider the Issues of Biosafety?

- Manufacturers
  - Vaccine production *(in combination with GMP)*
  - GMO *(Genetically Modified Organisms)*

- Hospitals/patient care facilities
  - Isolation rooms with or without airlocks

- Research, diagnostic and control laboratories
  - Vaccine production
  - Hospitals/patient care facilities
  - Biodefense
Biosafety levels

- **BSL1** - agents not known to cause disease (no or low individual and community risk).

- **BSL2** - agents that cause human or animal diseases with moderate individual or low community risk (e.g. blood borne diseases).

- **BSL3** - indigenous/exotic agents associated with human disease and with potential for aerosol transmission - high individual risk (respiratory) low community risk)

- **BSL4** - dangerous/exotic agents of life threatening nature – serious diseases readily transmitted.
### Relation of risk groups to biosafety levels, practices and equipment

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Biosafety level (BSL)</th>
<th>Laboratory type</th>
<th>Lab. practice</th>
<th>Safety equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basic BSL-1</td>
<td>Basic teaching and research</td>
<td>Good microbiological techniques (GMT)</td>
<td>None, open bench work</td>
</tr>
<tr>
<td>2</td>
<td>Basic BSL-2</td>
<td>Production/Diagnostic services and research</td>
<td>GMT + protective clothing biohazard sign</td>
<td>Open bench plus bio – safety cabinet (BSC) for potential aerosols, PPE</td>
</tr>
<tr>
<td>3</td>
<td>Containment BSL-3</td>
<td>Special production/diagnostic services and research</td>
<td>As BSL-2 plus special clothing controlled access directional airflow</td>
<td>Biosafety cabinet and/or other primary devices for all activities, Special PPE</td>
</tr>
<tr>
<td>4</td>
<td>Maximum Containment BSL-4</td>
<td>Dangerous pathogen units</td>
<td>As BSL-3 plus airlock entry, shower exit and special waist disposal</td>
<td>Class-3 BSC or positive pressure suites in conjunction with class-2 BSCs, double ended autoclave trough the wall and filtered air, highly specialized PPE</td>
</tr>
</tbody>
</table>
### Summary of biosafety level requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>BIOSAFETY LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation of laboratory</td>
<td>No</td>
</tr>
<tr>
<td>Room sealable for decontamination</td>
<td>No</td>
</tr>
<tr>
<td>Ventilation:</td>
<td></td>
</tr>
<tr>
<td>— inward airflow</td>
<td>No</td>
</tr>
<tr>
<td>— controlled ventilating system</td>
<td>No</td>
</tr>
<tr>
<td>— HEPA-filtered air exhaust</td>
<td>No</td>
</tr>
<tr>
<td>Double-door entry</td>
<td>No</td>
</tr>
<tr>
<td>Airlock</td>
<td>No</td>
</tr>
<tr>
<td>Airlock with shower</td>
<td>No</td>
</tr>
<tr>
<td>Anteroom</td>
<td>No</td>
</tr>
<tr>
<td>Anteroom with shower</td>
<td>No</td>
</tr>
<tr>
<td>Effluent treatment</td>
<td>No</td>
</tr>
<tr>
<td>Autoclave:</td>
<td></td>
</tr>
<tr>
<td>— on site</td>
<td>No</td>
</tr>
<tr>
<td>— in laboratory room</td>
<td>No</td>
</tr>
<tr>
<td>— double-ended</td>
<td>No</td>
</tr>
<tr>
<td>Biological safety cabinets</td>
<td>No</td>
</tr>
<tr>
<td>Personnel safety monitoring capability</td>
<td>No</td>
</tr>
</tbody>
</table>
Essential Building Principles

- Primary containment barrier is the first barrier between agent and man (PPEs such as gloves, gowns, masks, biosafety cabinets, respiratory protection etc.)
- Secondary containment barrier is the barrier between agents and environment (airtight rooms, air handling and filtration, air locks, showers, laundry, sewage treatment, waste disposal, sterilisers, redundant services as well as equipment and material niches).
- Tertiary containment barrier represents an additional organisational barrier with the physical operation with items such as walls, fences, security, quarantine and animal exclusion zones.
Biosafety Principles

- **Substitution** (replace hazardous material)
  - IIV vs LAIV
- **Technical safety measures** (engineering controls)
  - Facility design
  - Directional airflow, ventilation
  - Isolators for animals
  - ......
- **Organisational measures**
  - SOP
  - Practices, procedures
  - Training
  - Access control
  - ......
- **Personal Protective Equipment**
  - Does not necessarily eliminates the hazard!!
Personal Protective Equipment (PPE)

PPE is not panacea!
Production Work flow considerations

During the programming phase it is essential to define how various elements are processed, including production material (working seeds, culture media, chemicals) animals (clean and dirty), people, wastes (carcasses, solid, other), laundry, samples from animals, feed and bedding (if used).
Elements of Biosafety Program

- Risk assessment
- Accident and spills control and prevention and reporting
- Decontamination/ Disinfection
- Waste management
- Animal handling and safety
- Personal Protective Equipment (PPE)
- Medical check and records
- Biosafety committee (BC) and Biosafety officer (BO)
- Packaging and transport
- Training Managers, Experts, Co-workers is the MUST
- Biosecurity
GMP and Biosafety

- Where do we find synergies?
- Where do the guidelines contradict each other?
- And what to do about it?
GMP & Biosafety

• The definition of
  - Biosafety and GMP

• Synergies and clashes
  - Strategies for sorting out clashes
  - Risk assessments

• Examples
  - General layout
  - Ventilation systems
  - Cleaning flows
GMP - Good Manufacturing Practice

- Definition

- The Good Manufacturing Practices (GMP) are the part of the quality assurance that ensures that pharmaceutical products are produced consistently and controlled in accordance with the appropriate quality standards. These standards depend on the intended use of the product and the requirements issued by the health authorities (WHO, MOH) or the product specification.

- GMP applies to both production and quality control laboratory.

- Purpose

- To ensure that the product is safe and effective for the end user.
Biosafety – GMP: Synergies

- **Restricted access**
- **Segregation** of production areas
- Facility designed for **easy cleaning**
- **Minimize contamination**
- **Validate processes**, systems, equipment, and facilities
- Job **certification** and mandatory **training**
- Mandatory personal protective equipment (**PPE**)
- **Written policies and procedures**, **SOPs**
- **Documentation**, double signatures, etc.
Why do Biosafety and GMP Clash?

- **GMP (Keep Out)**
  - Protect the product
  - Minimize cross contamination
  - Production flow: **dirty to clean** (raw materials to purified product)

- **Biosafety (Keep In)**
  - Protect the employees
  - Prevent escape of materials
  - Work flow: **clean to dirty** (non-infectious to infectious)
GMP and Biosafety Design Clashes

- Risk assessment
- HVAC design
- Room pressure
- Doors
- Cleaning rooms
Biosafety - Risk Assessment

- Evaluate
  - Type of Hazard(s)
  - Reservoir
  - Volume
  - Concentration
  - Possible ways of escape
  - Route of transmission
  - Infectious dose
  - Susceptible hosts
  - Incubation period
  - Decontamination principles

Along with all other aspects of product safety
Production - Risk Assessment

- **In different situations**
  - During production
  - Planned start up/shut down
  - Unplanned start up/shut down
  - Fire/power failure
  - CIP/SIP

- **For different aspects of the production**
  - Temperature (high, low)
  - Pressure (high, low)
  - Flow (fast, slow, reverse)
  - Volume/level (high, low)
  - Mixing/surface tension/bubbles
  - pH, Redox/density
  - Leakage/breakage
  - Tanks/pumps/pipes/valves
  - Computer/alarms/communication
Due to GMP – we already have…

- **Closed systems** – a process requirement
- **Double filters & steam traps** on tanks etc. to keep all contaminating elements **out**
  - Thereby keeping the infectious agents **within** the tanks
- **Sterile tube welders** for inoculation and sampling
- Adequate monitoring and **alarms**
- **Automatic shut down** in response to critical alarms
- **cGMP procedures**
  - Batch records, GMP trained employees, SOPs, log books, etc.
WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines

This document provides guidance to national regulatory authorities and vaccine manufacturers on the safe production and quality control of human influenza vaccines produced in response to a threatened pandemic. The document details international biosafety expectations for both pilot-scale and large-scale vaccine production and control and is thus relevant to both development and production activities. It should be read in conjunction with the WHO Laboratory Biosafety Manual (1) and replaces the earlier WHO guidance Production of pilot lots of inactivated influenza vaccines from reassortants derived from avian influenza viruses: Interim biosafety risk assessment (2). Tests required to evaluate the safety of candidate influenza vaccine reference viruses by WHO Reference Laboratories prior to release to vaccine manufacturers are also specified in this document.
BIOSECURITY:
Public Health and security activities have traditionally had minimal overlap

Public Health Issues: Virus, Masks, Hospital

Security issues: Guards, guns, Gates (3 Gs)

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Challenges to health and security

Intentional misuse of biological agent

Public Health

Security

Ebola Zaire

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Deliberate Use of Biological Agents represents a challenge to both Public Health and Security.

Different roles and responsibilities, different mandates

Same objectives

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Combined Strength of Biosecurity and Biosafety

- Laboratory biosecurity and biosafety work together to keep dangerous biological materials safe and secure in the laboratory.

- Biosafety is the foundation for biosecurity
  - Biosafety is sufficient for certain risks
  - Biosafety needs to be augmented for unique higher biosecurity risks

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Laboratory biosecurity

Biosecurity measures apply to:
- laboratories
- during transportation
- in field investigations
- in manufacturing facilities
- in health-care facilities

“Laboratory biosecurity”
Refers to institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of valuable biological materials (VBM) including pathogens and toxins. (keeping the work safe)

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valuable biological materials (VBM)

Biological materials that require (according to their owners, users, custodians, caretakers or regulators) administrative oversight, control, accountability, and specific protective and monitoring measures in laboratories to protect their public health, economic and historical (archival) value, and/or the population from their potential to cause harm or death.

These may include: Vaccine strains, culture collections, dangerous pathogens, probiotics, research strains, industrial strains, etc.
Components of Institutional Biosecurity Program

- Risk Assessment
- Physical security system
- Personnel Management
- Material Control and Accountability (MCA)
- Information security
- Transport and transfer Security
- Managing the Biosecurity Program
Physical Security

Components of a physical security system

- Graded protection
- Access control
- Intrusion detection
- Response capability
- Training
- Performance testing
Personnel Management

- Employee screening
  - proportional to the roles and responsibilities of the individual
  - Correlate with access authorization

- Visitor control
  - Casual visitors should be escorted in restricted areas
  - Working visitors should be processed in the same manner as regular employees

- Badges
  - Identification badges should be worn in institutions that have higher risk pathogens and toxins
  - Badges should be returned upon termination of access

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Material Control and Accountability (MCA)

- Identify what materials to control
  - Identify pathogens and toxins of concern
- Identify how will materials be controlled
  - Containment
  - Procedures such as inventory and location of use
- Identify who is accountable for the materials
  - All material should have an “accountable person”
- Identify where is MCA applicable
  - In laboratories
  - In Culture Collection Centers
  - During transportation

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Managing the Biosecurity Program

- Role of management to ensure biosecurity program is:
  - Appropriate to need (based on facility risk assessment)
  - Resourced and cost-efficient for risk
  - Graded in protection activities
  - Coordinated with biosafety, good lab practices, security community, etc
  - Define roles and responsibilities in written plan
  - Provide regular training
  - Provide routine system assessments
  - Biosecurity plan is corrected/modified as needed
Conclusion

- Biosafety and biosecurity are essential practices to all biological facilities
- Complementary to GLP and GMP
- There are synergies and conflicts
- Should find the way to enhance synergies and reduce (or Resolve) conflicts
- Training of managers, experts and other personnel is an important task.
Wishing You All a Healthy, Safe and Secure World

Thank you

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