Course Objectives

- Introduce practices and principles of biorisk management as they can be applied to vaccine manufacturing
- Present practical, flexible and applied methodologies for use within production settings
- Share practical experiences and views in relation to the challenges faced in conducting biorisk management activities
### Schedule – Day 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>0830 – 0900</td>
<td>Background and introductions</td>
</tr>
</tbody>
</table>
| 0900 – 1230 | Biosafety and biosecurity  
  - Standards and regulations  
  - Principles of containment  
  1230 – 1330 LUNCH     |
| 1300 – 1730 | Containment levels and biorisk management  
  - Biorisk management system  
  - Risk assessment  
  - Biological agents and toxins inventory and information  
  - General Safety  
  - Personnel & competency  
  - Good microbiological technique  
  - Clothing & PPE |

### Schedule – Day 2

<table>
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<th>Time</th>
<th>Session Content</th>
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</table>
| 0830 – 1230 | Human Factors  
  - Healthcare  
  - Emergency response & contingency planning  
  - Accident/incident investigation  
  - Equipment and maintenance  
  - Facility physical requirements  
  - Equipment and maintenance  
  - Disinfection, Decontamination and Sterilisation  
  - Transport procedure  
  - Security  
  1230 – 1330 LUNCH     |
| 1330 – 1730 | Examples of biorisk management standards for vaccine production and discussion  
  - Open discussion and conclusion |
About Riskren

- Founded in Singapore to work primarily in fields of:
  - Laboratory biorisk management
  - Hospital acquired infections
  - Biological weapons control and threats from non-state actors
- Team experienced in working around the world with many laboratory categories:
  - BSL 1 to 4
  - ABSL
  - Pharmaceuticals and vaccines...
- Disease-specific programmes and situations
  - TB
  - Polio
  - Smallpox...

What We do

- National and strategic initiatives
- Development of regulations, standards and guidelines
- Management system development
- Risk assessment and design review
- Independent audit and inspection services
- Certification
- Tools and software
- Training and communication
Our Experience

- World Health Organisation
- Det Norske Veritas (DNV Biorisk)
- European Commission
- US State Department
- American Society for Microbiology
- Norwegian Ministry of Foreign Affairs
- National Institute for Hygiene and Epidemiology (NIHE), Vietnam
- Eijkman Institute, Jakarta
- Canadian Science Centre, Winnipeg
- LG Lifesciences
- Virolclinics
- AJ Vaccines

Introduction

- Your name and organization?
- Background and experience?
- Your involvement in risk assessment?
- What do you expect to get from this course?
**Biosafety vs Biosecurity**

**Biosafety** describes the containment principles, technologies and practices that are implemented to prevent the *unintentional exposure* to biological agents, or their accidental release.

*(WHO Laboratory Biosafety Manual, 3rd Edition)*

**Biosecurity** describes the *protection, control and accountability* for biological agents and toxins within laboratories, in order to prevent their loss, theft, misuse, diversion of, *unauthorized access or intentional unauthorized release.*

*(CWA 15793:2011)*
Informal definitions

**Safety**: Protection from *unintentional* events
(incidents, accidents, natural disaster...)

**Security**: Protection from *intentional malicious* actions (sabotage, espionage, terror, crime, blackmail...)

**Biosafety** is to **keep** bad **bugs** from people,
**Biosecurity** is to **keep** bad people from **bugs**

STANDARDS AND REGULATIONS
The basis

- Many reference documents available:
  - Laws or regulatory requirements
  - Standards
  - Guidelines
  - Reference documents
    - Published papers
    - Text books
    - Internet articles
  - Training materials
  - Etc...

Standards vs. guidelines

- Laws
  - Usually country-specific
  - Compliance Mandatory

- Standards
  - Based upon requirements
  - Use word ‘shall’
  - May incorporate guidance to explain the requirements

- Guidelines
  - Are NOT normally set of requirements
  - Should be considered and addressed as appropriate
  - Terms:
    - Should – recommendation
    - May – allowance
    - Can – possibility
Function?

Can be used for:

- Ensure compliance, including certification and accreditation activities
- Basis of safe and secure work practices
- Promoting good practices within an industry
- Provide framework for audits, inspections and trainings
- Promote international collaboration
- Pre-requisite for funding - providing stakeholders of responsible and proportionate biorisk management

Regulations

A regulation is a rule or law designed to control or govern conduct. In statist mechanisms it can also be extended to monitoring and enforcement of rules as established by primary and/or delegated legislation. In this form, it is generally a written instrument containing rules having the force of statist law (as opposed to natural law). Other forms of regulation are self regulation.

Ref: http://en.wikipedia.org/wiki/Regulation
In essence, a **standard** is an agreed way of doing something. It could be about making a product, managing a process, delivering a service or supplying materials – standards can cover a huge range of activities undertaken by organizations and used by their customers.


**Examples of Standards**

- CWA 15793:2011 Laboratory Biorisk Management
- ISO15190: Medical Laboratories; Requirements for Safety
- National Standards of the People’s Republic of China; GB 19489-2004
- NSF/ANSI Standard # 49 – 2002, Class II Biological Safety Cabinets Types
Guidelines

A guideline is a statement by which to determine a course of action. A guideline aims to streamline particular processes according to a set routine or sound practice. By definition, following a guideline is never mandatory. Guidelines are not binding and are not enforced. Guidelines may be issued by and used by any organization (governmental or private) to make the actions of its employees or divisions more predictable, and presumably of higher quality.


Relevant industry guidelines

- WHO Laboratory Biosafety Manual
- WHO Biorisk Management - Laboratory Biosecurity Guidance
- WHO Expert Committee on Biological Standardization, sixty-sixth report. (WHO technical report series ; no. 999) – Containment (p113)
Exercise

- In your groups discuss:

1. What regulations, standards and guidelines are used in your country and what do they cover in terms of biosafety / biosecurity?
2. Are there any important areas where there are no standards / guidelines in place?
3. Are they effective and followed by all relevant facilities?
4. Are there any inspection / certification schemes in place to ensure the requirements are being met?

15 minutes followed by group discussion
Transmission

- Critical but often poorly understood area
- Agents often have several transmission routes, with one being recognized as the most likely
- Vaccination may prevent infection but does not necessarily prevent transmission (e.g. polio)
- Some routes of transmission may not normally be probable in natural situation may become plausible when culturing
- Infectious dose may be critical issue, together with other factors, e.g. survival in environment

Routes of Transmission

- Contact transmission
  - Can be through direct contact, indirect contact or ingestion
- Airborne transmission
  - Inhalation of aerosols or small particles carrying microbes for >2m from source
  - Direct transmission from droplets / particles in suspension in air or deposition onto contaminated wounds
- Blood borne transmission
  - Percutaneous inoculation or transfusion
  - Injury (cut, prick)
Exposure

- Main objective should be to prevent exposure
- If no exposure, there is no infection
- Often difficult to manage situations once exposure has occurred but relatively easy to prevent exposure
- Exposure prevention can be described through the hierarchy of controls

Hierarchy of controls
Containment

- Primary containment (barriers):
  - Protection of personnel and the immediate environment from exposure to infectious agents
- Secondary containment (barriers):
  - Protection of the environment external to the facility from exposure to infectious materials
- Tertiary containment (barriers):
  - Represents an additional organisational barrier with the physical operation with items such as walls, fences, security, quarantine and animal exclusion zones
**Integrity**

- Ability to provide an assurance that system will not fail
- Often achieved through testing, alarms and other associated mechanisms
- Need for confidence based upon criticality of system and will be reflected in the standards and test methodologies

- Can be applied to:
  - Rooms and other spaces
  - Duct and piping (including production equipment, filter housings, etc.)
  - PPE (e.g. positive pressure suits)
  - Pressure vessels (e.g. autoclaves, kill tanks)
  - Pass through boxes

- Methods include:
  - Pressure decay testing
  - Bubble testing
  - Smoke testing

- Can be qualitative or quantitative
- Often important aspect in ensuring containment achieved
Positive or negative pressure?

Air

Air

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Filtration?

A

Product protection?

B

Containment?

A

B
Pressure cascades

INCREASING NEGATIVE PRESSURE (Pa)

0 -15 -30 -45 -60

Containment pressure cascades

INCREASING NEGATIVE PRESSURE (Pa)

0 -15 -30 -45 -60

Clean change  Ante-room  Prep room  Main facility  Waste handling / animal room
Discussion

- In your groups, discuss the agents that you work with and their modes of transmission.
- Do you have primary containment of these materials and if so how do you test for integrity of systems?
- What other measures do you rely on to keep people and the environment safe?
Table 1. Classification of infective microorganisms by risk group

**Risk Group 1 (no or low individual and community risk)**
A microorganism that is unlikely to cause human or animal disease.

**Risk Group 2 (moderate individual risk, low community risk)**
A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.

**Risk Group 3 (high individual risk, low community risk)**
A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.

**Risk Group 4 (high individual and community risk)**
A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

Source: WHO Laboratory Biosafety Manual, 3rd Edition
Types of BSL

- **BSL1**
  - Defined organisms, not known to cause disease in healthy adults

- **BSL2**
  - Moderate risk agents present in the community
  - Cause diseases of varying severity

- **BSL3**
  - Indigenous or exotic agents, aerosol transmission
  - Serious and potentially lethal infection

- **BSL4**
  - Dangerous or exotic agents, of high risk, aerosol transmission
  - Life threatening disease
BSL and risk groups

- BSL – Biosafety Level
- Risk groups are used as part of the comprehensive biosafety risk assessment
- Risk assessment is the backbone of biosafety practices, especially in determining the appropriate biosafety level
- Assignment of biosafety level: risk group and other factors
  - Nature of the organism
  - Amount used
  - Activities
  - Non-scientific factors, e.g. community perception

Biological containment facilities

- No conclusive definition for different facility types – guideline / risk based
- Organisms categorised by risk group from 1 to 4
- Facilities (and management controls) defined by containment levels ranging from 1 to 4 (e.g. BSL3, PC3, ACDP3, CL3...)
- Recent growth of such facilities around the world, including in developing countries
- Combination of engineering and management controls
- Relative sophistication can create confusion and practical difficulties in design, construction and operation
Hazard characterization of the biological agent

Critical factors of interest:
- Pathogenicity
- Mode of transmission
- Infectious dose of the agent
- Host range
- Agent stability
- Availability of an effective immunization or prophylaxis

Pathogenicity
- Pathogenicity is the ability of a biological agent to cause illness
- Pathogenicity of the infectious or suspected infectious agent, including disease incidence and severity (i.e., mild illness versus high mortality, acute versus chronic disease) is key
- Also may have infection without symptoms, but individual still infectious

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BSL1

- Basic microbiological facility
  - Surfaces: smooth, easy to clean, non-absorbing, resistant to chemicals and disinfectant, etc.
  - Sink for hand-washing
  - Windows that can be opened with fly screen
  - Adequate working space
  - Safety equipment as primary barriers
  - PPE (e.g. laboratory gown, gloves, face protection, eye protection)

Emphasis on Good and Safe Microbiological Technique!
BSL2 facility (cont.)

- Biosafety Cabinet (BSC) or others forms of primary containment if needed
  - As a primary barrier
  - Certified regularly (where possible)
- Facility design as secondary barriers
- Biosafety signs and biosafety manual
BSL2 facility (cont.)

- Closed windows and doors
- Inward flow of air without recirculation to non-contaminated areas
- Restricted access
- Hand washing sink near exit of the room / suite
- No cross-connections between sources of facility and drinking-water supplies
- Preferably, anti-backflow device fitted to protect the public water system
- \( \text{ACH} \geq 6 \)

BSL2 (cont.)

- Facilities for drinking, eating and rest are available outside facility working area
- Autoclave or other means of decontamination near the facility
- Equipment labelling
- Contaminated waste bin
- Proper waste disposals
- Leak proof transport containers
- Vacuum line has filters and traps
- First aid equipment with necessary prophylaxis
- Emergency back-up power provided if needed
- Maintenance of records: infection, incident, accident
BSL3

as BSL2 with addition:

- Separated from other areas with unrestricted traffic flow
- Access through an ante room
- Ante room doors self-closing and interlocking
- Exhaust not circulated to other areas
- Air exhaust may go through HEPA filter, depends on micro-organisms
- Air may be re-circulated within the laboratory if HEPA filtered
- HEPA filter can be tested and decontaminated
- Air ducts permit gaseous decontamination

Source: WHO Laboratory Biosafety Manual, 3rd Edition;
BSL3

Facility design as secondary barriers
- Exhaust air discharged outside and dispersed away from other buildings and re-entrainment is not possible
- Windows closed, sealed, break resistant
- Containment is fumigation tight
  - Sealed penetration
- Controlled pressure cascade
  - (corridor; ante room -; lab --)
- Directional airflow monitoring device
  - Pressure sensor, ball monitoring device
- System to prevent sustained positive pressurization
- Audible or visible HVAC alarm
- Hands-free hand washing station near each exit door

BSL3

- BSC away from walking areas and out of cross current from doors and ventilation
- Autoclave often inside containment
- Backflow prevention device or assembly on water supply and other services (e.g. gas lines, electrical cabling)
- Design and operation are documented
- Restricted access, e.g. key or card reader
- Emergency back up power for essential services
- Laboratory clothing of solid-front and wrap-around, head covering, full sleeved arm
- Health surveillance
Concept BSL4: different from BSL1-3

- Space suit “provides tertiary barriers – positively pressurized and HEPA filter
- Dedicated room air supply and exhaust system
- HEPA filters on both inlet and exhaust
- Personnel shower
- Disinfection shower with interlock
- Air lock with airtight doors and interlock
- Double door autoclave / barrier autoclave
- Waste water decontamination
- Breathing air for suit lab with redundancy
- High level of redundancies
BSL4 – cabinet line

- Cabinet lab
  - Biological agents are worked inside a BSC Class3 line
  - A dedicated non-recirculating ventilating system for the cabinet laboratory

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Biorisk Management Elements

- Transport procedures
- Decontamination, disinfection and sterilisation
- Equipment and maintenance
- Facility physical requirements
- Accident / Incident Investigation
- Emergency response and contingency planning
- Healthcare
- Biortsk management system
- Risk assessment
- Biological agents and toxin inventory and information
- General safety
- Good microbiological technique
- Personnel and competency
- Clothing and personal protective equipment
- Human factors

CWA 15793 Standard

- Define the scope for managing biorisks in biological facilities
- Facilitate the identification of current best practice in the field
- Allow for a variety of solutions when managing biorisks within a containment facility
- Drive continuous improvement
- Enable you to assure stakeholders of responsible and proportionate biorisk management
Biorisk management system

System and policy in place to manage biorisk. Effective management and organisation, management commitment and leadership.

- Biorisk management policy
  - Top management responsibility
  - Overall biorisk management objectives, commitment to continual improvement

- Objectives, targets and programme
  - Biorisk control objectives and targets put in place to control biorisk at relevant functions and levels

- Roles, responsibilities and authorities
  - Top management to ensure roles, responsibilities and authorities are defined, documented and communicated

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Biorisk management system

- Consultation and communication
  - Relevant biorisk information is disseminated to employees and other relevant parties

- Work programme, planning and capacity
  - Programme of work to be defined, documented and reviewed
  - Criteria for approval
  - Sufficient resources to manage workflow – planned and unplanned

- Conformity and compliance
  - All relevant requirements (including legal) shall be identified and fulfilled

- Continual improvement
  - Continue to improve the effectiveness of the biorisk management system

Corrective action
- Action taken to eliminate causes of non-conformities

Contractors and suppliers
- Consider contractors / suppliers that provide products / services that may impact biorisk (e.g. cleaning services, laboratory equipment)

Biorisk management review
- Biorisk management system reviewed by top management at planned intervals
- Records of management review maintained
Risk assessment

Are effective mechanisms implemented to identify, assess and manage risks. Is the fundamental basis underpinning the standard.

- Planning and resources
  - Establish, implement and maintain system for risk assessment
  - Performance of system reported to senior management
  - Provide adequate resources including trained personnel

- Assessment, timing and scope
  - Defined scope, nature and timing
  - Proactive as opposed to reactive

CWA 4.3.1.1
CWA 4.3.1.2
Risk Assessment

- Hazard identification
  - Hazards associated with work are identified, assessed and documented
  - Hazard identification exercise

- Risk assessment
  - Suitable methodologies for assessing and recording risk

- Risk management
  - Suitable methodologies for allocation of actions resulting from risk assessments, including time lines, responsible persons and reporting / approval mechanisms

Definitions

- A **hazard** is defined as a situation with a potential for causing harm to human safety, the environment, property or business.

- It may be a physical situation (e.g. a delivery truck may collide with another vehicle at a site), an activity (e.g. fork lift operations are a hazard because the load might drop) or a material (e.g. fuel oil is a hazard because it might catch fire).

- The essence of a hazard is that it has a potential for causing harm, regardless of how likely or unlikely such an occurrence might be.

- A **risk**, strictly speaking, is the chance of something happening expressed in terms of **consequence and likelihood**

- These terms are frequently interchanged, but have different meanings
What is Risk?

Risk matrix

Risk matrix

Risk matrix

Risk matrix

Determine
- Consequence category and level
- Likelihood criteria
- Risk acceptance criteria
- Risk matrix

Risk Criteria | Description
--- | ---
Low | Low risk, acceptable with review
Medium | Work conducted towards reducing the risk (green zone).
High | High risk, unacceptable. High priority and implementation of recommendations to reduce the risk
Risk matrix

Risk Assessment Methods

- SWIFT = Structured What If Technique
- Bow-Tie
- HAZOP = HAZard and OPerability
- FMEA = Failure Mode and Effects Analysis
- SIL = Safety Integrity Level
- LOPA = Layer Of Protection Analysis
- AR&M = Availability, Reliability and Maintainability
Risk Management

- Identify the risk

Risk Management

- Analyse and evaluate the risk
Risk Management

- Eliminate the risk

- Find an alternative
Risk Management

- Isolate the risk

Risk Management

- Reduce the consequence
Biological agents and toxin inventory and information

- Systems in place to identify, record and review the organisms stored, received and transported from a facility
- Level of detail and nature of the system will depend upon the biological agents being held
- Can range in complexity from simple lists to secure databases
- Also examines the way materials are stored and control of stocks of cultures
Biological agents / toxin inventory & information

- Inventory
  - Accurate and up-to-date biological agents and toxin inventory established and maintained
  - Records are current, complete and stored securely
  - Transfers between laboratories at the facility or into and out of the facility are recorded and controlled in line with risk

- Inventory monitoring and control
  - Review of inventory conducted at planned intervals in line with risk
  - Measures put in place to minimise quantities of biological agents and toxins in the inventory

CWA 4.4.2
CWA 4.5.3

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General safety

- Examples of issues to address:
  - Fire safety
  - Electrical safety
  - Chemical safety,
    - e.g. Decolourising solvents, acid-alcohol, fixing fluids, etc.
  - Use of gasses (including risk of asphyxiation)
  - Laboratory animal care and use
  - General housekeeping, storage requirements and tidiness
  - Personal tidiness
    - e.g. unsecured long hair, use of mobile phone in lab etc.

Processes in place to ensure hazards associated with personnel’s work in the facility are identified and managed while addressing their implications on biorisk.

- Formal process in place to identify and manage risk with general safety

CWA 4.4.4.1
Exercise

Read the following statement

The biggest and perhaps only hazard in a vaccine production facility are the biological agents. All our efforts should go towards controlling these as other hazards are relatively minor in comparison.

Discuss in your group:-
1. Is this statement true or false.
2. Any other hazards that may be present in the facility (e.g. chemical, physical...).
3. Are there situations where the general safety risks may be greater than the biorisk.
Personnel and competency

Processes in place to ensure that people with appropriate qualifications and backgrounds are recruited, trained in all aspects of the work programme, and their competency assessed and monitored in a structured way.

- Recruitment
  - Qualifications, skills and aptitudes
- Training
  - Requirements and procedures training of personnel
- Competence
  - Must be demonstrated before working unsupervised
- Continuity and succession planning
  - Adequate backup required
- Exclusion
  - Measures for the removal and exclusion of personnel

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Good microbiological technique / practice

Identifying, implementing and reviewing appropriate microbiological techniques and controls

- Good Microbiological Technique / Practice
  - Personnel handling biological agents and toxins are competent
  - Adequate time and equipment

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Good microbiological technique / practice

- How an organization identifies appropriate microbiological techniques and controls
- How these are then implemented and reviewed
- Development of a biosafety or operations manual
  - Identify hazards that may be encountered
  - Specifies practices and procedures
  - Minimize or eliminate risks

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Examples of procedures which should be addressed:

- Animal handling
- Centrifugation
- Control of needles and sharps
- Correct use of vacuum pumps
- Culture, purification and storage techniques
- Minimization / containment of aerosols
- Pipetting
- Sonication and other mechanical forms of cell / tissue disruption
- Use of biological safety cabinets and other primary containment devices
- Use of disinfectants, including spill control, routine decontamination, hand washing and showering

Look out, sharps!!
Sharps

**Definition:**

Any object that can be reasonably anticipated to penetrate the skin and result in an exposure

- Prevent glass materials
- Never recap the needle
- Use only sharps approved by the BSO
- Use disposable sharps
- Use certified sharp containers

Centrifugation

- Beware any procedure that adds energy!!
- Highly effective way to generate and spread aerosols
- Containment principles apply, e.g. sealed rotors / buckets
- Great care should be taken on loading and unloading
- Balancing critical
- Allow time (10 minutes?) for the aerosol to settle before removing the caps/ covers
Biosafety Cabinets (BSC’s)

- EU or US: that’s the question
- EU: NEN-EN 12469:2000
  - BS 5726
  - DIN12950 Teil 10
  - Test certificate per model and per size!
  - Certify bodies: TÜF, HPA

- US: Biosafety in Microbiological and Biomedical Laboratories

Cross flow cabinet

- Laminar flow hoods are NO biological safety cabinets
- Vertical or horizontal laminar flow
- HEPA filtered air (intake)
- Product protection only
- Not to use for pathogens or even primary cell lines!!!!!
Types of BSC

Class I

Figure 1. Class I Biological Safety Cabinet.

Class II: protection of worker and product

- Class IIA: one HEPA filter on exhaust and work area
- Class IIB: two HEPA filters on exhaust and work area
Types of BSC

Class III cabinet: inlet and exhaust HEPA filtered
Total protection for worker and environment

Isolator BSL3 with independent ventilated lock
Isolator BSL3

Isolator BSL3 with removable waste container (RTP port)
Connection to the exhaust: yes or no

Depending the type of micro-organism, but to be flexible worst case i.e. airborne recommended

Options:
- stand alone
- thimble unit
- hard ducted

Hard ducted when using volatile toxic chemical (growth inhibitors) or volatile radio nuclides

Position of the BSC in the lab

- Not close to the door
- Quiet area, the less possible traffic of persons
- Do not block the grills
- Place no other equipment like incubator, refrigerator, freezer, centrifuge close to the BSC
- Take care to correctly position of the inlet and exhaust of the lab air

All this to prevent disruption of the air-circulation in the cabinet
Biosafety Cabinet (BSC)

- Place items in the center of the BSC.
- Do not block air grills with any items including paperwork, apparatus, pipettes and etc. This is to avoid to disturb the proper down stream of the air in the BSC;
- Minimize the amount of apparatus in the BSCs and must consist of at least biological waste container and disinfectant bottle;
- Do not open the glass viewing panel (the glass separating BSC user and interior work space of BSC) when the BSC is in use.
Personal protection

- PPE = Personal protective equipment

- Selection PPE based on risk-assessment:
  - biological agent: mode of transmission
  - activity: mode of exposure

Dr. Schnabel: a Plague doctor of Rome with PPE in 1656

Clothing and PPE

- Clothing and PPE
  - Needs are identified
    - Adequate information used to select PPE?
      - Risk assessments
      - Review and analysis of tasks
      - Employee feedback
    - All personnel who need PPE are identified and supplied with correct fitting equipment and clothing
      - Scientific staff
      - Visitors
      - Contractors
  - Suitable equipment specified, available, used and maintained

Ensuring that staff are provided with the right tools to minimise potential exposures, and making sure they know how to and when to use them

CWA 4.4.4.5.4
Respirators

- Surgical mask: no respirator!

Particulate respirator
- 3M FFP1 (1861-N95) 75-78%
- 3M FFP2 (1862, 1872V - N99) 89-92%
- 3M FFP3 (1863, 1873V - N100) 95-98%

Respirators (continued)

- PAPR = Powered Air Purifying Respirator
**PAPR**

- Battery operated, not disposable
- Particulate filter (HEPA)
- Fit test not required
- Training required
- Used when:
  - FFP respirators does not fit
  - Employee has facial hair
  - High-risk aerosol generating procedures present

**Respirators**

- Combination of biological and chemical protection
- ABEK2P3 = protection against formaldehyde and BSL3 organism
Protective Clothing

- **Purpose**: to protect worker and to protect from taking out infectious material
- **Disposable**: discard by leaving the lab
- **Non-disposable**: autoclaving by leaving the lab
- **Cuffs**: to enable to take gloves over the sleeves
- **In high containment**: always long sleeves

The overall, the gown and the scrub suit

(the scrub suit to be used as underwear)
Other types of PPE

Gloves
- Vinyl, nitrile, latex
- double gloves yes or no
- long enough to overlap the cuff of the gown/overall
- Kevlar in case of working with sharps

Goggles or safety glasses
- protect eyes from splashes

Face shield
- protect face from splashes

Head cover
- protect hair from airborne infectious materials

Sleeves
- Protect sleeves of lab coat in BSC from aerosol and splashes
PPE video

How many mistakes can you spot?
Human factors

Addresses issues such as raising awareness of biorisk issues and how to measure and improve the biorisk culture within the organisation.

- Behavioural factors and control of workers
  - Human factors
  - Management of behaviour
  - How workers interact with facility and equipment

- Behavioural and attitude factors
  - Conflict management and resolution
  - Human reliability and behavioural safety
  - Adherence to procedures
  - Willingness to report accidents, incidents or unsafe conditions, behaviours.
  - Avoidance of ‘blame culture’ and protection of workers
  - Hierarchies and culture
  - Motivation, communication and team work
Discuss

1. How important are human factors in keeping a facility safe and secure?
2. What issues need to be considered in terms of human factors (compliance culture, common behaviours, attitudes, etc.)?
Healthcare

System in place to protect workers from injuries and illnesses resulting from exposure to biological agents and toxins

- Worker health programme
  - Health surveillance programme
  - Health hazard identification and risk assessment for all relevant personnel

- Vaccination of personnel
  - Define a policy
  - Need for vaccination based on risk

- Medical emergencies
  - A system in place to manage medical emergencies

Healthcare

- Health hazard identification and risk assessment for all relevant personnel
  - Relevant personnel to be consulted:
    - Biorisk management advisor
    - Occupational health professional
    - Facility personnel
Healthcare

- Vaccination of personnel
  - Define a policy
  - Need for vaccination based on risk
  - Provide evidence of vaccination or established immunity
  - Current vaccination certificates are valid
    - Cross-check with doctor/clinic that administered the vaccine
  - Is only a risk mitigation strategy and does not mean good microbiological techniques or PPE use can be relaxed

- Medical emergencies
  - A system in place to manage medical emergencies
    - Antivirals
    - First aid kits

Occupational Health

- Medical examination
- Vaccination program
- Serum banking
- Medical surveillance
Skin and eyes

- In case of broken skin a means of entry to the body may be created for the pathogen.

- High air flow rates can result in a dry atmosphere and problems to those wearing contact lenses.
Emergency response and contingency planning

Structures and mechanisms in place to cope with working outside the normal operating conditions

- Emergency response and contingency plans
  - Plans and procedures to identify potential incidents and emergency situations
  - Includes general safety, security & medical issues

- Emergency scenarios
  - Identify credible and foreseeable emergency scenarios that may impact the organisation’s biorisks

- Emergency plans
  - Medical and or environmental emergencies
  - Reasonable and proportionate control measures
  - Emergency plans effectively communicated

Emergency response and contingency planning

- Emergency exercises and simulations
  - Structured and realistic
  - Emergency exercises and simulations conducted at regular intervals
  - Plans are tested
  - Personnel are prepared
  - Learn from good practices or identified deficiencies

- Contingency plans
  - Adequate contingency measures to ensure safety and security of continued operations

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Informal definitions

**Incident:**
release of biological agent but release is still contained in the lab

**Accident:**
injury of employee (with or without exposure to biological agent)

**Emergency:**
release of biological agent crossing the barrier of the containment of the lab
Accident / incident investigation

- Accident / incident investigation
  - Define, record, analyze and learn from accidents and incidents

Iceberg Principle
- Underlying Causes Of Incidents
Accident / incident investigation

Causes Of Injuries

- Most injuries are caused by unsafe acts and unsafe behaviors not unsafe conditions and equipment.
- This is typical for all industries

- Initial studies show for each disabling injury, there were 29 minor injuries and 300 close calls/no injury.

Accident / incident investigation

- Investigation process should include:
  - Identify those responsible for maintaining the reporting system
  - Define what is an incident and accident
  - Identify reports that will be generated
  - Analysis of trends
  - Identifying root causes
  - Providing regular feedback and action tracking to prevent recurrence of similar events
Biological Spill

- Spill response will vary depending on:
  - What material was spilled?
  - How much material was spilled?
  - Where was the spill?
  - Was there exposure to the worker?
  - What is the potential for release to the environment?
- Make sure the response procedures are available, known and trained

Response on biological spills

**Surface/room contaminations**

Immediate actions
- Alert co-workers
- Ensure appropriate PPE is worn
- Define/isolate contaminated area
- Ensure clean-up equipment is readily available

Follow-up & disinfection/decontamination actions
Spill clean-up video

Element 12: Facility Physical Requirement
Facility physical requirements

Addressing biorisks when something new is introduced or the existing setup is changed

- Planning, design and verification
  - Risk based approach
  - Formal planning, design and redesign process is adopted
  - Design process to incorporate legislative requirements, standards, guidelines, industry good practices, facility specific risk assessments
  - Design features, construction etc. specified and documented
  - Organisation ensures that construction and modifications are carried out according to an approved plan

CWA 4.4.4.8.1

- Infrastructure and operational management
  - Facilities, equipment and processes designed to run in a safe and secure way with respect to biorisk management

CWA 4.4.4.8

- Commissioning and decommissioning
  - Formal process in place

CWA 4.4.4.8.2
Facility physical requirements

- Some questions to consider during planning and design
  - What is the budget?
  - What are the real needs of the facility?
  - What has been identified but is not necessary?
  - Will the design work?
  - How long will it work?
  - Where has it worked before?
  - Are current methods of operating the best?
  - Does the design reflect the protocols and practices that will be used?

Containment room arrangement

- Room arrangement considering the way personnel ingress, egress and regress through a series of rooms which may consist of
  - Airlock anteroom
  - A ‘clean’ change room outside containment
  - A shower room at the non-containment and containment boundary
  - A ‘dirty’ change room within containment
Air system

- Dedicated?
- Single pass?
- Directional and pressure gradient ventilation system
  P/S: Directional airflow – from area of least hazard potential toward area of greatest hazard potential
- Negative air pressure
- Reversal airflow prevention
- HEPA filtration
- Exhaust air discharge
  P/S: Exhaust air discharged in a manner CANNOT be drawn into outside air intake system
- Redundancy
- Life expectancy and maintenance

HEPA Filters

- HEPA filters are OUTSIDE CONTAINMENT but located as near as possible to containment space to minimise length of potentially contaminated duct
- HEPA filter housings permit scan testing of filter in place after installation and filter decontamination before removal
- HEPA filters arranged both in series and in parallel on the exhaust side
- Air system equipped with pre-filters to prolong life of HEPA filters
HEPA Housing

- DOP port
- Biological indicator port
- Damper to facilitate gaseous decontamination
- Decon port to inject gas decontaminant

HEPA filters on the exhaust
Fire extinguishing systems

- Sprinkler
- Aqua mist
- Gaseous extinguisher
  - Oxygen displacement gas
    - CO₂
    - Inergen/Argon
  - Chemical gasses
    - FM200
    - Novec 1230
- Oxygen reduction
Equipment and maintenance

- Maintenance, control, calibration, certification and validation
  - Control of identification of plant and equipment, maintenance, calibration, certification and validation

Selection procedures, maintenance of asset registers, movement of equipment and purpose of equipment

Common problems

- Cost – 20% of construction cost each year to operate
- In house or contract
- Overseas or local
- Spare parts
- Competence of service providers
- Ability to decontaminate
- Potential to create hazards (e.g. aerosols)
- Breakdown and shutdown maintenance
- Validation
- Standards
Liquid nitrogen (LN2):

- Risk of cross-contamination
- Regular maintenance needed
- Interference with disinfection gas
- Risk of exposure LN2 to worker
- Risk of explosion of vials
- Need of adapted floor for storage of container
**Definitions**

- Decontamination is the collective of processes like disinfection and sterilization.

- Disinfection: a chemical/physical process for reduction of the micro-organisms to an acceptable level.

- Sterilization: a physical process to inactivate all micro-organisms.

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**Decontamination, disinfection and sterilisation**

Controls to ensure that appropriate disinfection, decontamination and sterilisation routines are in place.

- Inactivation of biological agents and toxins
  - Establish and maintain procedures
  - Waste items identified and documented
  - Emergency situations also to be addressed

- Waste management
  - Establish and maintain a waste management policy

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Decontamination, disinfection and sterilisation

Controls to ensure that appropriate disinfection, decontamination and sterilisation routines are in place

- Inactivation of biological agents and toxins
  - Risk assessment is essential to develop effective decontamination regimes
  - Important to demonstrate that methodology selected is capable of inactivating the materials under the specific conditions encountered in the facility
    - Nature of material (e.g. volume, proteins)
    - Contact time, materials compatibility (e.g. stainless steel, rubber seals)
    - Potential health hazards associated with the disinfectant

- Waste management
  - Establish and maintain a waste management policy
  - Minimise waste
  - Effective waste audit trails
  - Appropriate packaging material used to contain the waste during decontamination, storage and transport
  - Remember you may need to decontaminate specimens etc. as well as waste!
Select the right decon method depending on

- Biological agent
  - type of micro-organism (virus, parasite, prion, spores)
- Concentration of contamination
  - surface disinfection
  - inactivation of a culture
  - minor or major spill
- Resistance of materials
  - disposable or re-usable
  - synthetic surface or stainless steel

Resistance against chemical disinfectant

- Prions
- Bacterial spores
- Mycobacterium
- Non-lipid viruses (HepA, polio, adeno)
- Fungi
- Rickettsiae, Chlamydia
- Vegetative bacteria
- Envelope viruses (HIV, HepB, EBV)
The perfect disinfectant

- Broad spectrum high efficiency
- Not inactivated by organics like protein, soap, hardness of water or the pH
- Not toxic, corrosive or inflammable
- Odorless
- Stable
- No environmental burdening
- Inexpensive

Autoclave

Moist heat kills more effective because the mass transfer of heat by steam is very efficient

- Moist heat (steam): 121°C during ±30 minutes
- Dry heat: 160 - 170°C during 2-4 hours
Double-door autoclave

Points to consider for autoclaves

- During vacuum process contaminated air will leave the chamber: filters may be needed on exhaust
- Condensate in chamber is contaminated and has to be sterilised in line
- In case process is interrupted chamber should be kept closed and isolated until next successful sterilisation run
Containers or bags

- steam must be in contact with the biological material to assure effective sterilisation
- to open bags and containers exposure might be a risk
- bags may leak during transport, transport them in containers

Load and programs

Different types of load to autoclave:
- disposables
- re-usables
- liquids
- sharps
- textile

Different programs needed for:
- disposable, re-useable, sharps
- large volumes liquid in closed bottles
- textile
**Effluent treatment**

- Can be heat or chemical
- Liquid effluents may need to be collected and decontaminated in central liquid waste sterilisation system before discharge into sanitary sewer.
- For heat decontamination system, equipment be provided to process, heat and hold contaminated liquid effluent to **temperature, pressure** and **time sufficient to decontaminate** all biohazard materials that can be studied at the facility in the future
- System can operate at wide range of temperatures and holding times to process effluent economically and efficiently

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**Kill-tank for waste water**

- In- or outside containment?
- Thermal or chemical treatment of liquid waste
- In case of chemical treatment: stir mechanism
- filter(s) on Kill-tank
- filters should be sterilized in line
- discussion about integrity test of filters
Transport procedures

- Transport procedure
  - Procedures for safe and secure transport
  - Cultures, specimens, samples, contaminated & potentially contaminated materials
  - Comply with legal requirements for transport of dangerous goods

Issues associated with internal and external transport of biological materials

CWA 4.4.4.9
Transport procedures

Issues associated with internal and external transport of biological materials

- Transport procedure
  - Procedures for safe and secure transport
  - Cultures, specimens, samples, contaminated & potentially contaminated materials
  - Comply with legal requirements for transport of dangerous goods
  - Trustworthy carrier
  - Formal documented transfer forms
  - Traceability of material movements
  - Adequate and proportionate emergency response and contingency plans
    - Suspicious packages/Quarantine areas/Explosive stand-off

Transport and shipping

Transport can occur:
- within a facility
- within a country
- across international borders (by road or by plane)
Security

Management of security with regard to biorisk

- Physical security
  - Risk assessment to identify controls for security of cultures, specimens, samples and potentially contaminated materials or waste
  
- Information security
  - Policy and procedure to identify sensitive information
  - Review and approval process for release of information
Security

- **Personnel reliability**
  - Policy for personnel reliability required and work controlled accordingly

- **Personal security**
  - Personal security support for staff

Security video
Relevant industry standards / guidelines

- WHO Laboratory Biosafety Manual
- WHO Biorisk Management - Laboratory Biosecurity Guidance
- *WHO Expert Committee on Biological Standardization, sixty-sixth report. (WHO technical report series ; no. 999) – Containment (p113)*
- WHO GAPIII:2014, WHO Global Action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral vaccine use
Biorisk management - containment reference documents

- Global Action Plan (GAPIII)
- GAPIII Containment Certification Scheme (GAPIII-CCS)
  - Supersedes Annex 4 of GAPIII
- TRS 926 – poliovirus vaccine production post-eradication
  - Revision ongoing...

### WHO TRS 941

**Assignment of containment level for highly pathogenic H5 and H7 wild-type viruses**

- **BSL3 enhanced**
  - Pandemic influenza vaccine production
  - Pilot-scale and large-scale production during interpandemic phase and pandemic alert period when site of vaccine production is geographically remote from site of emerging pandemic
  - Parts of facility where work is done (both production and quality control) should meet OIE requirement for containment (i.e. for both biosafety and biosecurity)
  - Egg-based vaccine production **not** recommended since cannot operate in BSL3 enhanced conditions given the open nature of large scale egg-based vaccine production

- **BSL2 enhanced**
  - Pandemic influenza vaccine production

### WHO TRS 941

**Assignment of containment level using other type of vaccine viruses**

- **BSL2 enhanced**
  - Reassortant derived from non-H5 and non-H7 virus
  - Egg and cell vaccine production and quality control with wild type viruses (non-H5 and non-H7) of demonstrated low pathogenicity in ferret
  - Pilot-scale and large-scale production during interpandemic phase and pandemic alert period when site of vaccine production is geographically remote from site of emerging pandemic

- **Any relaxation of containment level during developing pandemic to be decided on case-by-case basis after careful evaluation of risks**
WHO TRS 941

- Each vaccine manufacturer must review their own control measures in light of:-
  - Intended work
  - Nature of laboratory and production facilities
  - Need to maintain GMP
- Containment measures should be in place for open manipulations with live virus especially virus harvesting in egg production facilities
- Decontamination methods should be validated
- Decontamination of waste should take place on-site if possible
- If not, there should be procedure to ensure material is safely contained and transported to decontamination off-site

WHO TRS 941

- Staff should be vaccinated prophylactically with seasonal influenza vaccines given the possible exposure to high titre pandemic strain virus and to reduce chance of simultaneous infection with human influenza viruses
- Antiviral treatment must be available in case the situation warrants it
- Risk assessment of risk of contamination of birds or pigs based on likelihood of presence in vicinity of the manufacturing plant and the manufacturing controls in use
WHO TRS 941

Specification for BSL2 Enhanced

- Follow the principles for BSL2 facilities as specified in WHO Laboratory Biosafety Manual with additional features including:
  - Facility should be designed and operate to protect:
    - the recipient of the vaccines
    - the staff producing and testing the vaccine
    - the environment
  - Specialised engineering solutions that may include:
    - Use of relative negative pressure BSC when possible
    - Use of HEPA filtration prior to exhaust into public area/environment
    - Use of positive pressure with negative pressure in-line sinks prior to exhausting to the non-viral zone

- In addition, the following decontamination procedure should take place:
  - Decontamination of all wastes
  - Decontamination of manufacturing and quality control area at the end of a production campaign through cleaning and validated decontamination

- Full-body protective lab clothing (e.g. Tyvek disposable overall) in controlled BSL2 enhanced area

- For open activities and activities cannot be contained in primary containment, use of respiratory protective equipment (e.g. N95, FFP3 or equivalent) is strongly recommended and must be fit tested

- Minimum specification for filtering/absorbing capacity of PPE should be met
WHO TRS 941
Specification for BSL2 Enhanced

- Written agreement and instruction to personnel not to have any contact with birds/ pigs, in particular farm animals, for 14 days after departure from production facility
- Staff should be prophylactically vaccinated with seasonal inactivated influenza vaccines
- Experimental vaccines inducing protective antibody levels are recommended for use by staff before commencement of large scale vaccine production
- Antiviral treatment must be available in case the situation warrants it
- Cleaning and decontamination methods need to be validated periodically as part of the master validation plan

WHO TRS 941
Specification for BSL2 Enhanced

- Master validation plan to be in place to demonstrate that protocols, reagents and equipment used are effective in the inactivation of pandemic influenza virus on:
  - Facility and equipment surfaces
  - Garments of personnel
  - Waste materials
  - Within cell growth and storage containers
- Decontamination procedure for influenza virus have to be fully described and validated but there is no need to repeat them for each new strain
- Validation studies using influenza viruses may be supplemented by studies with biological markers (e.g. bacterial) selected to be more difficult to inactivate
WHO TRS 941

Specification for BSL3 Enhanced

- Includes specification for BSL2 enhanced
- Follow the principles for BSL3 facilities as specified in WHO Laboratory Biosafety Manual with additional features including:
  - Facility should be designed and operate to protect:
    - the recipient of the vaccines
    - the staff producing and testing the vaccine
    - the environment
  - Specialised engineering solutions that may include:
    - Negative pressure secondary containment areas
    - HEPA filtration on supply and exhaust air
    - On-site decontamination of liquid effluent
    - Floor dams should be erected around bioreactors and other large scale equipment including storage tanks

- All clothing worn outside facility should be replaced by manufacturing facility garments upon entry into the facility
- Personnel to gown full-body single-use protective laboratory clothing (e.g. disposable Tyvek overalls) upon entry into the containment zone
- Eye protection and use of respiratory protective equipment (e.g. N95, FFP3 or equivalent) is required when open activities are being conducted
- Minimum specifications for filtering/absorbing capacity of PPE should be met and masks must be fit tested
WHO TRS 941
Specification for BSL3 Enhanced

- Full body shower upon exit is recommended. It is mandatory following situations when staff may have been exposed to vaccine virus.

Management Structure

The institution needs to have:
- An institutional biosafety officer:
  - knowledgeable in large-scale production and containment
  - **independent** of production in reporting structure
  - reports directly to the highest management level within the company
  - is a member of the biosafety committee
  - is responsible for:
    - Independent oversight of implementation of biosafety practices
    - Policies
    - Emergency procedures in place
- A qualified person for overall responsibility for medicinal product
WHO TRS 941
Management Structure

- A Biosafety Committee comprising of representatives of viral production and quality control responsible for reviewing the biosafety status within the company and for coordinating preventive and corrective measures
- Chairperson of the Biosafety Committee should be independent of both production and quality control
- The management and governing board should ensure adequate priority and resources are made available to the Committee to implement the required measures

WHO TRS 941
Medical Surveillance

- Occupational health department at vaccine manufacturers of pandemic strain influenza to provide training in recognizing the clinical signs of influenza infection to company physicians, nurses and vaccine manufacturing supervisors
- Local medical practitioners caring for personnel from manufacturing site should receive special training in diagnosis and management of pandemic influenza infection
- A documented procedure, including diagnostic procedures and prescribed treatment protocols, for dealing with influenza-like illness in the staff involved or their family members
Medical Surveillance

- Ensure staff understand that they have obligation to seek medical attention and report any influenza-like illness to Occupational Health department or equivalent
- Hold supplies for one or more effective antiviral agents
- Have defined means of quarantining staff if necessary

Implementation

- A detailed and comprehensive risk analysis should be conducted to define possible sources of contamination of personnel or the environment
- The analysis should take into account:
  - The concentration and stability of the virus at site
  - The potential for inhalation or injection that could result from accidents
  - The potential consequences of a major or minor system failure
  - The procedural and technical measures taken to reduce the risks to the workers and the environment
- The result of the risk analysis should be documented
WHO TRS 941 Implementation

- A comprehensive Biosafety Manual, fully describes the biosafety aspects of the production process and quality control activities, must be created and implemented.
- It should define items such as:-
  - Emergency procedures
  - Waste disposal
  - Requirement for safety practices and procedures as identified in the risk analysis
- The Biosafety Manual should be made available to all staff of production and quality control units with at least ONE copy in the containment area(s).

- The manual should be reviewed and updated when changes occur or at least annually.
- Comprehensive guidelines outlining responses to biosafety emergencies, spills and accidents to be prepared and made available to key personnel for co-ordination with emergency response units and be reviewed and updated annually.
- Rehearsal of emergency response procedure is recommended.
- Implementation of appropriate biosafety status should be verified through an independent assessment.
- National requirements concerning verification mechanism should be in place and complied with.
WHO Expert Committee on Biological Standardization, sixty-sixth report. (WHO technical report series; no. 999, 2016) – Containment (p113)

- Airborne dissemination of live microorganism and viruses used for production, including those from personnel, should be avoided.
- Adequate precautions to avoid contamination of drainage system with dangerous effluents.
- Drainage system design to allow effluents to be effectively neutralized or decontaminated to minimize risk of cross-contamination.
- Specific and validated decontamination system should be considered for potentially infectious materials.
- Compliance with local regulations.
WHO technical report series; no. 999

- Production areas, for handling live cells capable of persistence/pathogenic organism in risk group 3/4/spore forming organism, should be dedicated until inactivation process is accomplished and verified.
- Strictly dedicated facilities should be utilized for each product of Bacillus anthracis, Clostridium tetani and Clostridium botulinum.
- Means of obtaining up-to-date information of the biological agents used.
- Risk assessment of biological product and its emergency demand for use of pathogenic organism above risk group 3 permitted by NRA.

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WHO technical report series; no. 999

- Dedicated area, equipment and utilities (i.e. HVAC) used for production of BCG-related product.
- Compliance with WHO GAPIII and WHO guideline for safe production and quality control of IPV from WPV.
- Need for dedicated air-handling units or singlepass system based on QRM principles, taking into account the biohazard classification and containment requirements.
- For risk group 3 organisms, air should not be re-circulation of air to any other area in the facility and exhaust should be HEPA filtered.
- HEPA filtered should be check regularly for performance.
WHO technical report series; no. 999

- For risk group 4 organisms, dedicated non-recirculating ventilation system and HEPA filtered exhaust are required.
- Primary containment equipment should be designed and initially qualified for integrity. Periodic tests, inline with relevant guidelines and QRM principles, should be performed to ensure that equipment is in proper working condition.
- Activities which can lead to aerosol (e.g. centrifugation or blending of products) should be contained.
- Validated decontamination measures should be available.

WHO technical report series; no. 999

- Area where risk group 3 or 4 organisms are handled should always have:
  - negative air pressure
  - Interlock air-lock doors
  - differential pressure alarms – should be validated and monitored
- Air-vent filters should be hydrophobic and subject to integrity testing at interval determined by QRM approach.
- Safe changing of HEPA filters should be ensured (e.g. bag-in-bag-out housing).
- HEPA filters removed should be decontaminated and properly destroyed.
Current status of biorisk management in vaccine production?

- In your groups discuss the current practice with regard to biorisk management in vaccine production based on your own experience and what we have discussed.
- Suggested areas for discussion:
  - Are the available standards and guidelines being incorporated and implemented effectively?
  - How does biorisk management relate to GMP and can you see any potential conflicts?
  - How do you see this area developing in the future?
  - Will you take any immediate action when you return to your facility?
- Present your views to the group.