Large Scale
Bio- Manufacturing

How to comply with GMP and Biosafety regulations:

In one place,
At the same time,
With one product,
with the same people,
. . . . . ?

Per Staugaard , december 2016

Biosafety

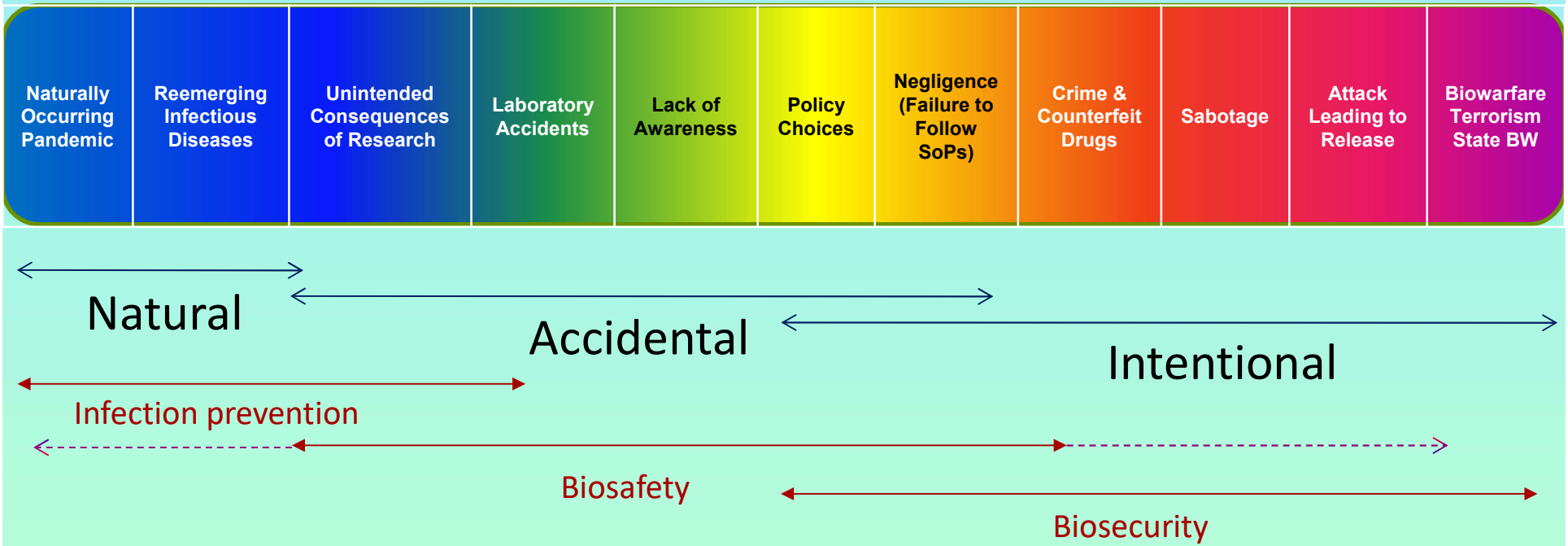
- Definition

  A combination of procedures, containment systems and construction technologies with the purpose of **minimizing the risk** of infecting laboratories and **prevent escape** of microbes into the surrounding environment

- Purpose
  - To create a safe environment in which to research infectious diseases
  - To **prevent escape** of infectious agents
  - To **minimize** staff member's and other people's **contact** with infectious agents both within and outside the containment zone
  - To **prevent** the **introduction** of infectious agents into the nature

The full spectrum of the global chalenge: biosafety

Biological risks can be seen as a spectrum:

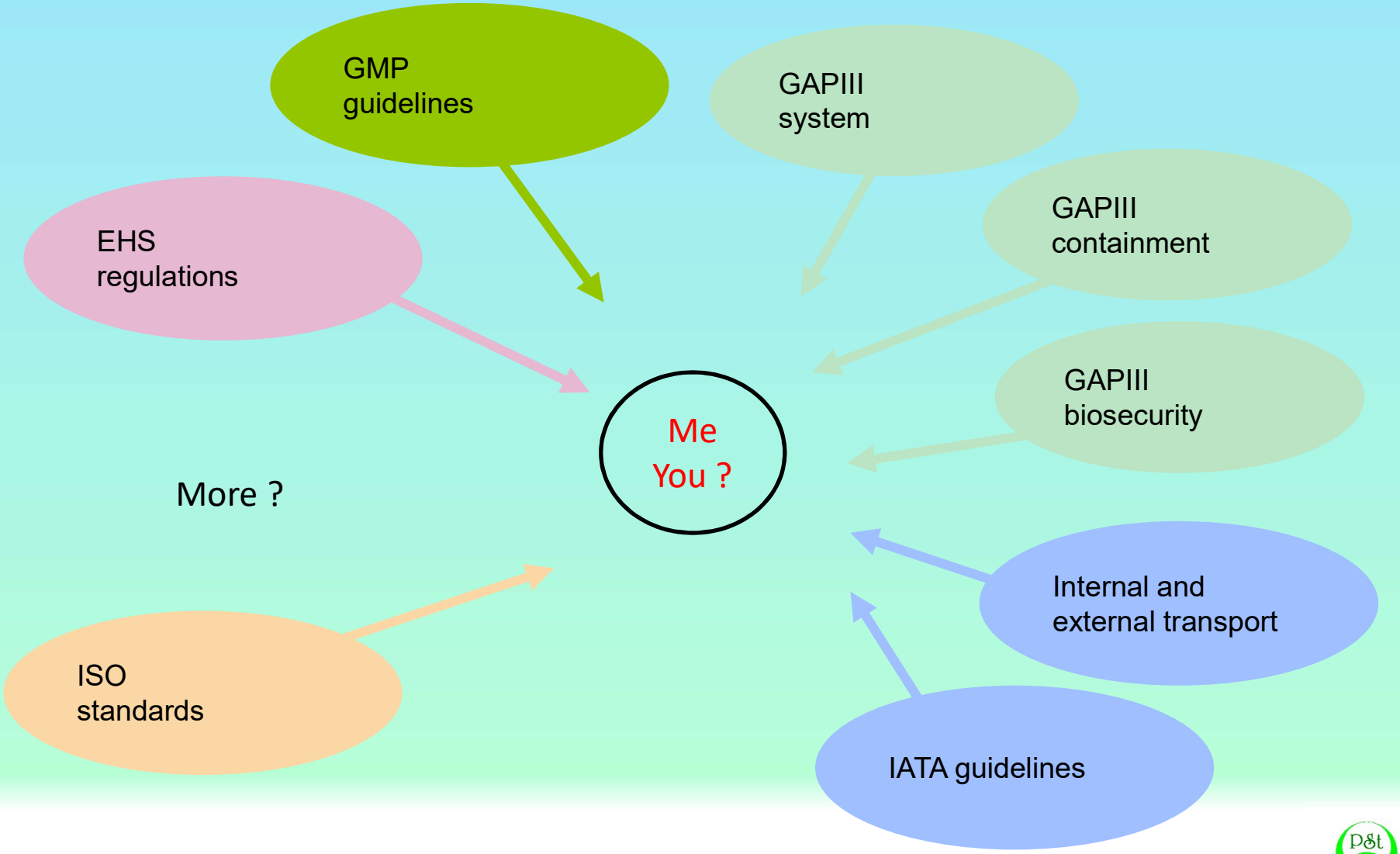


By courtesy of Tim Trevan

Biosafety Guidelines

- Some guidelines take a **performance** approach
  - Define the intended result (e.g. WHO)
- Other guidelines are more **prescriptive**
  - Outline specific requirements
  - Acceptance criteria (e.g. Canada and BMBL (USA))

Systems come together



Biosafety - Risk Assesment

- Evaluate
  - 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

Large Scale Production Risk Assessment

- 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.

Biosafety ←→GMP

GMP

- BSL1
  - Basic hygiene & Common sense

Need for specific and innovative solutions

- BSL2
  - + standard precautions
    primary proces & primary containment
- BSL3
  - + specific measures
    based on RA – including secondary process
- BSL4
  - + ...
    redundancy

BioSafety

Bio-Occupational Health strategy

- Source
- Technical measures
- Organization
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Technical measures
- Organization
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Containment [Primary & Secondary]
- Organization
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hygiene
- PPE
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hand wash: prevent spreading in environment [shower out]
- PPE
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hand wash: prevent spreading in environment [shower out]
- Coat/gown, gloves, glasses, respirator, . . .
- Vaccination
- Post exposition prophylaxis

Bio-Occupational Health strategy

- Change material: safer strain
- Containment
- Training, SOPs, access control
- Hand wash: prevent spreading in environment [shower out]
- Coat/gown, gloves, glasses, respirator, . . .
- Vaccination : necessary & sufficient
- PEP: very much dependant on organism

Bio-Occupational Health strategy

- Change material: safer strain
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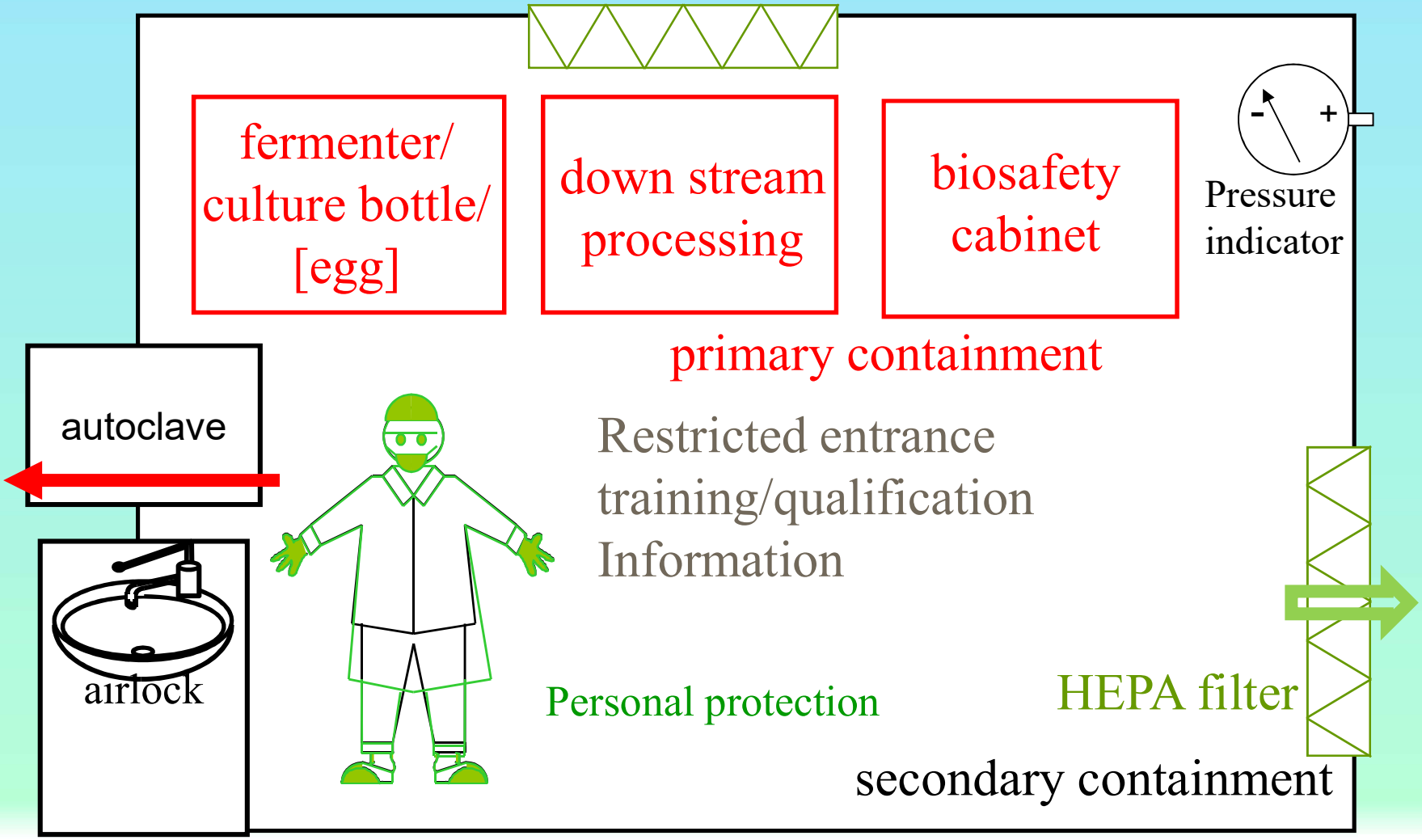
Self contained equipment

containment & procedures

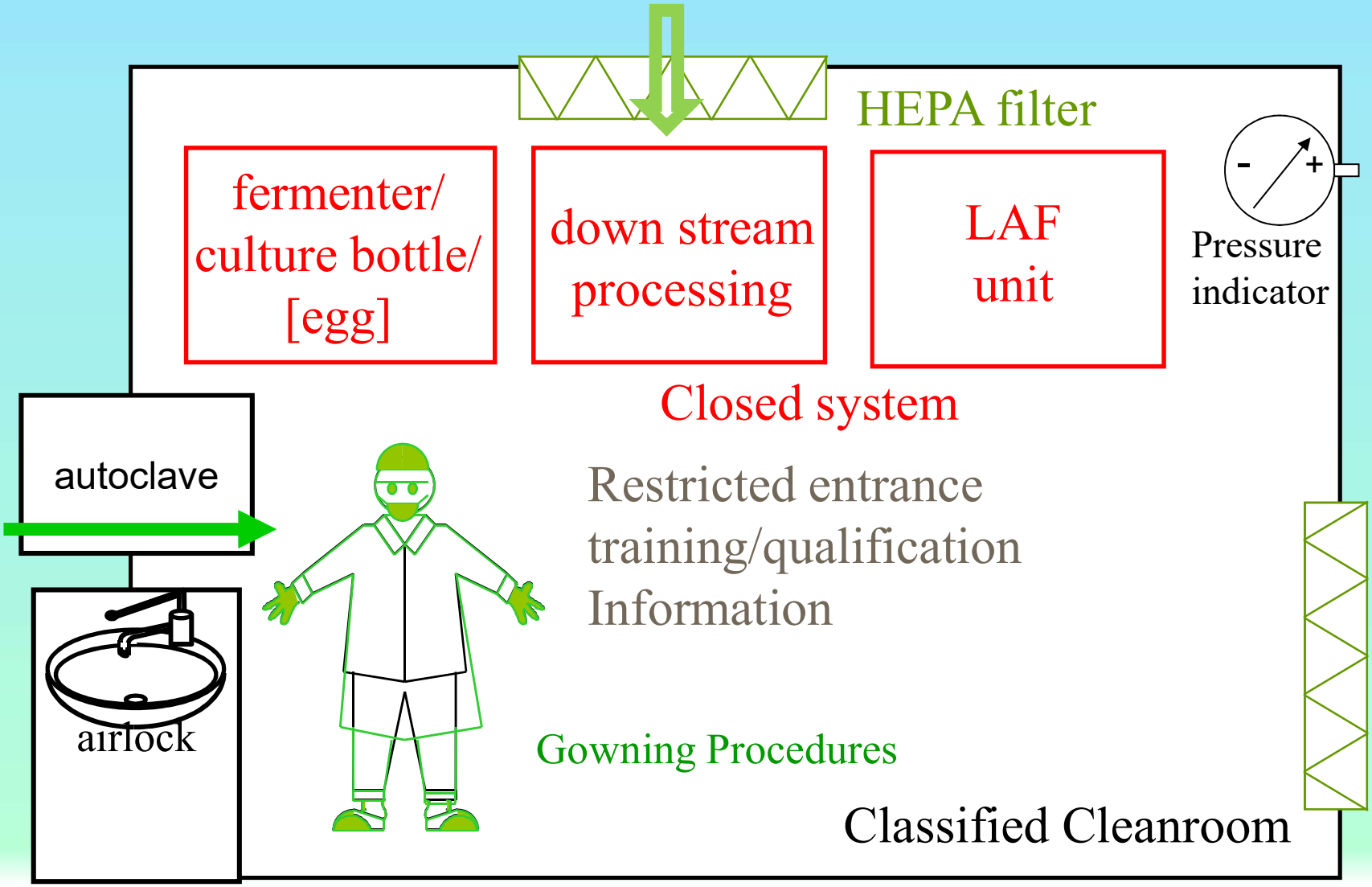


medical control & vaccination ; post exposition treatment

Biosafety – GMP: Synergies

- Restricted access
- Segregation of production areas
- Facility designed for easy cleaning
- Minimize contaminants
- Validate processes, systems, equipment, and facilities
- Job certification and mandatory training
- Mandatory personal protective equipment (PPE)
- Written policies and procedures
- Documentation, double signatures, etc.

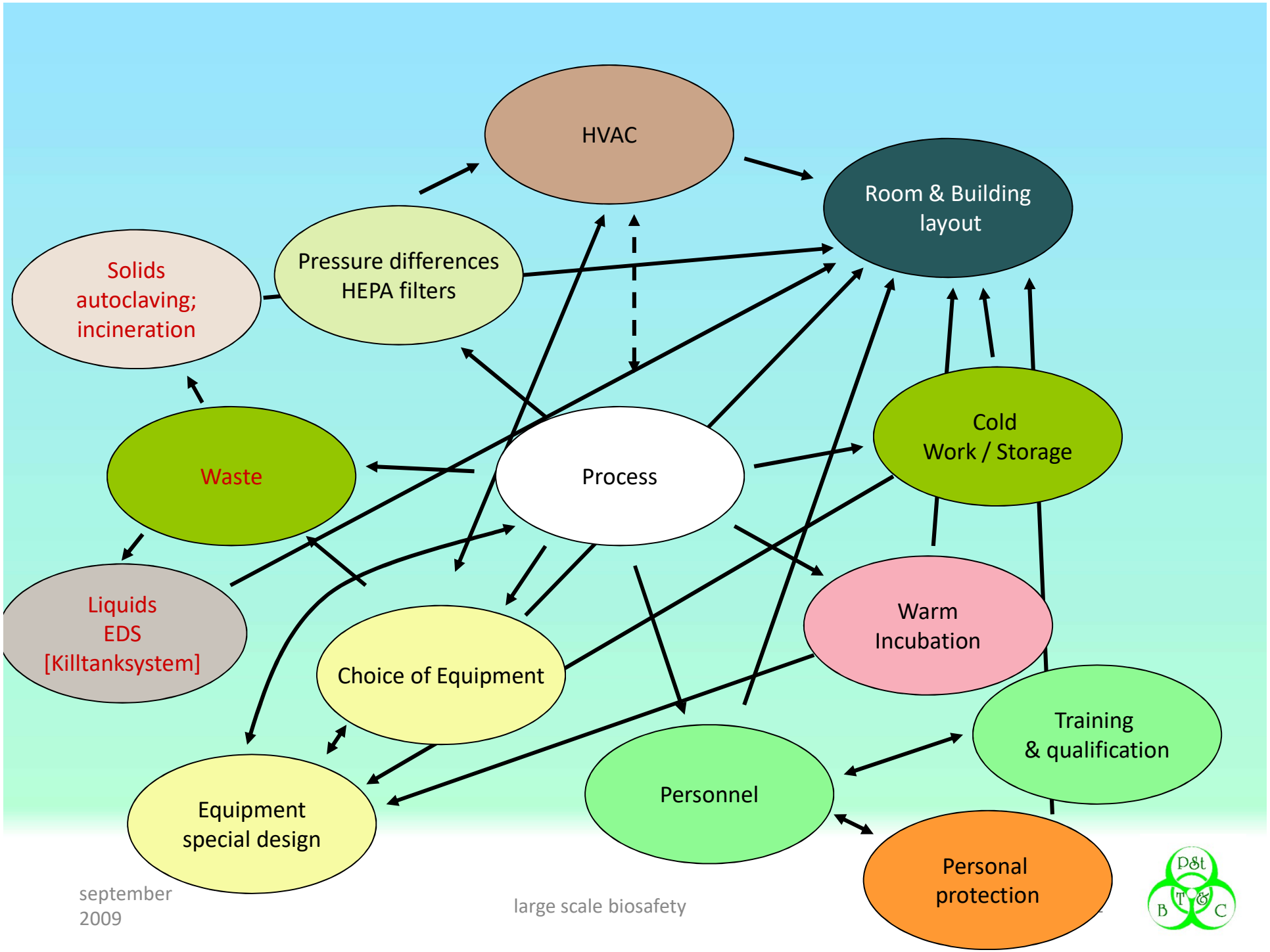
cleanroom



medical control & vaccination to protect products

GMP and Biosafety Clashes
Then what?

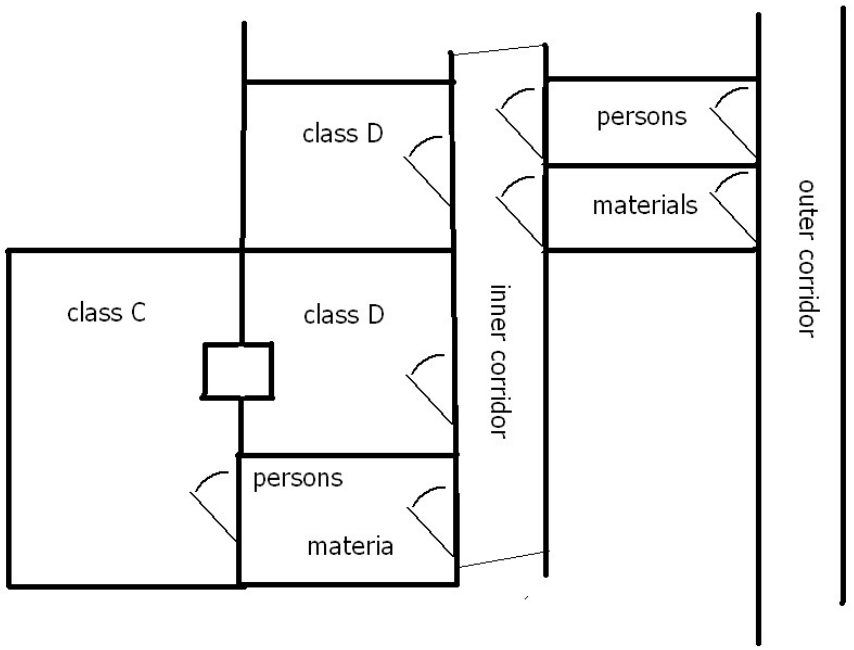
- Read the guidelines
  - Understand them
    - Not only **what** they say –
    - But also **WHY** they say it
- Is there another way to do it?
- Risk assessments
- Decide on a solution
- Brace yourself to face the authorities


HVAC
Room & Building layout
Pressure differences HEPA filters
Solids autoclaving; incineration
Waste
Process
Cold Work / Storage
Liquids EDS [Killtanksystem]
Choice of Equipment
Warm Incubation
Training & qualification
Equipment special design
Personnel
Personal protection

Pressure difference unidirectional airflow

Positive Pressure

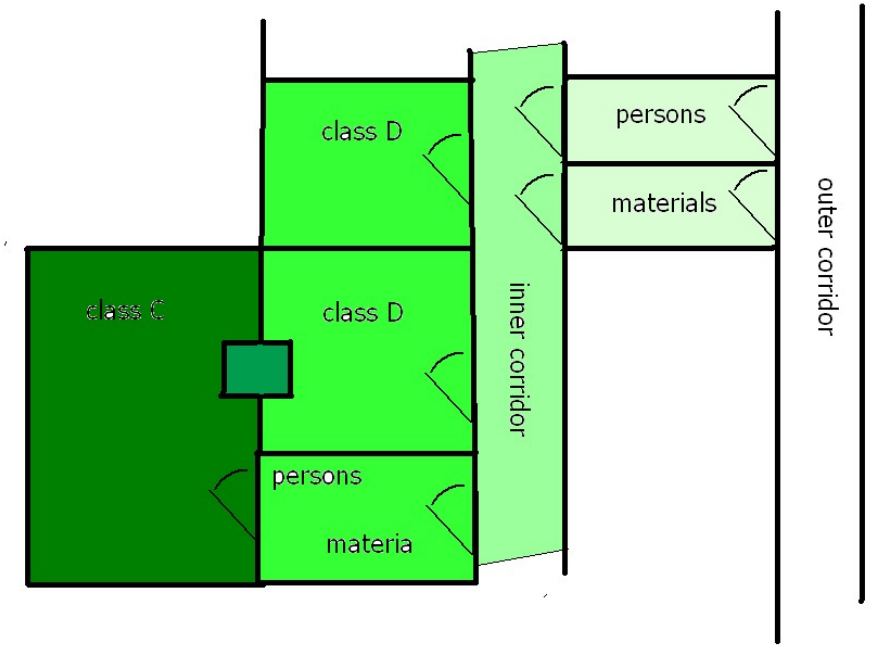
Negative Pressure



Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure

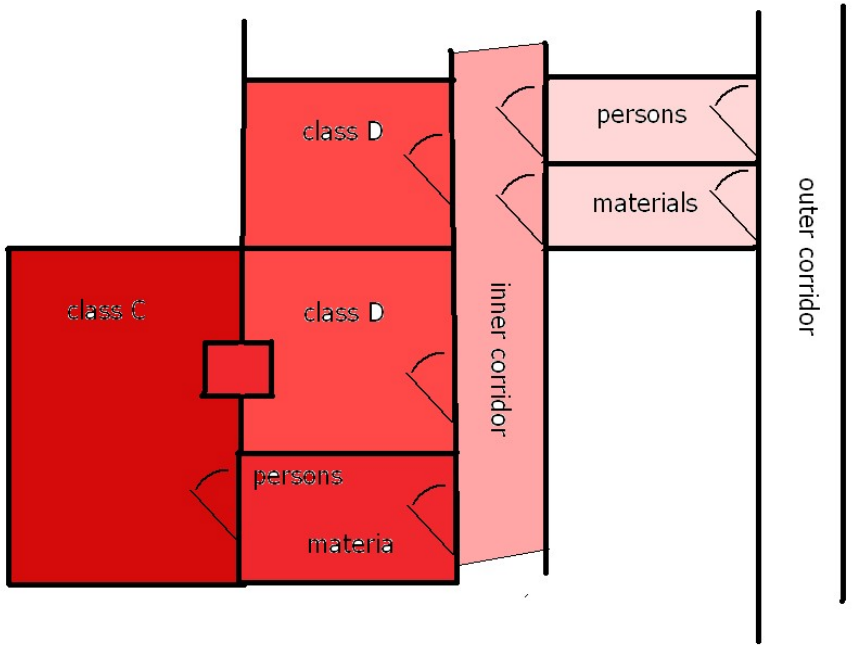


"standard cleanroom"

Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure

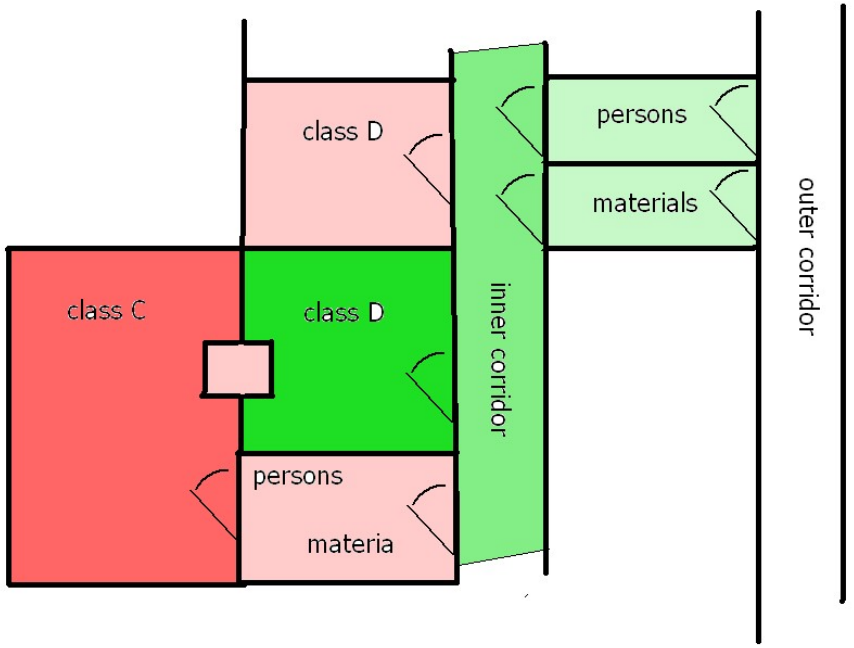


"standard BSL-3 lab"

Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure

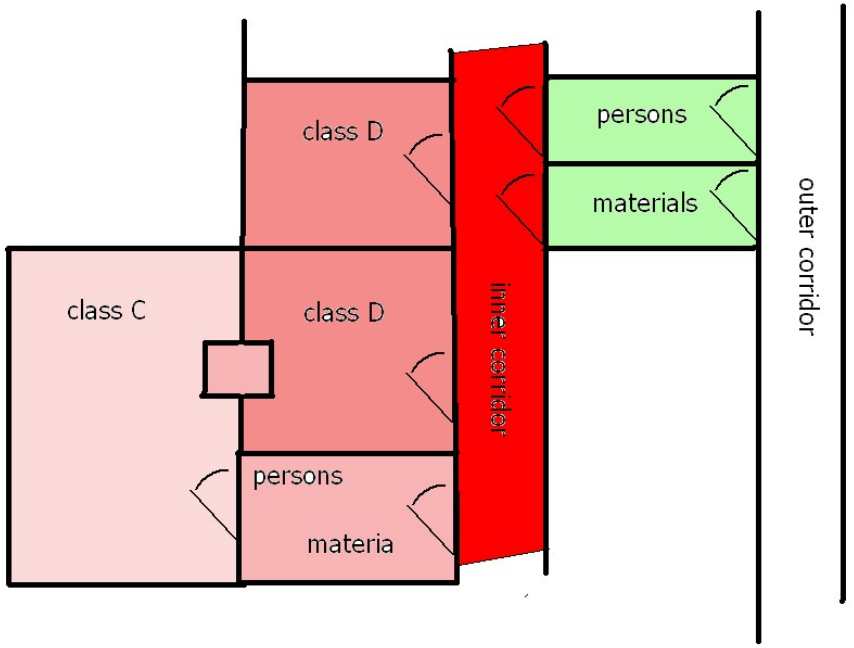


dedicated design with “safe biopositive room”

Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure

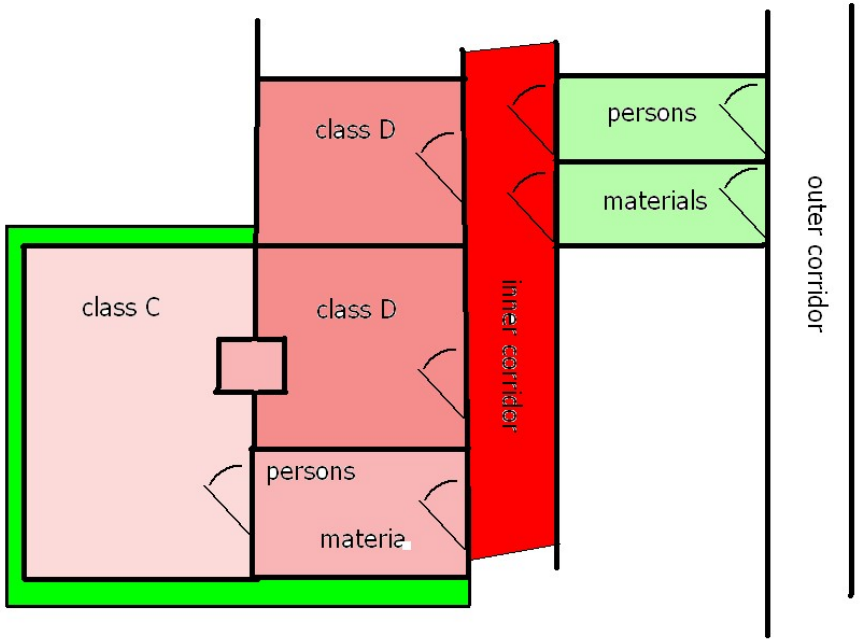


BSL – solution with overpressure protection in airlock

Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure

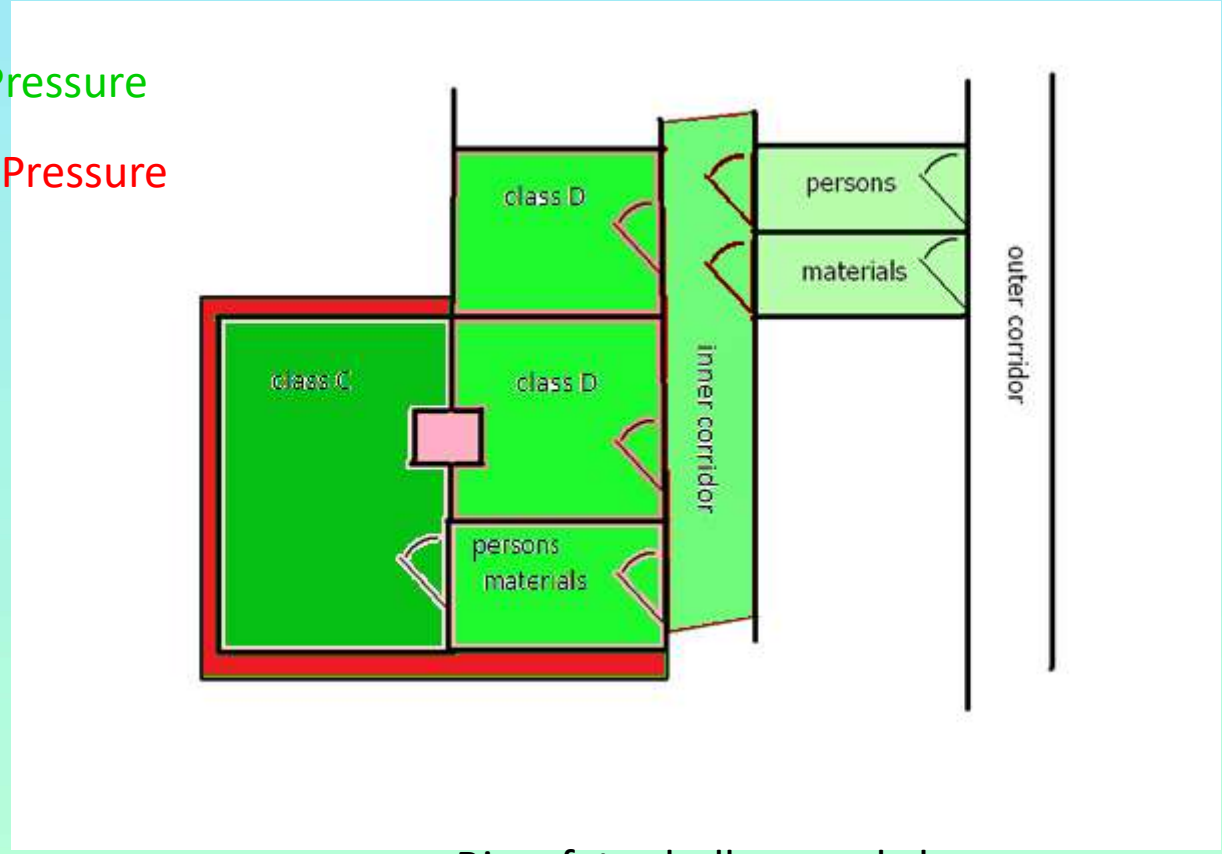


Clean shell around bio + rooms

Pressure difference unidirectional airflow

Positive Pressure

Negative Pressure



Biosafety shell around clean room