3rd International Conference on
Biosafety and Laboratory

State-of-the-art safety engineering for BSL-3 labs

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Basler & Hofmann

Agenda

Source: Basler & Hofmann

- Integral risk control approach
- Current BSL-3 base design characteristics
- Integrated protection layers
- The V-model for BSL-3 systems development and verification

Integral Risk Control Approach

Which Combination Do You Prefer?

A	B
	
Very safe car	Old, dilapidated but functional car
Driven by “dumb” driver	Driven by ”good” driver

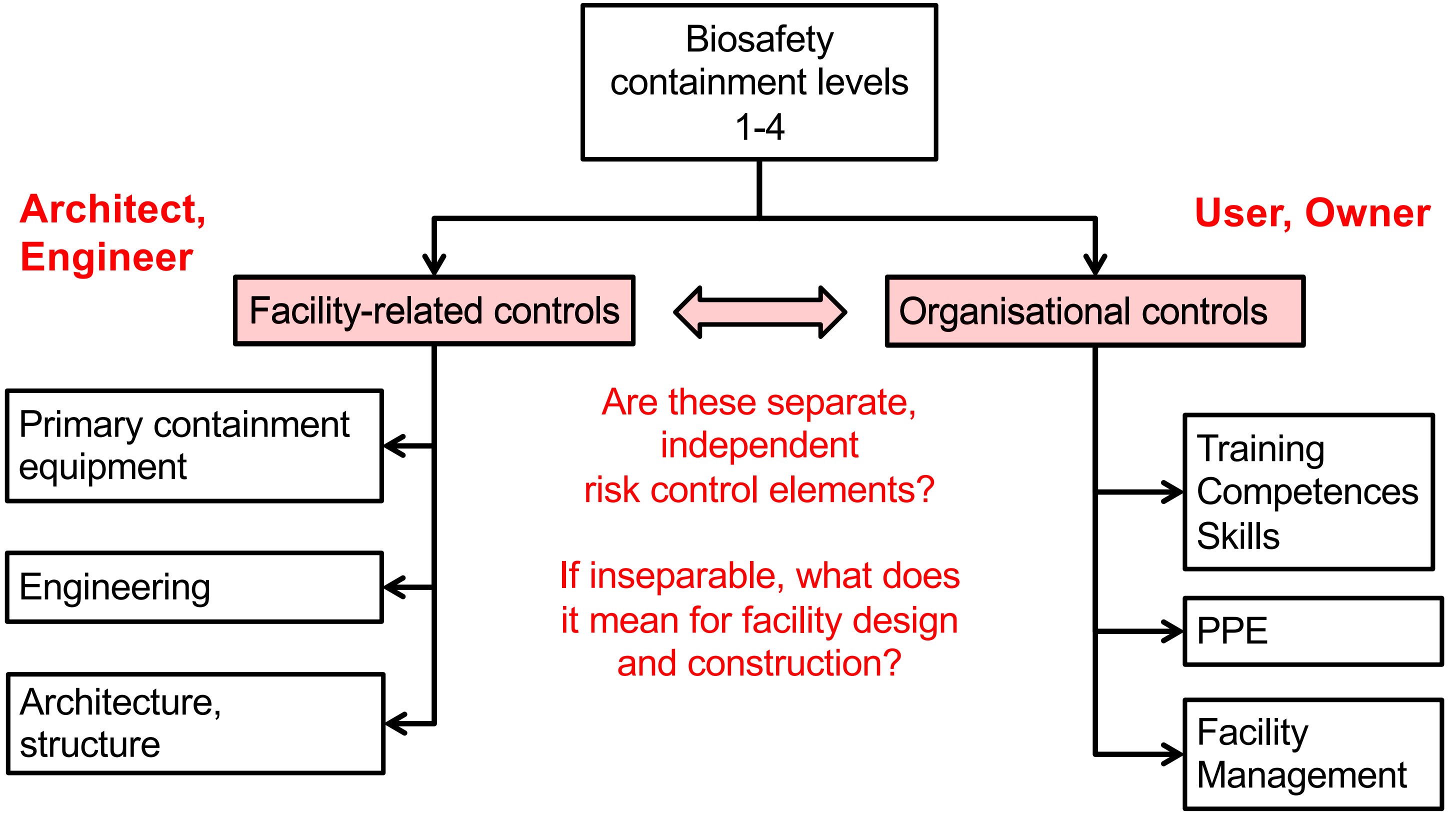
Ideal Combination

C

Very safe car

Driven by “good” driver

Containment Risk Controls



Conventional OHS Hierarchy of Controls

- **S** • Substitution
- **T** • Technical risk controls (Facility related)
- **O** • Organisational risk controls
- **P** • Personal risk controls

Architecture introductory course:

Form Follows Function

The shape of a lab should primarily relate to its intended function

Actual OHS Hierarchy of Controls in BSL-3 Labs

S
- Substitution

TOP
- Facility-related risk controls
- Organisational risk controls
- Personal risk controls

A
- Attitude & discipline
- Safety awareness, safety culture, compliance with Standard Operating Procedures

Integral risk control approach (TOP and A)

WHO Laboratory Biosafety Manual 2019

"It is important to note that while a hierarchy of control measures has been defined by many countries, it cannot be assumed that one control measure is always preferable to another (e.g. engineering controls versus personal protective equipment)"

Take-Home Message 1

Source: Basler & Hofmann

- “Hardware”,
- “Software” and
- “Peopleware”

are inseparable risk controls that have an effect on safety in BSL-3 Labs

State-of-the-art safety engineering for BSL-3 labs must factor in non facility-related controls such as administrative and personal controls

Current BSL-3 Base Design Characteristics

Basler & Hofmann

High Biocontainment Base Design Concept

https://en.wikipedia.org/wiki/Biocontainment

- It appears that structural/engineering measures are based on a heuristic* “very-low” and “zero-release” tolerance concept:
- Originally borrowed from 1940s – 50s nuclear industry:
  - Isolators / safety cabinets as primary containment
  - “Leaktight” secondary containment with airlocks
  - High air exchange rates, negative pressure
  - Exhaust HEPA-Filter
  - Redundant critical systems (UPS, Fans, Filters, etc.)

* An approach to problem solving that employs a practical method, sufficient for reaching an immediate goal.

Empirical* Evidence

- Empirical evidence indicates that lack of containment integrity *per se* is rarely a source of a lab outbreak
  - Provided containment was built and is maintained according to proper biosafety design and engineering practices!
- How about the Pirbright 2007 FMDV outbreak?
  - "The effluent pipes from IAH and Merial to the caustic soda final treatment plant are old and appear not to have been subject to regular thorough inspections to ensure their integrity." (Spratt report, 2008)
  - Cost (government and industry): ca. US$ 300 million

* Gaining knowledge by means of observation or experience.

Laboratory-Associated Infections

LAI Frequency per 1000 person years	Source
0.83	Clinical laboratories (BSL-2) Grist & Emslie, 1991
3	Research laboratories (BSL-2/3) US Dept Homeland Security, 2008
0	Research laboratories (BSL-4) US Dept Homeland Security, 2008
All occupational incidents	
60	OSHA incident rates for General Medical and Surgical Hospitals (2015)
64	Switzerland incident rates for healthcare (2014)

Take-Home Message 2

- Risk assessment on BSL-3 *structural/engineering measures and effectiveness* in its classic meaning is not possible:
  - No realistic models of containment failure exist
  - No failure data on individual containment measures available
  - No acceptability criteria: “It is unknown how safe is safe enough”
  - **ALARA (as low as reasonably achievable)**
  - At any cost? Overdesign issues?
- Instead a heuristic/deterministic approach with adequate protection layers should be used:
  - **ALARP** (**as low as reasonably practicable**)

Integrated Protection Layers

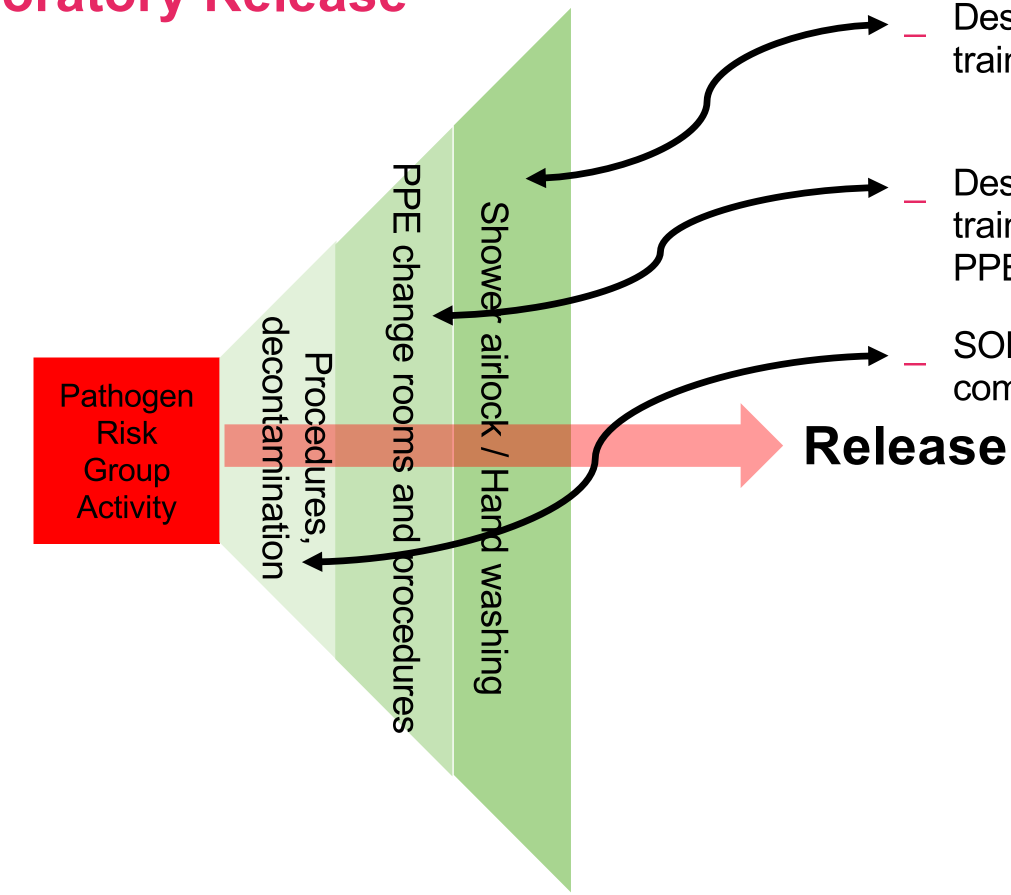
Basler & Hofmann

Predominant Release Routes (Alphabetic Order)

Source: Basler & Hofmann

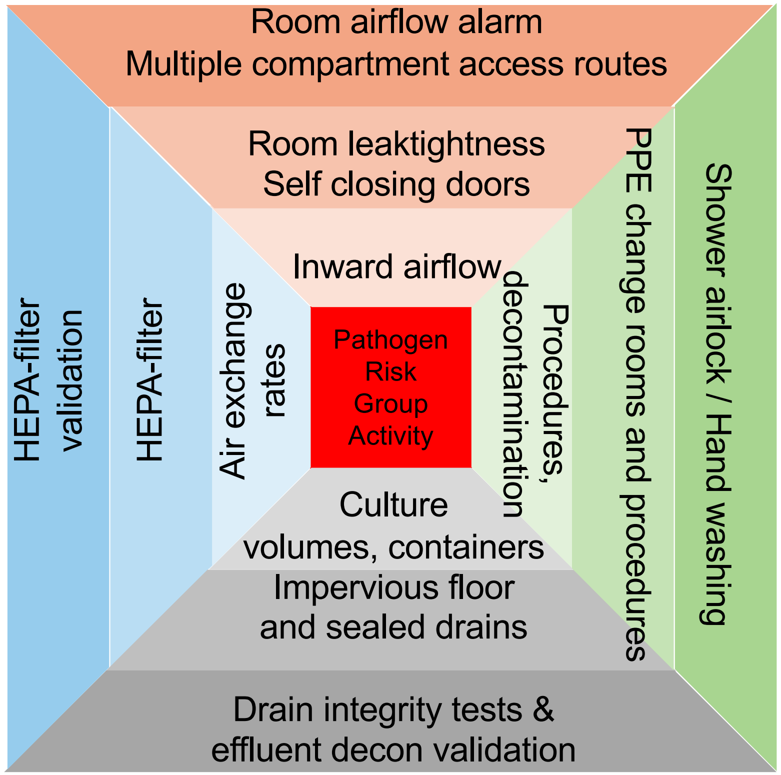
- Air
- Effluent
- Equipment
- Personnel
- Samples and reagents
- Solid waste

Preventing Laboratory Release



- Design, construction, SOPs, training, competences, skills
- Design, construction, SOPs , training, competences, skills, PPE
- SOPs, training, competences, skills, PPE

Integrated Protection Layers (Illustrative Examples)



- For simplicity and illustration of the principle of integrated protection layers the number in this schematic is limited to three layers
- Note that protection layers along a path are always combinations of facility and organisational controls
- Redundant facility controls (backup systems) for critical paths
- This emphasises the need for pre-qualification of the design

Engineering Systems: Single Point of Failure Resilience

Aerosol release via fabric and closed doors	Inward airflow	Room leaktightness Self closing doors	Airflow alarm Multiple compartment access routes	SPOF Testing Physical inspections
Risk	Protection Layers			Verification

- A single point of failure (SPOF) is a part of a system that, if it fails, will stop the entire system from working properly
- To make the BSL-3 ventilation resilient to single point of failure, two redundant exhaust fans are required, and the reliability and availability of the system must be tested
- Enhanced resilience of the BSL-3 systems may be required as per risk assessment or legally required controls

BSL-3 Systems that May Require Backup/Redundancy

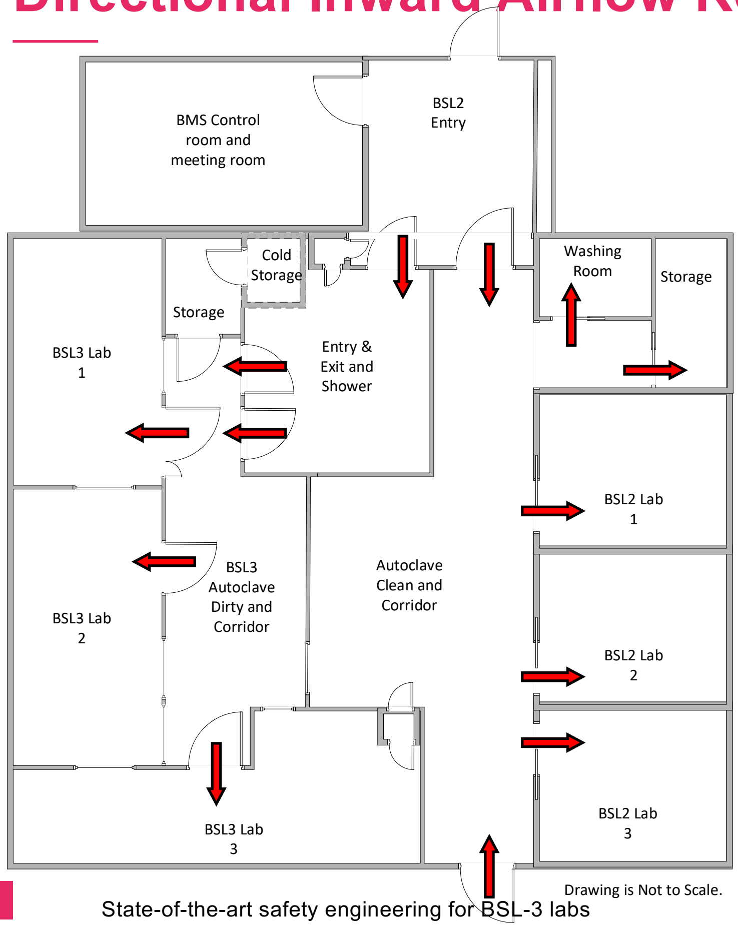
System	As per local legislation	Operational (e.g. 24/7 lab)
Inward airflow (2 exhaust air handlers)	X (e.g. DE, US, SG, AS/NZ)	
EM-power (incl. UPS)	X (e.g. DE, SG)	X
2 supply air handlers		X
Exhaust stack/High plume dilution fan	X (e.g. US, SG)	
Backup autoclave		X
Backup effluent decon		X
Backup HEPA-filters (parallel config.)		X
Etc.		

Redundant Systems and Their Verification (Examples)

Source: Basler & Hofmann

Primary System	Backup System	Verification
Exhaust air handler	Backup air handler	SPOF test
Grid Power	UPS EM-Power Genset	SPOF test
Supply air handler	Backup air handler	SPOF test
Effluent decon lift pump	Backup pump	SPOF test
Critical sensor	Backup sensor	SPOF test
HEPA-Filter	2nd filter in parallel	Validation only (manual switchover)
HEPA-filter	Exhaust stack/High plume dilution fan	Method of construction Discharge velocity

Directional Inward Airflow Requirements

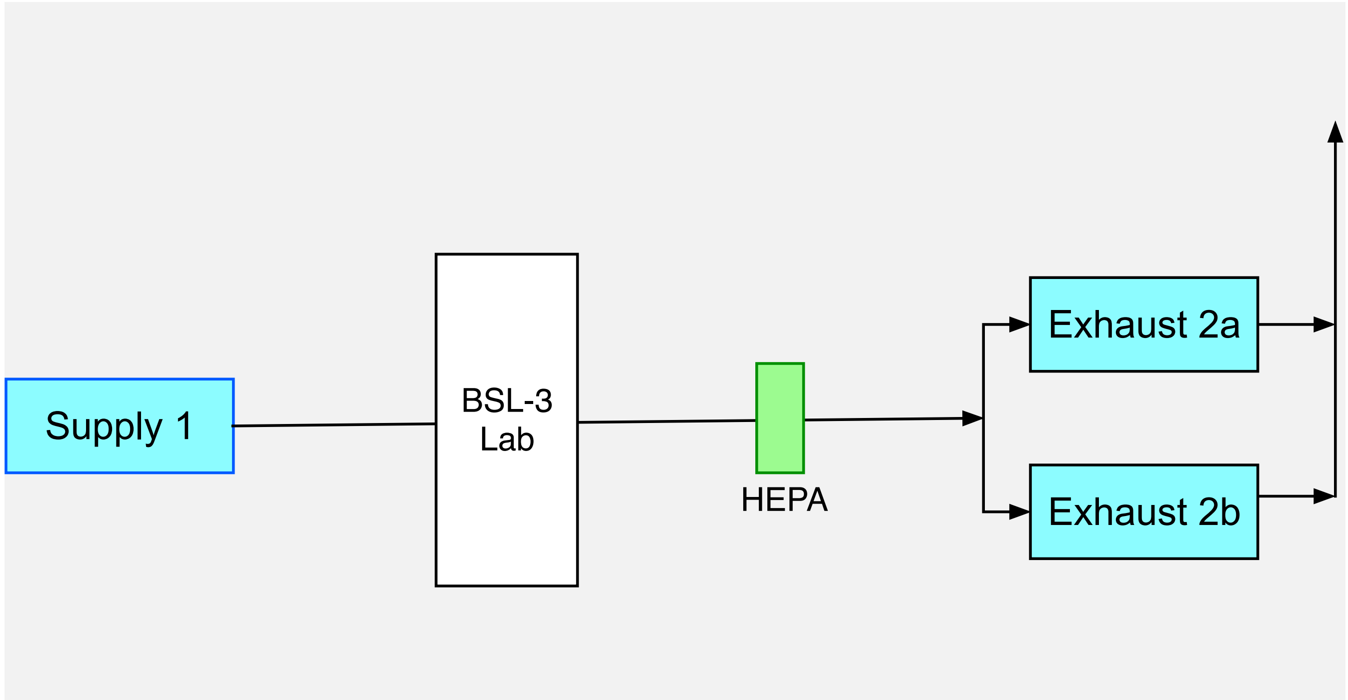


- Inward airflow into laboratory **is maintained** (WHO, 2004)
- Inward airflow **at all times** (AS/NZS 2243.3:2010)
- The laboratory shall be designed such that **under failure conditions** the airflow will not be reversed (BMBL, 2009)
- A constant, controlled negative pressure must be **maintained** in the biosafety level area (TRBA 100, 2018)

Selected BSL-3 Risk Control and Oversight Guidance Documents

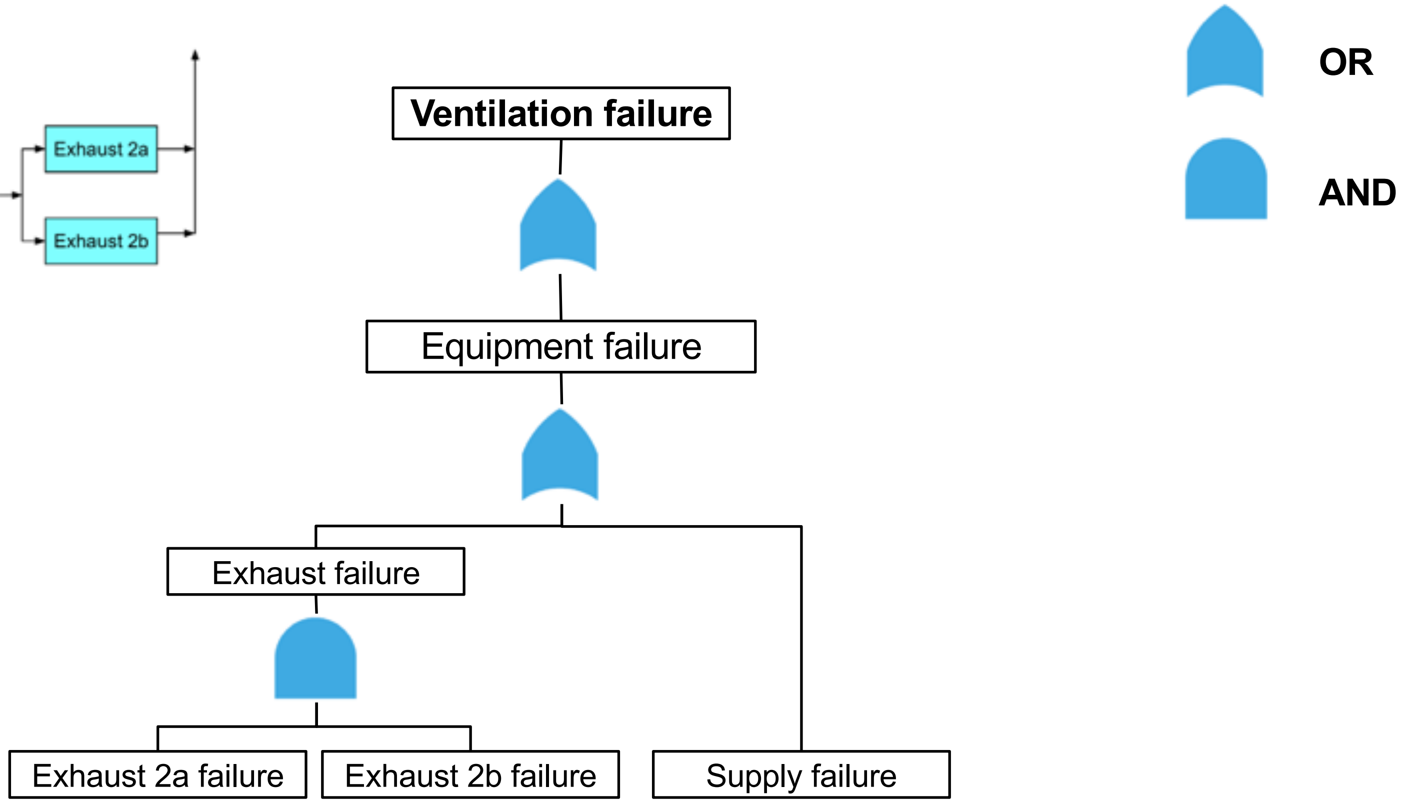
Control Measure	2000/54/EC (OHS)	2009/41/EC (GMO)	EN 12128	WHO (2004)	AS 2243.3:2010	TRBA 100
Sealable for fumigation	Recomm'd	Yes	Yes	Yes	Sealed	Yes
Negative pressure	Recomm'd	Yes	Yes	Yes	Yes	Yes
UPS/Genset	No	No	Option	No	Yes (BSC)	Yes
Effluent decontamination	Validated	Option	Yes	Option	Option	Thermal

Current Minimum BSL-3 Ventilation Setup



- In order to maintain inward airflow (whichever standard or guideline is used)

Ventilation Failure Fault-Tree Analysis



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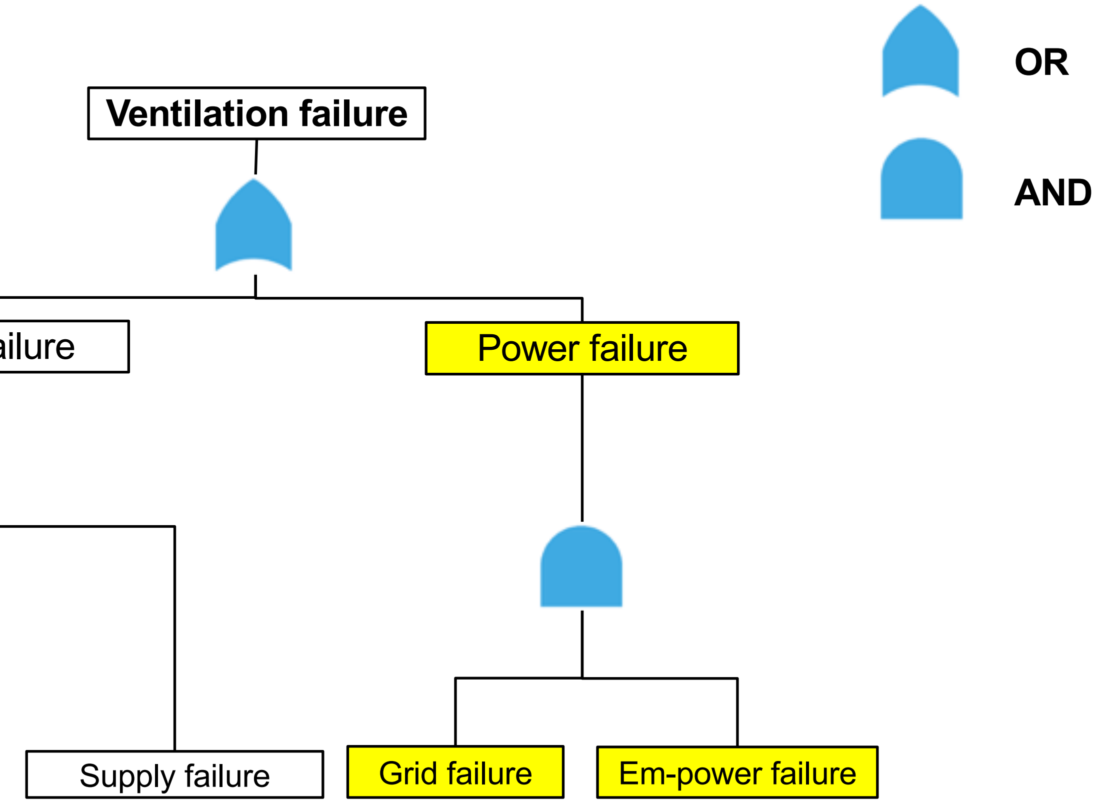
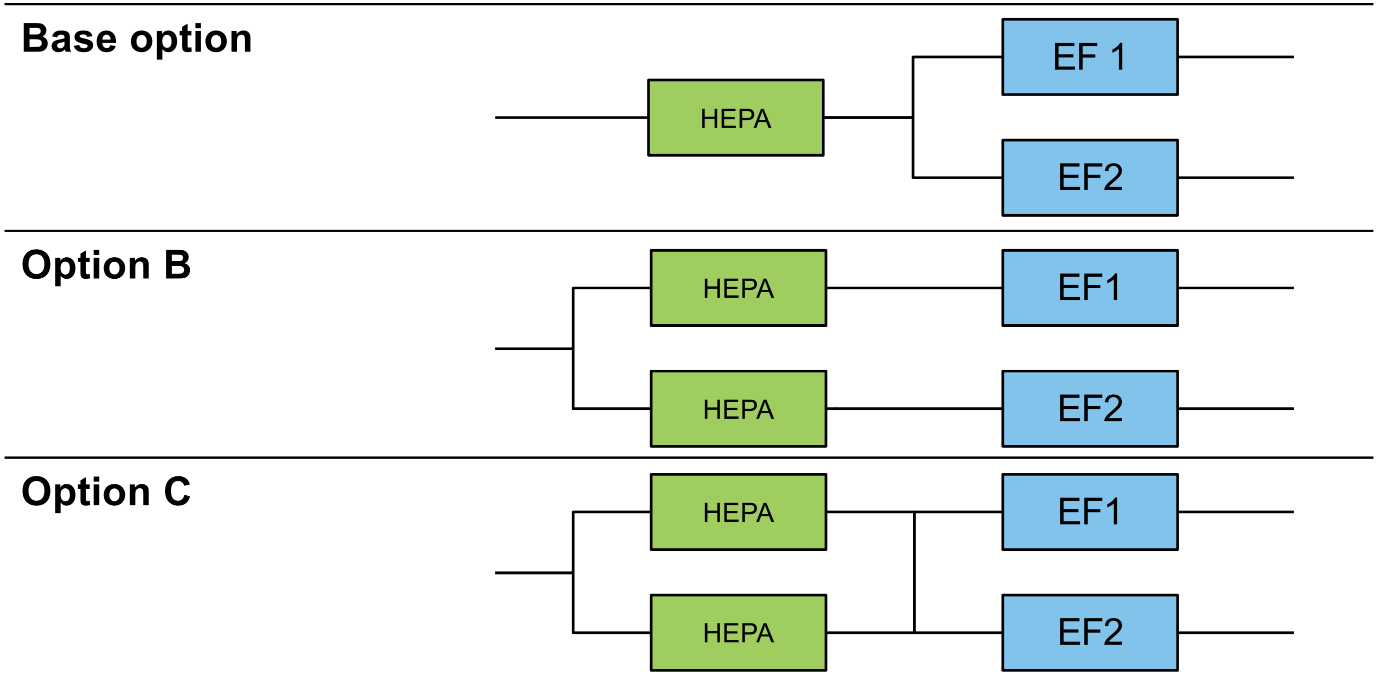


Expanded Exhaust-Side Redundancies (Operational Requirements)



Example Exhaust Fan Redundancy Options

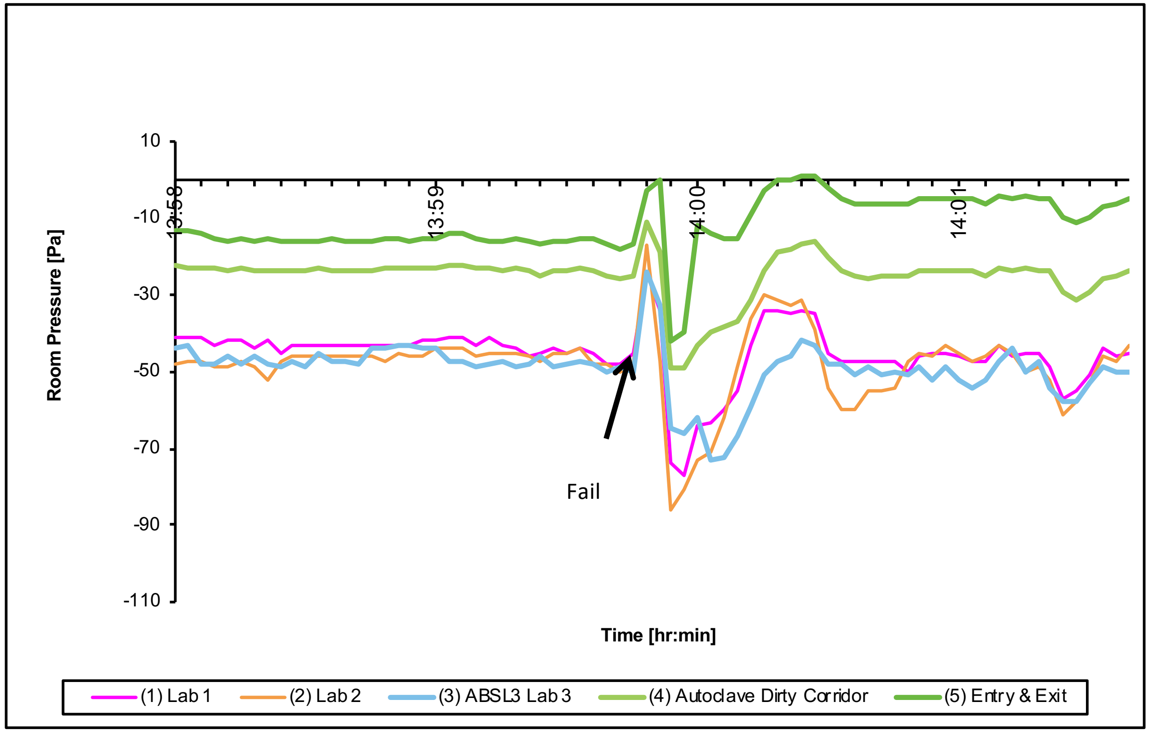
Type	Capacity	Explanation	Comment
N + 1	2 x 100%	Cold redundancy	Stand-by equipment is off Stand-by equipment may fail on demand
2N	2 x 100%	Warm redundancy	50%–50%–Operation Reduced energy efficiency
2N	2 x 100%	Duty-standby	100%-100%-Operation (Stand-by equipment is on, switchover) Running cost
2 x 0.5N + 0.5N	3 x 50%	Warm redundancy or duty-standby	Running cost

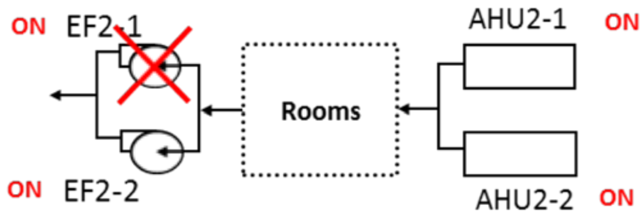
Verification Method: Pressure Differential Trending Logs

Source: Basler & Hofmann

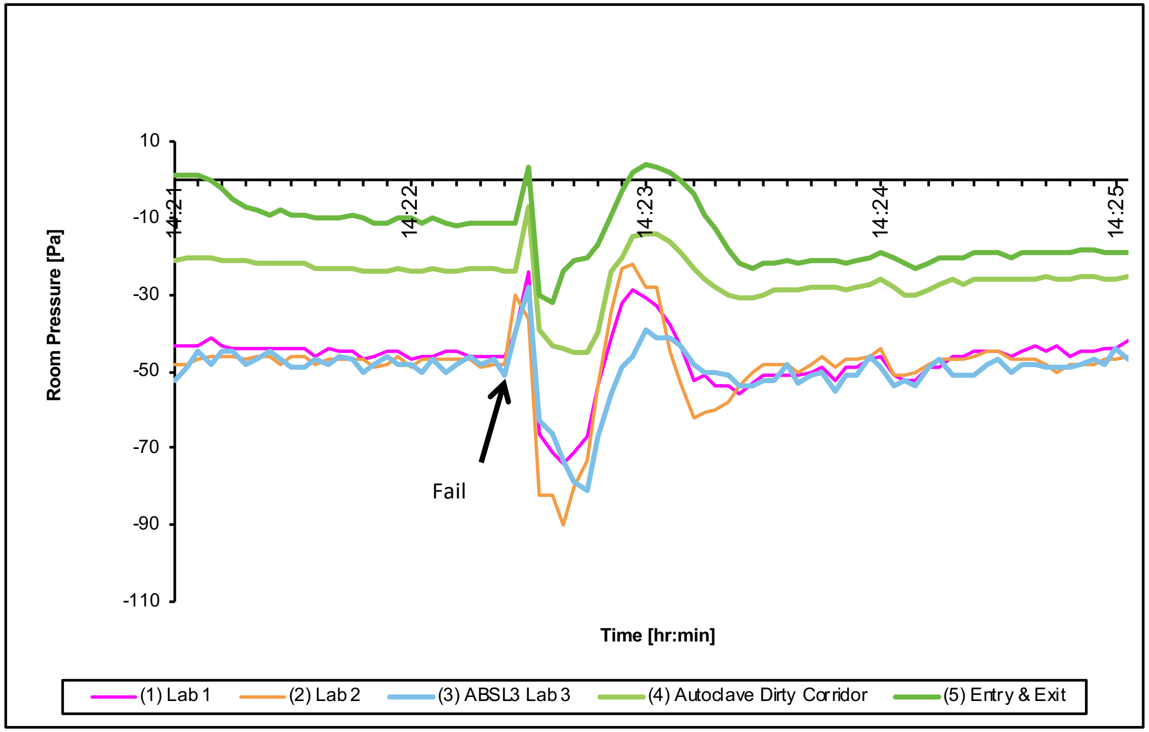
- Ventilation system controlled on and off, normal operation
- All relevant, probable failure scenarios
  - SPOF of mechanical and electrical systems

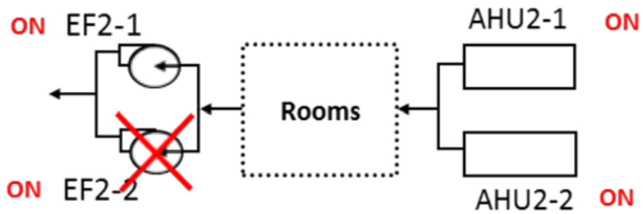
Ventilation SPOF Test (Warm Redundancy Configuration)



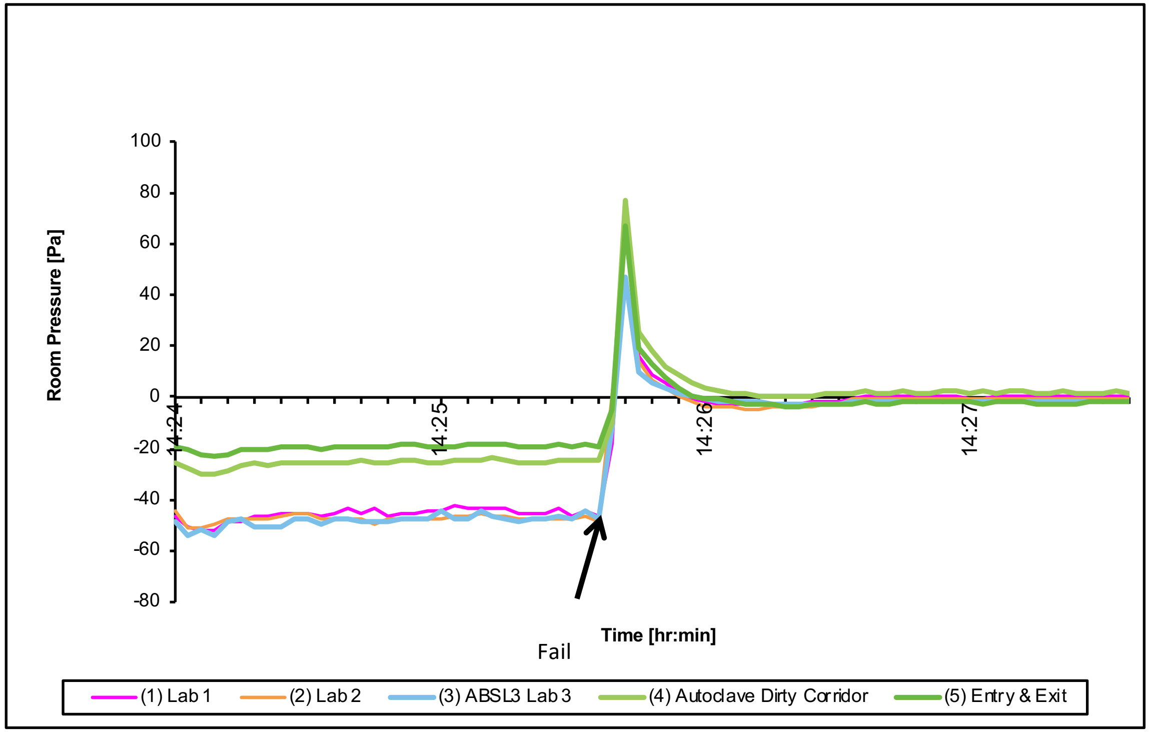


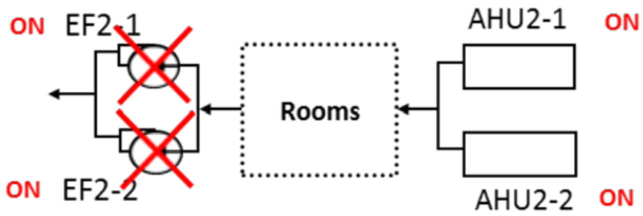
Ventilation SPOF Test





Ventilation SPOF Test





Take-Home Message 3

Source: Basler & Hofmann

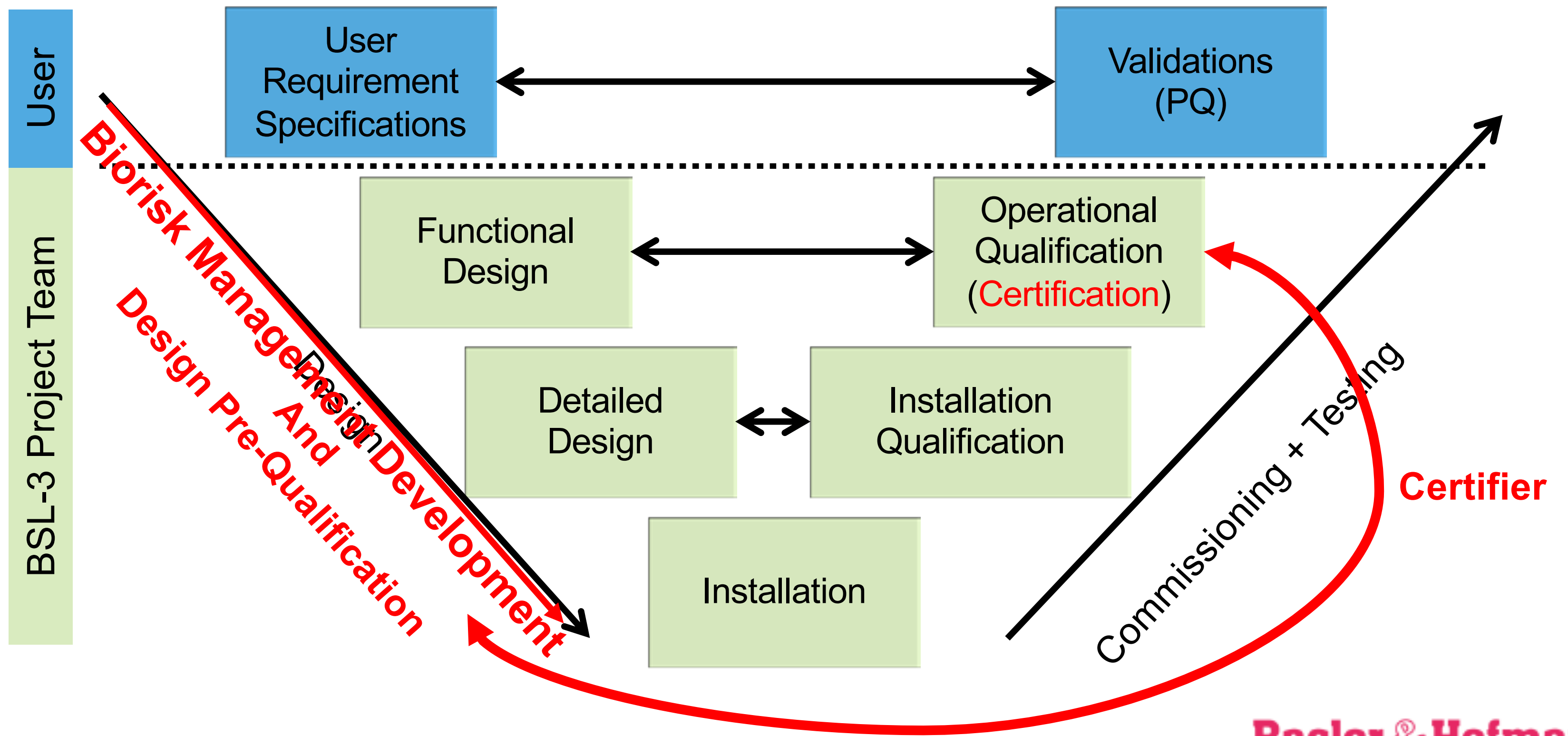
- Choice of BSL-3 protection layers and redundancies is a result of (performance) requirements and risk assessments determined in design phase

➢ Design or pre-qualification

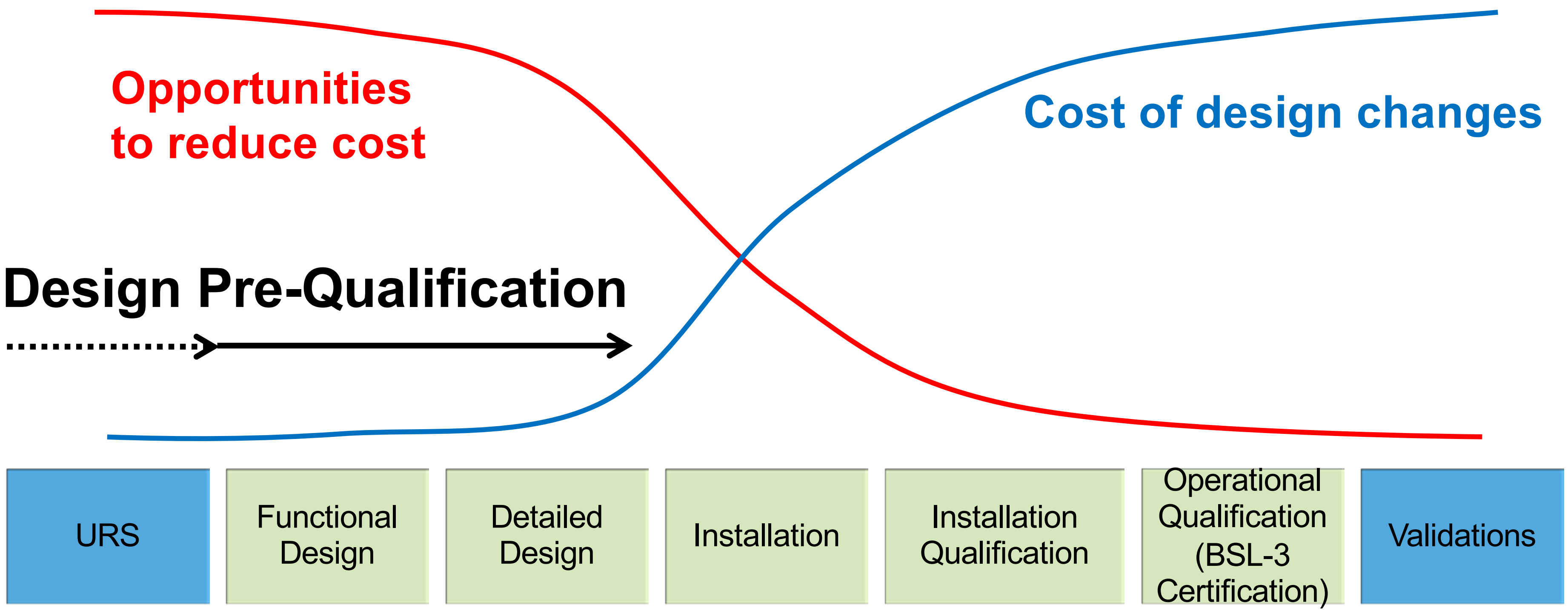
- Implementation and performance to be verified during testing and commissioning (IQ, OQ)

The V-Model for BSL-3 Systems Development and Verification

The V-Model for Biosafety Labs



Cost and Control Impact: Design Phase



Take-Home Message 4

Source: Basler & Hofmann

- Pre-Qualification (DQ): Include design review by competent biosafety professional and engineer, preferably 3rd party
- A testing and commissioning plan (IQ, OQ) is equally important as the design
- Check the consultant’s and contractor’s competences before placing order
- Validations are carried out by user (e.g. autoclave, fumigation, surface decontamination)

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Thank you very much

Basler & Hofmann Switzerland