Evolution of Aseptic-Containment in Biological and ATMP product filling

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Aseptic-Containment and control measures to achieve OEB 5/6

Health Based Exposure Limits

Toxicological Data

- NOAEL
- NOEL

Health Based Exposure Limits

- PDE
- ADE

Occupational Limits

- OEB
- OEL

Health Based Exposure Limits (HBELs) are derived from toxicological data

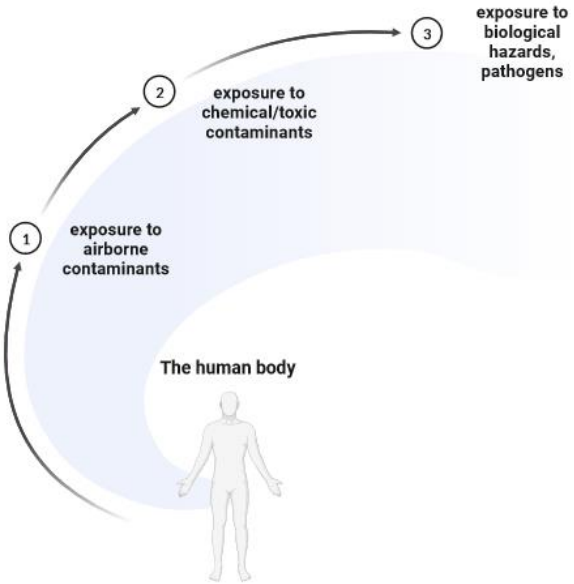
→ **Permitted Daily Exposure (PDE)**

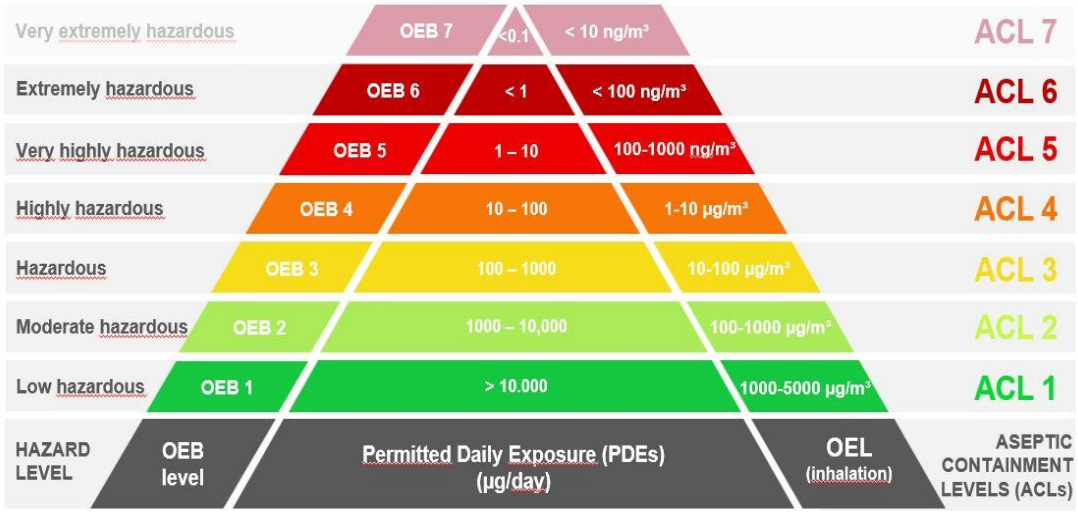
$$\text{PDE}[\mu g/\text{day}] = \frac{NO(A)EL(\frac{\mu g}{day}) * \text{Weight Adjustment (kg)}}{F_1 * F_2 * F_3 * F_4 * F_5}$$

Occupational Exposure Limit (OEL): respiratory uptake of permitted daily exposure (PDE)

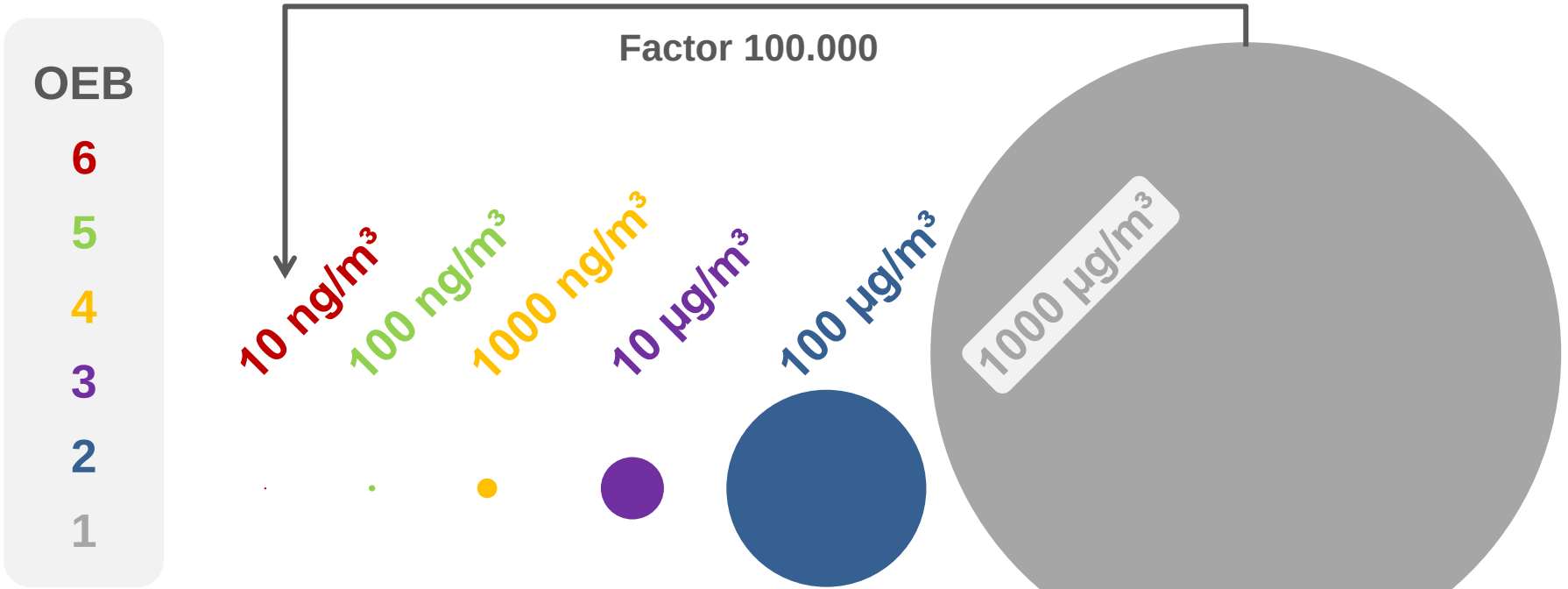
$$\text{OEL}\ [\mu g/m^3] = \frac{PDE}{10\ \frac{m^3}{day}}$$

Environmental risks





Visualisation of OEB exposure amounts



Occupational Exposure Bands (OEBs): Groups of OELs, classification may differ

primary and secondary containment measures

different systems of containment strategies:

- primary Containments:

  physical isolation:

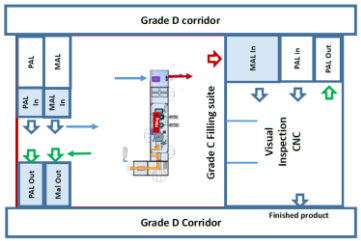
  equipment must provide a complete barrier between hazardous process/material and external environment

  ➔Isolators, bioburden control - API in solution - sterile filtration - positive pressure **vs**. API powder – negative pressure - glove boxes, closed transfer-systems (RTPs), SUS

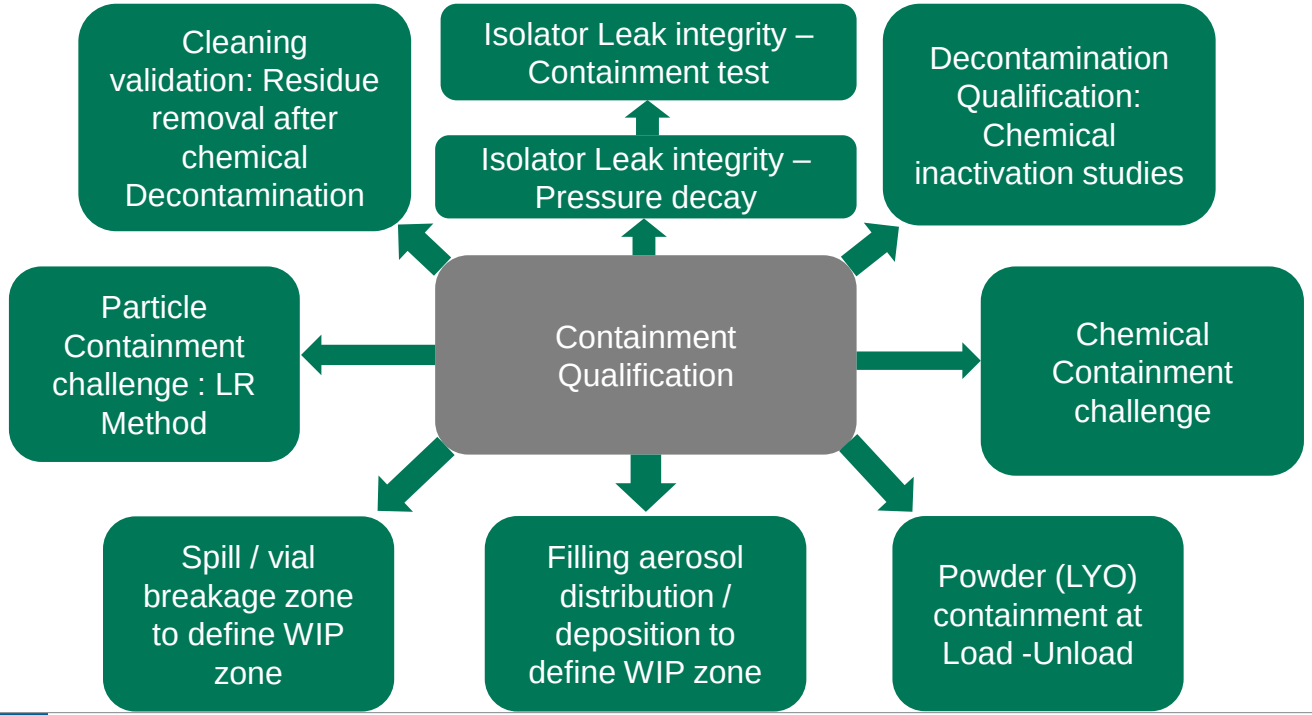
- secondary Containments:

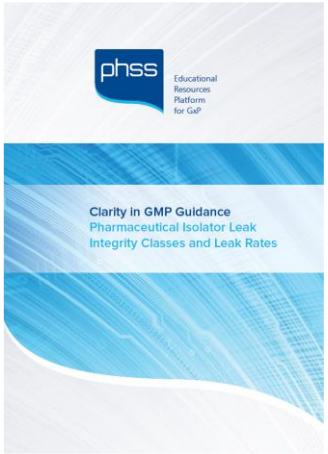
  safeguards and strategies:

  support and enhance primary containment measures, particularly in the context of preventing the release of hazardous substances or protecting against contamination (e.g. first air).



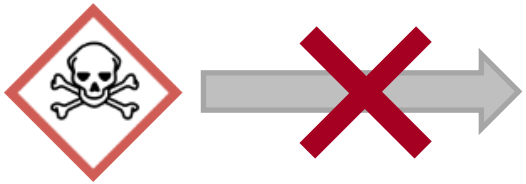
Containment Qualification: Aseptic process filling OEB 5/6 hazardous products





Strategies for personnel and product safety

Aseptic product (toxic)

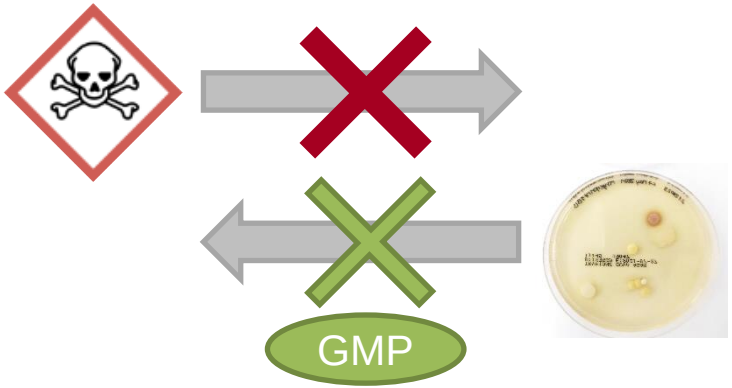


Personnel Protection (Negative Pressure Isolator)

Operator

Aseptic product (toxic)

Personnel Protection
(Negative Pressure Isolator)



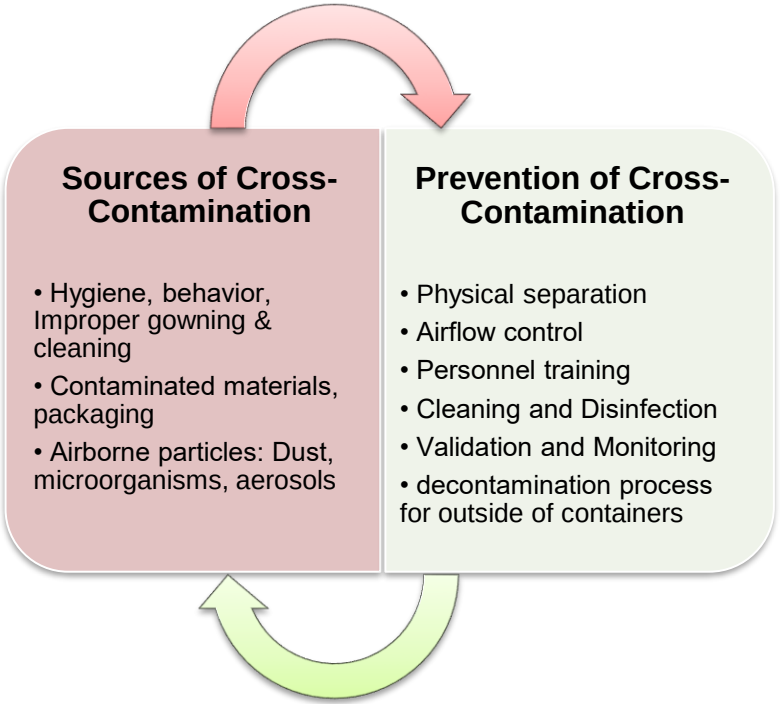
Operator

Product Protection
(Positive Pressure Isolator)

Aseptic Containment Strategy (ACS) for operator protection and Cross Contamination Control

1. Containment is essential for operator protection and preventing cross-contamination
2. Aseptic processing requires an Aseptic-Containment Strategy (ACS) – complementary to CCS
3. Containment strategies involve primary and secondary measures working together
4. Hazardous product exposure requires characterization with health-based exposure limits (HBELs)
5. Aseptic-Containment involves SUS, closed processing, and barrier technology
6. Open system isolators use measures like pressure bubbles and directional airflow management for material transfer

Cross-contamination control



1. **Product Quality:**

crucial to maintain the **purity** and **quality** of products, **contaminants** can be harmful or lead to **product defects**

2. **Safety:**

ensures the **safety** of consumers, workers, and the environment by **preventing** the unintended transfer of **hazardous substances**, **allergens**, or **pathogens**

3. **Regulatory Compliance:**

essential for adhering to strict **regulatory standards** and requirements to **protect public health** and ensure **product integrity, guidance of HBELs**

Viral Containment -Aseptic Containment Strategy (ACS)

Aseptic-Containment Strategy (ACS) connects to a Contamination Control Strategy (CCS: Annex 1) when products are biologically active, hazardous or toxic or require containment as a control measure in Cross-contamination control. Both a CCS and ACS need documenting (**critical control points**; **assessment for monitoring measures**).

For Viral vector containment a series of primary containment and secondary containment control measures are integrated to contain the viral vector so it can be decontaminated in-place. Containment measures include: Closed barrier systems, Closed Material transfer systems, Single Use systems and Open Barrier systems with protective airflow 'Bubbles' and airflow patterns.

In-place decontamination is effected by hydrogen peroxide vapour, used as a post-production decontamination cycle after batch completion and before open door barrier set up for the next batch.

Virus may pass through HEPA Filters, so a full 'System' Decon is required in the post-production decontamination cycle. Barrier system exhaust to outside via double HEPA filtration.

Viral containment measures apply to airborne contamination (protective airflow patterns) and surface contamination. Out surfaces of filled units require outer surface Decontamination.

The Cleanroom, surrounding barrier systems are not a primary Containment but do provide measures in cross contamination control via PALs/MALs pressure containment 'bubbles'.

Aseptic/toxic containments are largely, internationally harmonized

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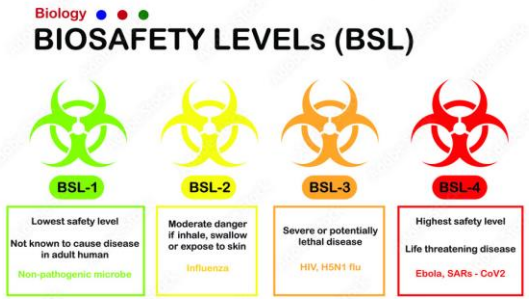
harmonisation for better health



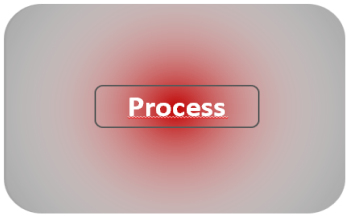
- Foundational principles for biosafety given by WHO Laboratory Biosafety Manual (handling pathogens in research) – level for biosafety and GMP conformity need to be aligned
- Balance risk between operators and patients !
- Biosafety practices often depend on local agencies

Decontamination strategies for aseptic/toxic and biohazard products

A

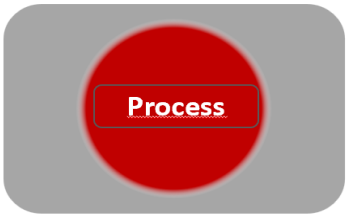
Full spread of contamination inside barrier

B

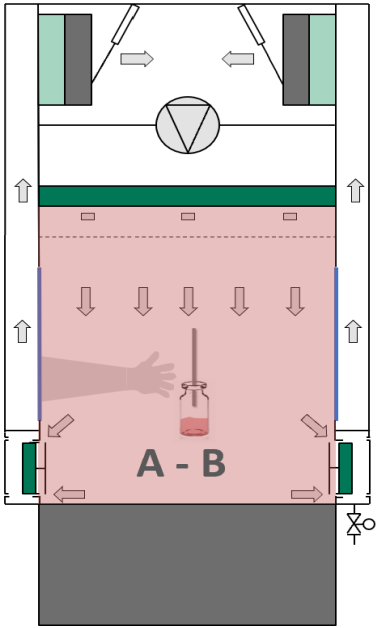


Diffused spread of contamination inside barrier

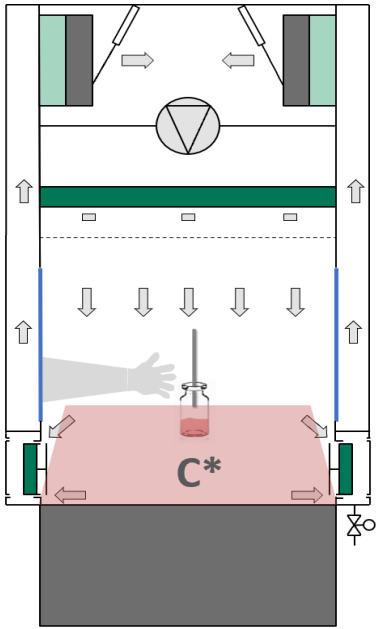
C*



Localised spread of contamination inside barrier



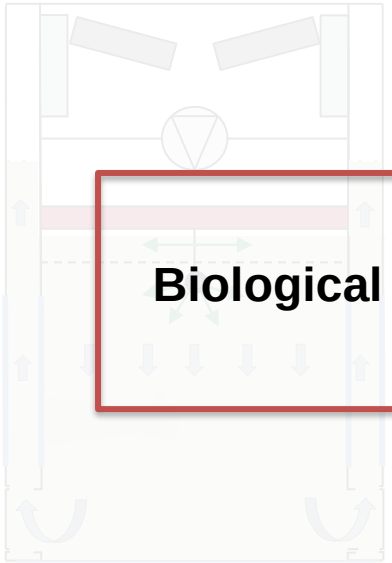
Contamination spread suppressed by UDAF



Most Aseptic process filling operations can be considered as localised ‘C’ contamination for an ACS

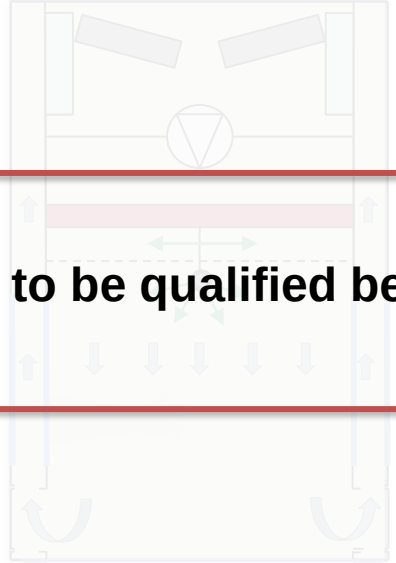
End-point qualification

Pre-Production-Biodecontamination



- establish Grade A conditions for production process
- End-Point: < 0.1 ppm for biological products
- Short cycle - longer aeration

Post-Production-Decontamination

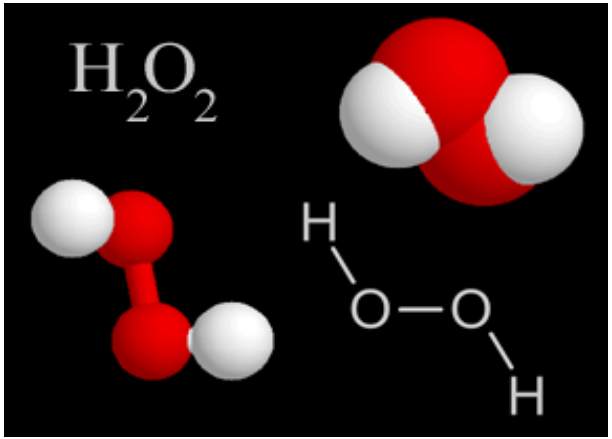


- Complete system cycle
- Operator safety & cross-contamination control
- long cycle - short aeration
- End-point: < 1 ppm

Biological products end-point need to be qualified below 0.1 ppm!

Exposure studies for end-point validation

- vH_2O_2 is initially used to achieve Grade A conditions within an Isolator barrier system.
- Pre-Production: end-point qualification, Amplex® Red studies for determination of vH_2O_2 residuals
- Post-Production: For viral containment vH_2O_2 is used as the principle Post-Production decontamination cycle to facilitate open barrier door access for set-up of next batch.



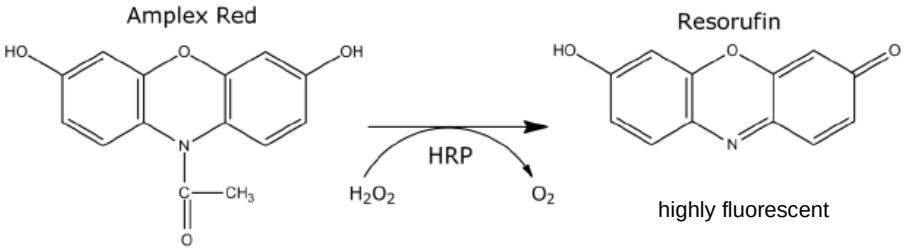


Figure 1: Mechanism.

- Detection and quantification of H_2O_2 residues
- HRP catalyzes oxidation of Amplex® Red to highly fluorescent Resorufin
- Emission intensity is proportional to H_2O_2 concentration

FZ analytical chemistry laboratory:

- H_2O_2 measurement device for ppb concentrations (Picarro)
- Amplex red studies for residual analysis can be performed

On-site:

- after qualification of the gassing cycle, FZ laboratory experts test on site for residuals in operation on the installed Isolator line

Amplex® Red (10-acetyl-3,7-dihydroxyphenoxazine):

- Fluorogenic probe widely used to detect and quantify H_2O_2 in biological systems
- MoA: Peroxidase-catalyzed oxidation of Amplex® Red to resorufin.

Summary

1	2	3	4
Achievement of **OEB 5/6 by Aseptic-Containment Strategy (ACS) that connects to a Contamination Control Strategy (CCS: Annex 1)**	For Viral vector containment: combination of **primary** and **secondary containment** strategies and **qualification is required** (PHSS)	Decontamination strategy for **aseptic-toxic API** by **WIP/CIP** Decontamination for biological hazards/viral vectors ensured by **Post-Production**-Decontamination cycle → Full System Decon is required in Post-Production-Cycle!	**Pre-Production**: End-point qualification necessary Qualified by laboratory analysis!

Thank you !

Follow up contact details

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