BPSA 2020 Speaker Series

Wednesday, October 21, 2020
10:00-11:00 AM EDT

Building an Integrity Assurance Approach in Single-Use Processing through the SUS Whole Life Cycle

Featured Speakers

Marc Hogreve,
Sartorius Stedim Biotech

Charlotte Masy,
GSK Vaccines

Hélène Pora,
Pall Biotech

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Webinar Speakers

Marc Hogreve
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Charlotte Masy, PhD
GSK Vaccines

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Integrity Assurance Approach in Single-Use Bioprocessing through SUS Life Cycle

Marc Hogreve , Sartorius Stedim Biotech

Charlotte Masy, GSK Vaccines

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Agenda

- Why integrity assurance is important
- Building an integrity assurance strategy as a combined responsibility between suppliers and end-users
- Case study: adjuvant storage & transport in vaccines

Most figures and tables coming from *: Design, Control, and Monitoring of Single-Use Systems for Integrity Assurance, BPSA, July 2017*

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Definitions

Leak test – a test used to identify leaks of certain sizes in a SUS.

Integrity Test – a test used to confirm the defined barrier properties of a SUS

Maximum Allowable Leakage Limit –the greatest leakage rate (or leak size) tolerable for a given product package that poses no risk to product safety and no or inconsequential impact on product quality.

Integrity Assurance – a holistic approach of risk analysis and mitigation by means of product and process robustness, quality and process control and integrity testing.

Non-destructive Test Method – a test method that maintains the tested SUS in a condition for further use, without impacting its quality attributes.

Destructive Test Method – a test method that may destroy the tested SUS during the test and not allow further use.

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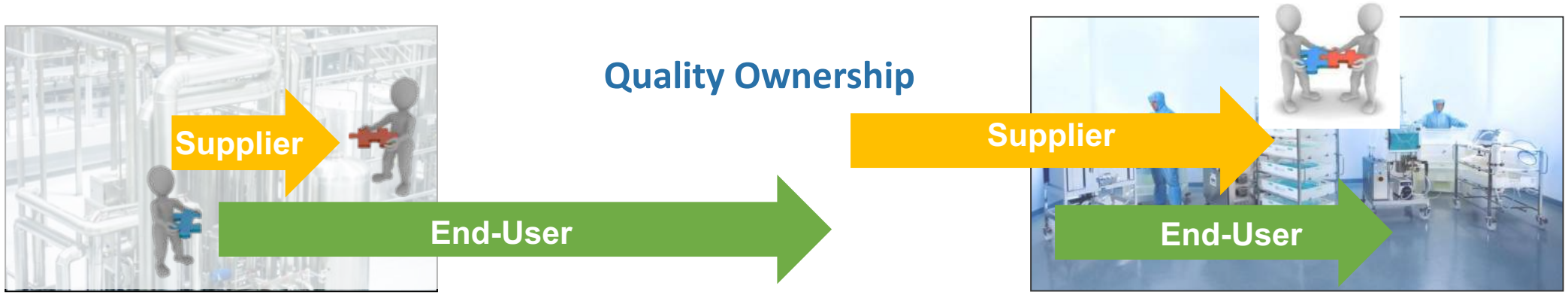
Single-Use Systems vs 'Traditional' Stainless Steel

- 'Consumable manufacturing equipment'
  - Material flow, logistics and supply chain management
  - Every new copy should be the same than the initial one
  - Part of supply and **quality chain shifts** to supplier



Higher potential impact on drug substance/ product

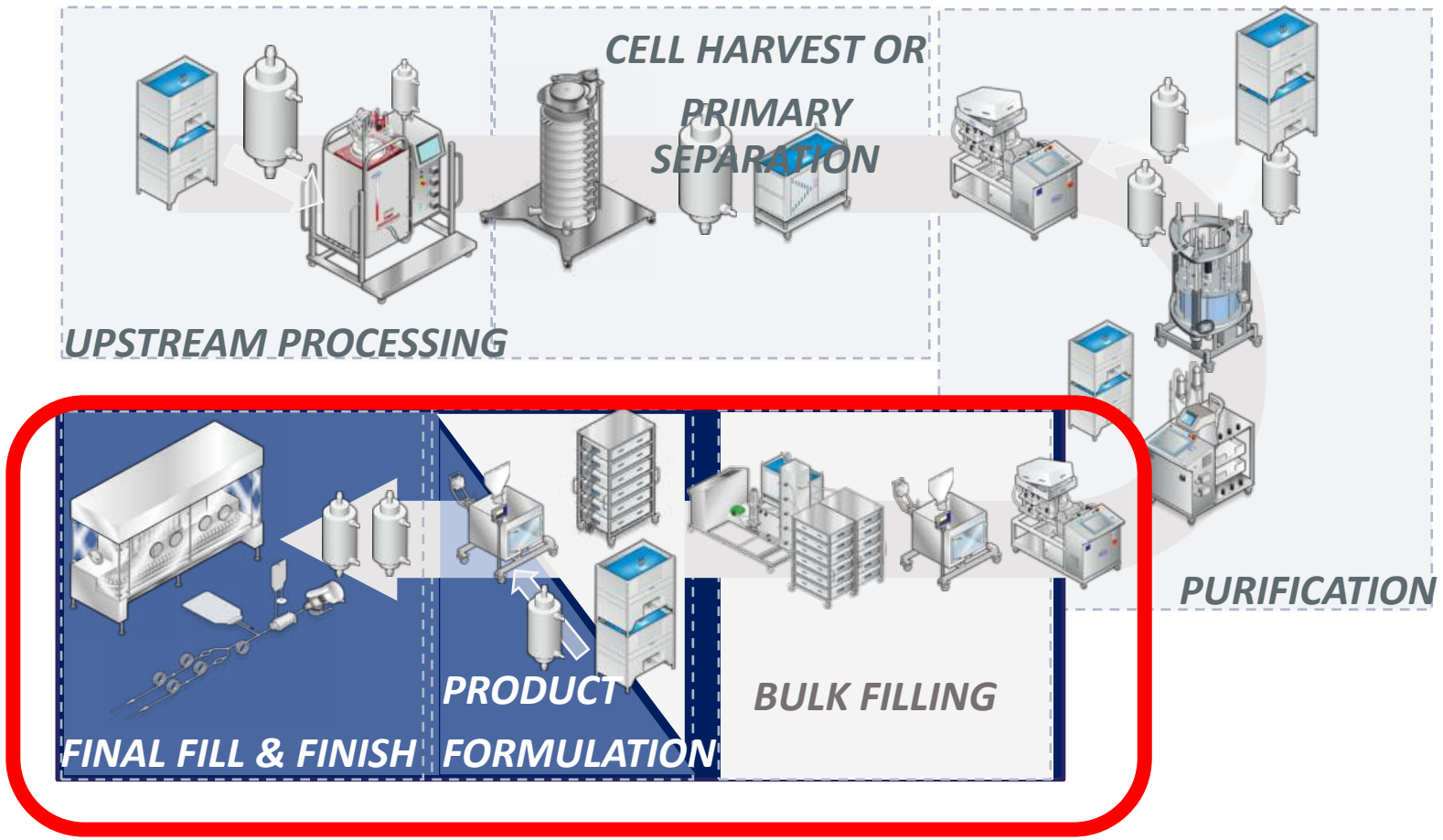
What is Limiting the Use of SUS ?

WWW.BIOPLANASSOCIATES.COM

Seventeenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

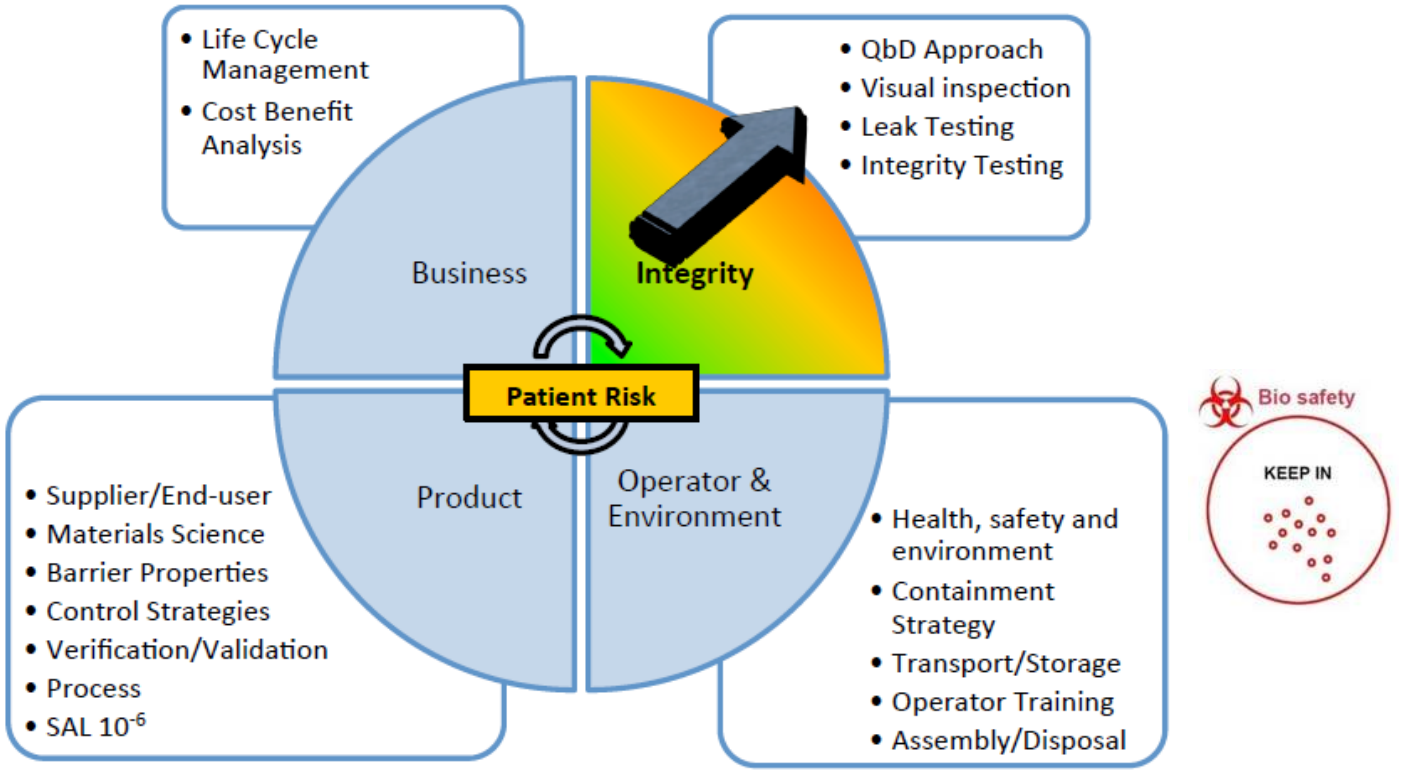
Loss of integrity is an important concern; especially when single-use systems (SUS) are implemented in critical sterile applications. It is a critical point of attention during regulatory audits.

Typical Applications Where Integrity is Requested



Integrity of SUS

- Integrity: ability of a container to
  - Keep the contents IN
  - Keep the contaminants OUT
- Integrity assurance is fundamental to patient safety



'Leak' = **not** correlated to barrier properties

'Integrity' = correlated to barrier properties (e.g. microbial ingress)

Current Industry Guidance and Standards Initiatives

- Annex 1 - Manufacture of Sterile Medicinal Products *(Revision – Not yet published)*
- USP<1207> 2016 Package Integrity Evaluation – Sterile Products
- ASTM E3244 Standard Practice for Integrity Assurance & Testing of SUS
- ASTM E3251 Test Method for Microbial Ingress Testing on SUS
- NEW PDA TR on Pharmaceutical Package Integrity *(to replace existing TR27)*
- BPSA 2017 Design, Control, and Monitoring of SUS for Integrity Assurance

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Regulatory Bodies Are Pushing for More Testing

Annex1 - Manufacture of Sterile Medicinal Products (Revision – Not yet published)

- 8.119 Appropriate measures should be in place to **ensure the integrity** of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS*. **Appropriate system integrity tests should be considered** when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

- 8.121 SUS are those technologies used in manufacture of sterile products [...].

- 8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS*. These risks include but are not limited to:

  i. [...]

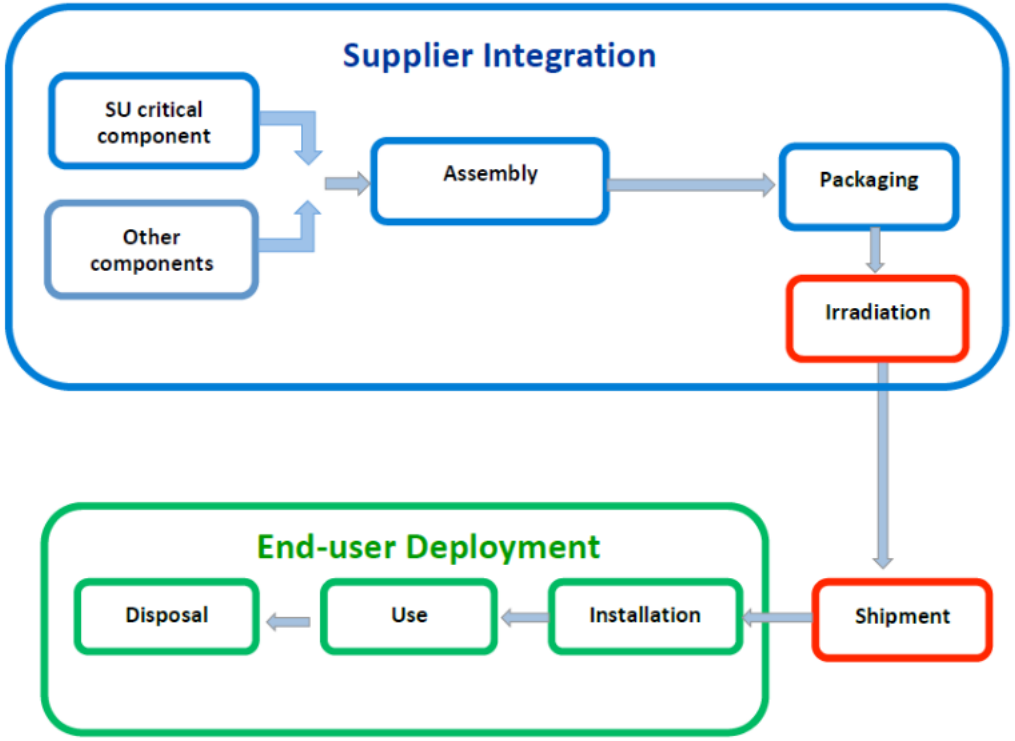
  vi. The risk of holes and leakage.

  vii. The potential for compromising the system at the point of opening the outer packaging.

*Contamination Control Strategy

Shared Responsibilities between Suppliers & End Users along the SUS Life Cycle

- Understanding the risks and potential failure modes associated with each stage of the SUS life cycle
- Design, development & validation stages at component and assembly suppliers
- Assembly process, shipping & packaging validation
- After irradiation & shipment, the end user is responsible for deployment, operator training, assembly installation, use and disposal



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Potential Testing & Qualification Approach Performed by SUS Suppliers for Integrity Assurance

	SUS Development & Validation	SUS Manufacturing	SUS Shipment (empty systems)
Criticality, Intended use	**QbD, Risk Assessment & Process validation**	**Process Control & QC Testing**	**Design & Packaging of SUS before use**
Upstream Sterile filtration possible Low risk	1. Individual component validation 2. Mechanical tests 3. Assembly validation => Junction test 4. Shelf life	1. Component testing 2. Seal quality tests 3. Visual inspection of SUS	1. Packaging validation 2. ASTM/ISTA transportation validation
Downstream Sterile filtration possible Medium risk		*In addition to 1.-3.* 4. Leak testing of bags	
Final Formulation & Compounding Sterile filtration possible Medium risk			
Filling No sterile filtration possible High risk	*In addition to 1.-4.* 5. Microbial aerosol or immersion challenge test	*In addition to 1.-3.* 4. Integrity testing of entire SUS	

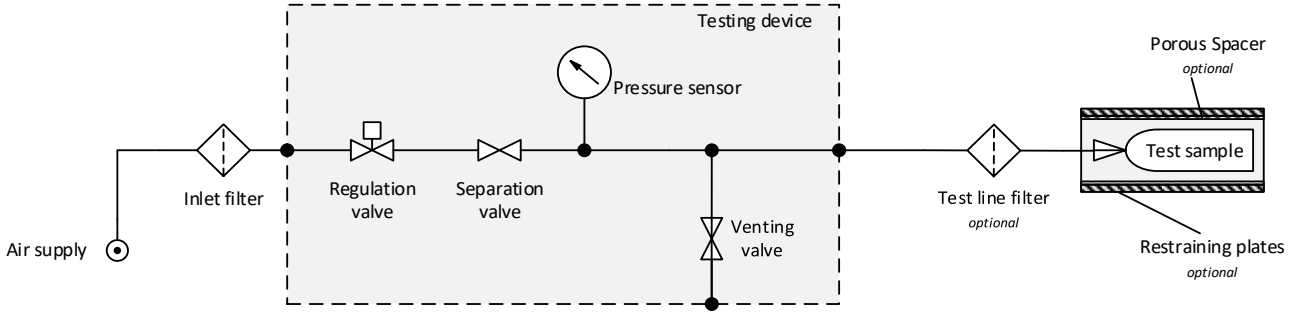
Potential End User Strategy for Integrity Assurance throughout SUS Life Cycle based on Risk Assessment

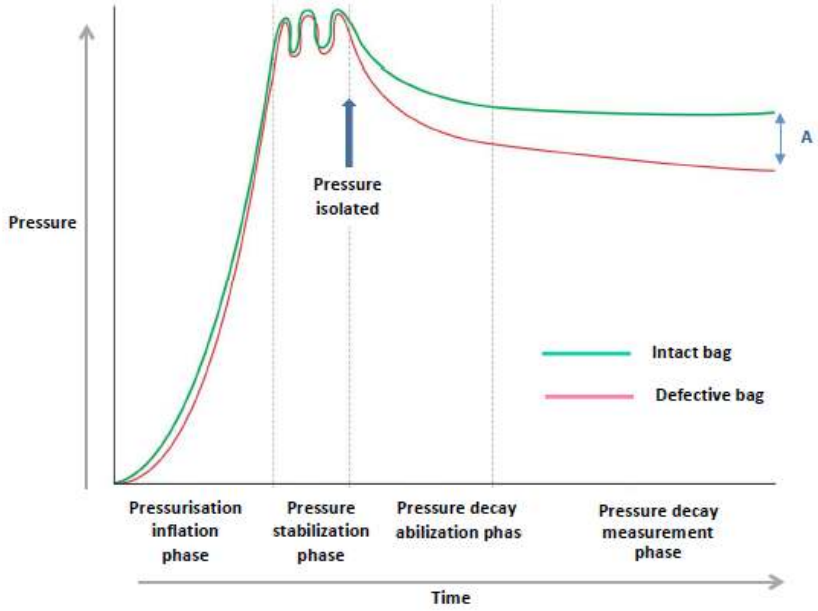
End-user Evaluation → End-user Implementation → SUS Product Shipment → SUS Commercial Pre-use → SUS Commercial Post-use

Design & Development	Validation & Training	Incoming Inspection	Pre-use Installation	Post-use
Process/application mapping for intended use Design space; Review of existing validation & gaps identification Definition of expected manufacturing control strategy (supplier and end user) Verification of supplier validation package Establish process and storage conditions for unused SUS, based on supplier recommendations	User qualification package IQPQ & Aseptic broth validation Consistency batches Training by supplier and/or end-user SME, Visual inspection of SUS Verification of integrity: non-destructive and destructive testing For critical applications, submit SUS to full life cycle and verify integrity at the end	Check at reception and any intermediate storage location for any visible damage QC Inspection Documentation	Visual inspection of packaging and SUS (gross defects, integrity of secondary packaging) Non-destructive testing Visual checks during use: Connectivity, tubing installation, clamps, special attention to sterile connections	Visual inspection for absence of liquid leaks (also during operation) Sterility testing of product Additional testing as per user's requirements

Physical Leak Test Methods - Pressure Decay

- Working principle

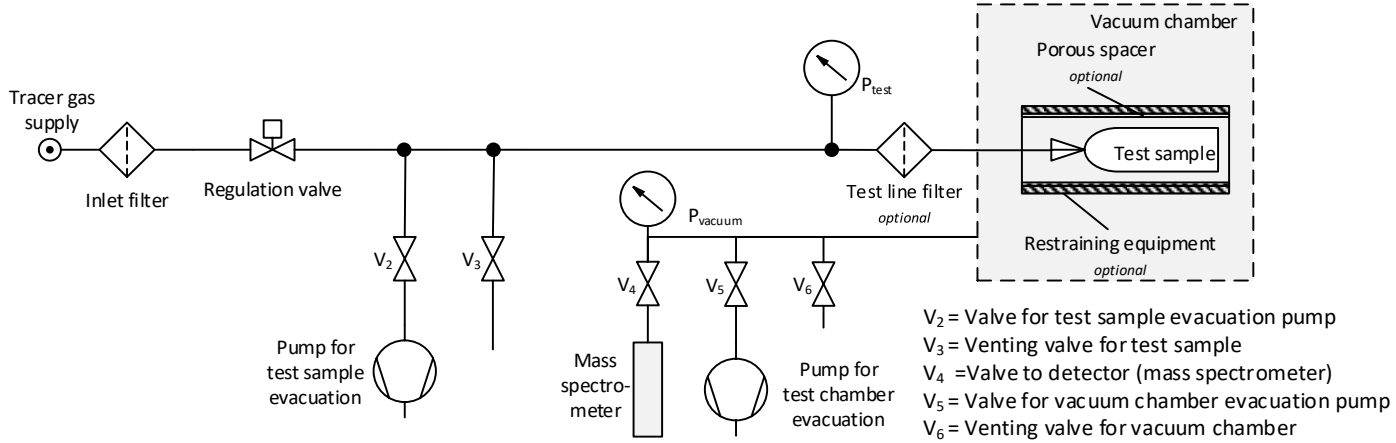


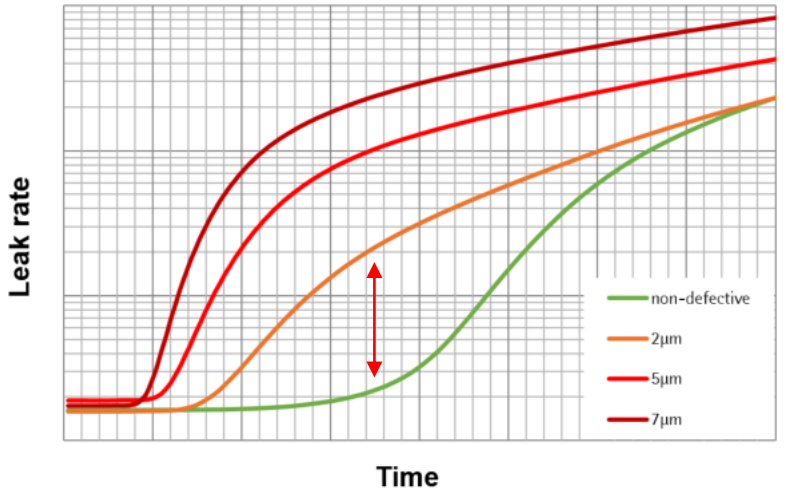


- Sensitivity
  - proportional to test pressure
  - inversely proportional to inner volume of the test article

Physical Leak Test Methods – Helium Tracer Gas

- Working principle





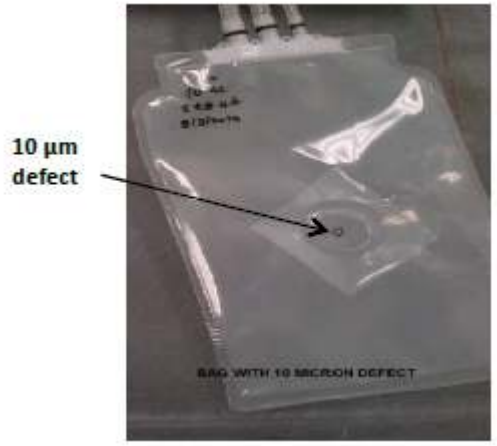
- Sensitivity
  - Materials composition
  - Volume / design complexity

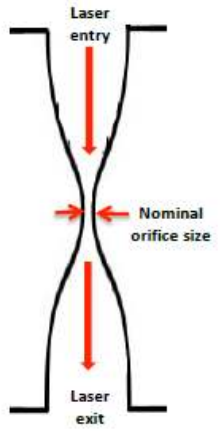
Comparison of Physical SUS Integrity Testing Methods

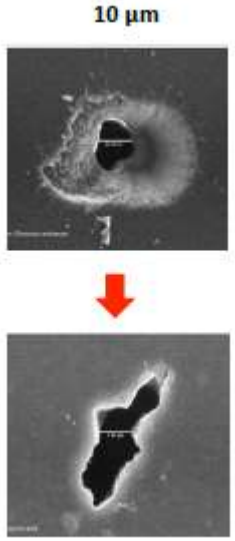
Feature	Tracer-gas-based Technologies	Pressure-based Technologies
Sensitivity	≥ 2 µm	≥ 10 µm
Environmental effect	Low	Medium (Temperature)
Volume impact	Low to Medium	Medium to High
Material impact	Medium to High	Low to Medium
Handling	Medium to Complex	Simple
Test time	Low to Medium	Medium to High
Maintenance	Complex	Simple
Investment costs	High	Low

Correlation to Microbial Challenge

- Principle:
  - Set of defective parts, with known defect size
  - Subject to microbial challenge (use-case or worst-case conditions conditions)
  - Cut-off limit ⇨ critical defect size or MALL*







- Defect size usually given in 'Nominal Diameter Orifice Size'

* Maximum Allowable Leakage Limit: is the greatest leak size tolerable that poses no risk to product safety, USP<1207>

Risks & Limitations Associated with Physical SUS Integrity Testing Methods

Risk/Limitation	Pre-Sterilization Testing	Pre-Use Testing	Post-Use Testing
Sterility loss	No	Yes, but can be mitigated with appropriate test setup and/or SUS design.	No
Mechanical stress causing additional leak(s)	Yes, but can be mitigated with respective mechanical support. For post-use testing, there is no risk of damage to the SUS to be used, but it could theoretically lead to a false negative integrity evaluation.		
Masked leaks by test setup	Yes, but can be mitigated with appropriate test setup, for example porous spacer.		
Masked leaks by residual product	No		Yes

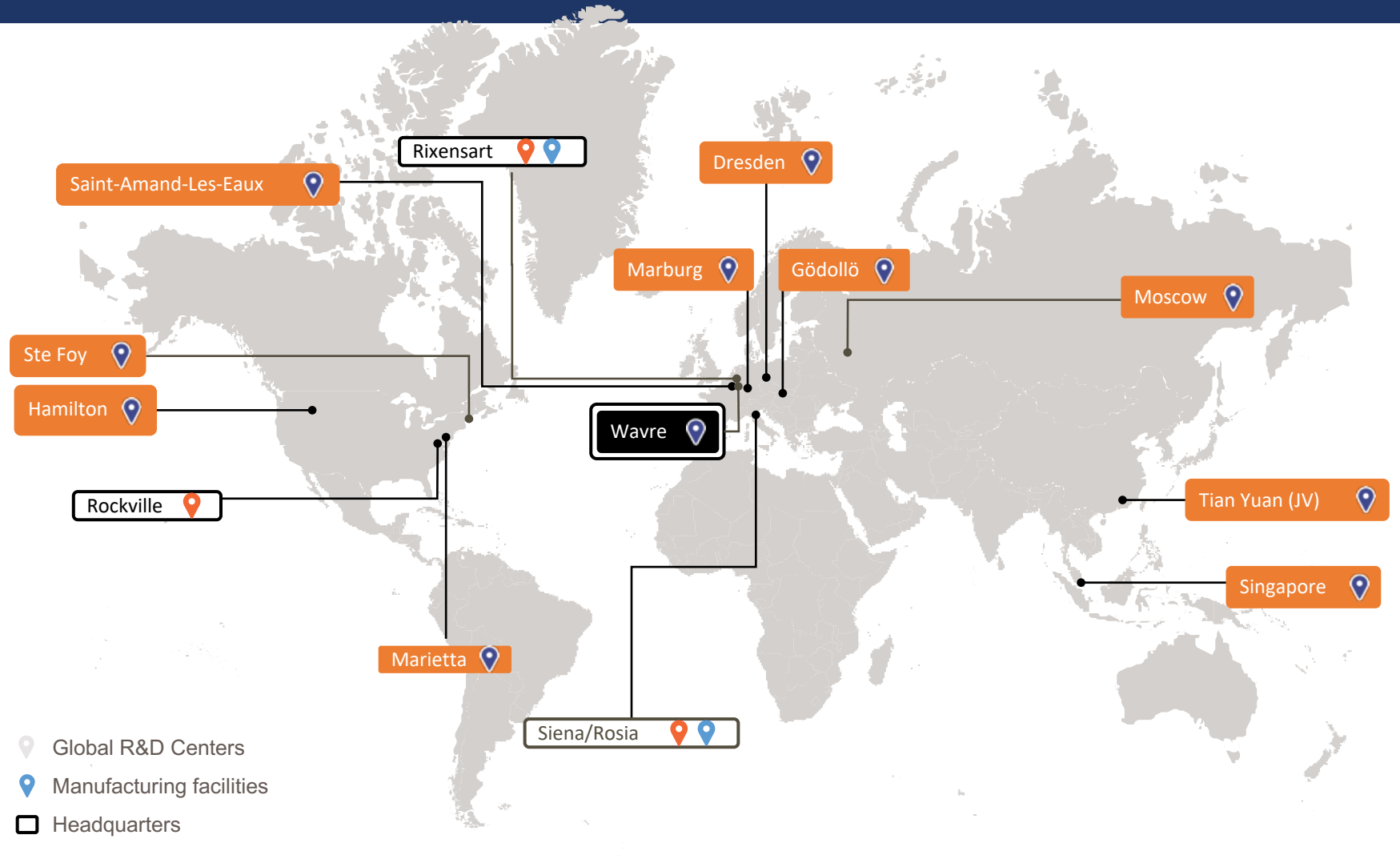
Integrity strategy and case study

Charlotte Masy, *Manufacturing Sciences and Technologies,*

GSK Vaccines

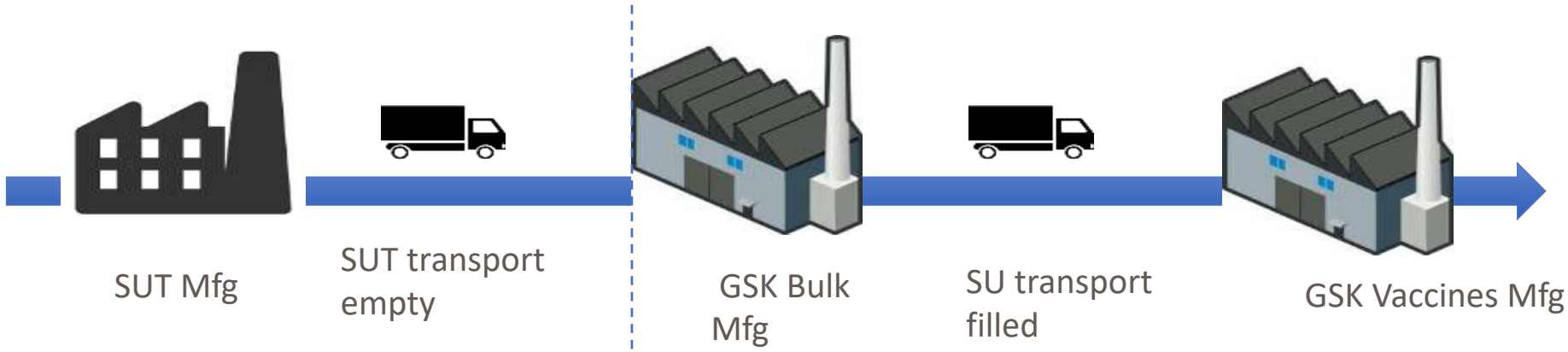
GSK Global Presence

+17,000 employees on 14 sites strategically positioned around the world



GSK Integrity Strategy

- Key points based on BPSA white paper on Design, Control, and Monitoring of Single-Use Systems for Integrity Assurance



- Control of manufacturing:
  - First layer: Validation (incl .transport)
  - Second layer: manufacturing under control
  - Third layer: Physical test is mandatory:
    - ➢ 100% integrity test is preferred
- Assessment of use:
  - Qualification has to confirm integrity after life cycle
  - Microbial challenge (BCT) or physical tests acceptable

Case Study : Adjuvant in Vaccines

→**Vaccines process:**

- No thermal sterilization
- No potential filtration

→Critical to maintain system closed and integral

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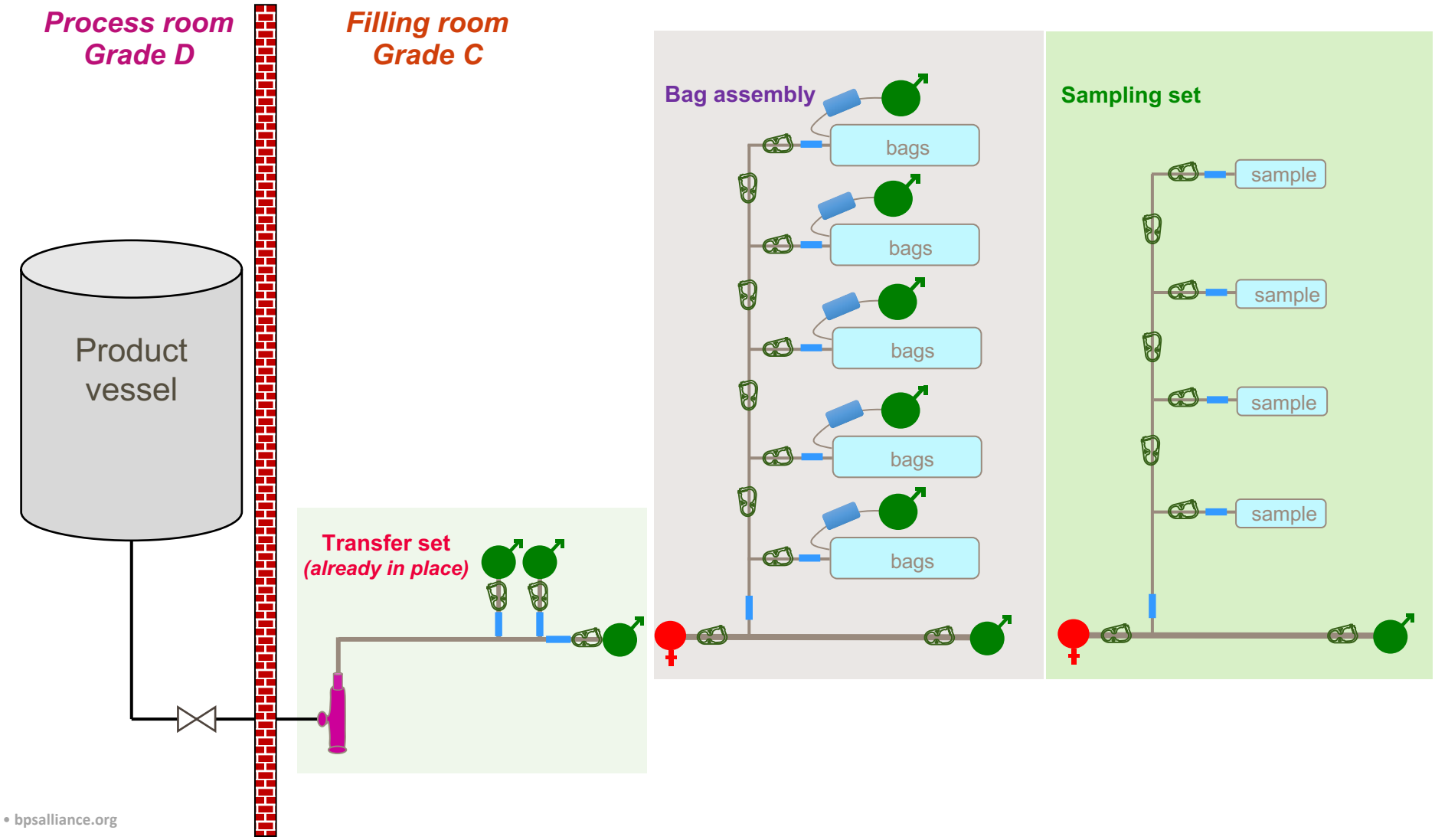
Adjuvant Process

- Closed system filling in bags & sampling



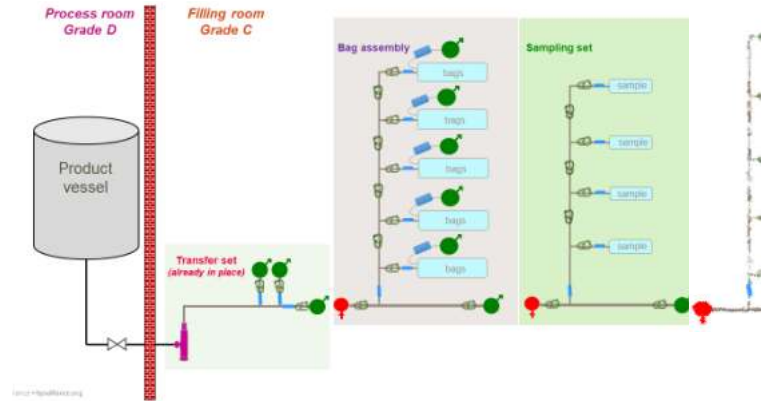
Process Challenge –Transportation

Akilux® box

- Challenge :
  - Transport of different bags
  - Sterility during transport

Process Summary

Filling

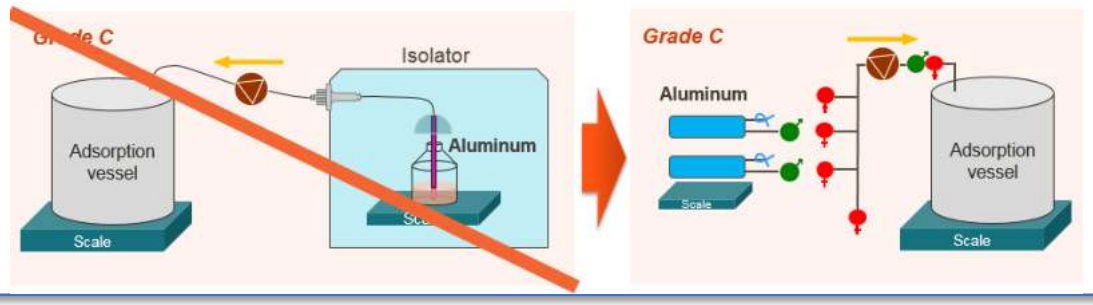


Product sterilization in the vessel and fully closed system filling process

Transportation

Standard shipment configuration

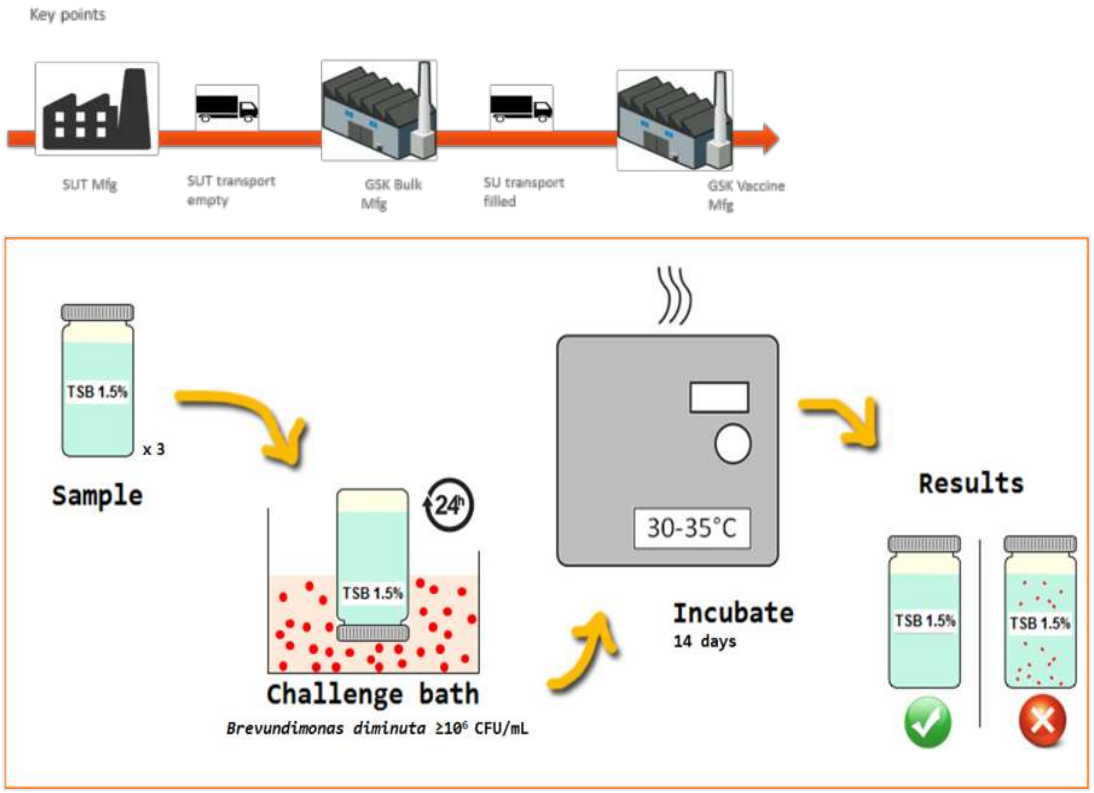
Use in GSK Vaccines

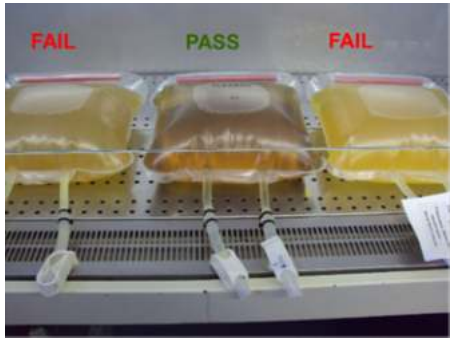


Fully closed system transfer in Adsorption & Formulation

Validation of Integrity

Bacterial challenge test by immersion after life cycle





Example of PASS / FAIL tests

Principle: Microbial ingress

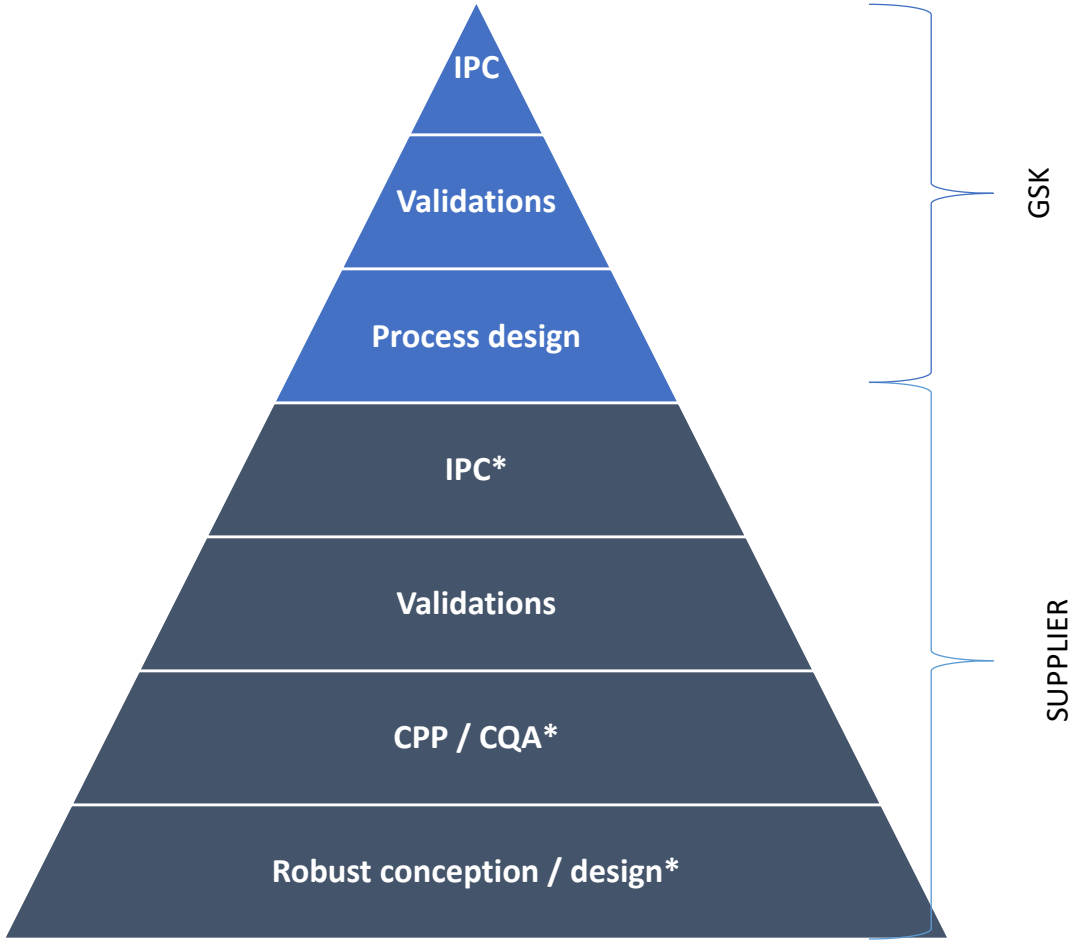
Operating conditions:

- Liquid bath (10^6 CFU/ml)
- Time: 24h

Tips & tricks:

- Limit handling during test
- Use robust design

GSK Strategy



	Critical application
GSK	**Storage part**: Validation with **bacterial challenge test by immersion.** **Transfer part:** Worst case conditions tested during validation (CCIT, liquid pressure test, ...)
Supplier	**Storage part: 100% integrity tested (Helium test).** **Transfer part**: 100% leak tested (Pressure decay) **Sterile connection / critical component:** Validation by specific BCT depending on technical aspect (e.g. membrane).

* Quality by design principle

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Conclusions GSK Case Study– Lessons Learnt

→ Integrity management is shared between supplier & user

→ Risk assessment approach allows to define the appropriate strategy for assurance of integrity

→ QbD is key – no integrity test can replace a bad design!

→ Guidance for training on integrity is important

→ A good collaboration between user & supplier is KEY to succeed

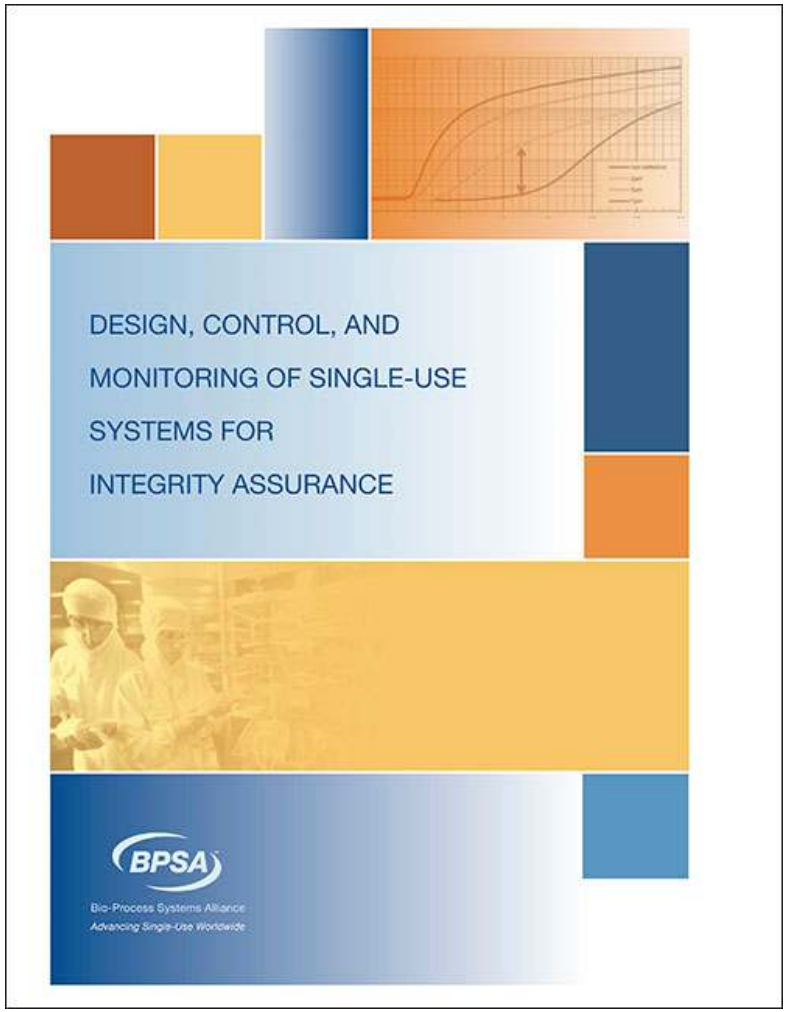
→ Continuous improvement is needed

Conclusions- Lessons Learnt Globally

- Integrity strategy is a key element to be defined when implementing SUS
- Cooperation between end-users /suppliers
  - To set-up the directions
  - Risk assessment
  - Technologies
- Increasing regulatory authorities focus on SUS
- QbD is a pre-requisite
  - Controls and testing come on top of an optimum QbD approach
- Importance of training

Integrity is a continuous improvement work

Integrity Assurance White Paper



The full document can be found on the BPSA website, along with over a dozen additional white papers and technical documents

https://bpsalliance.org/technical-guides/

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