

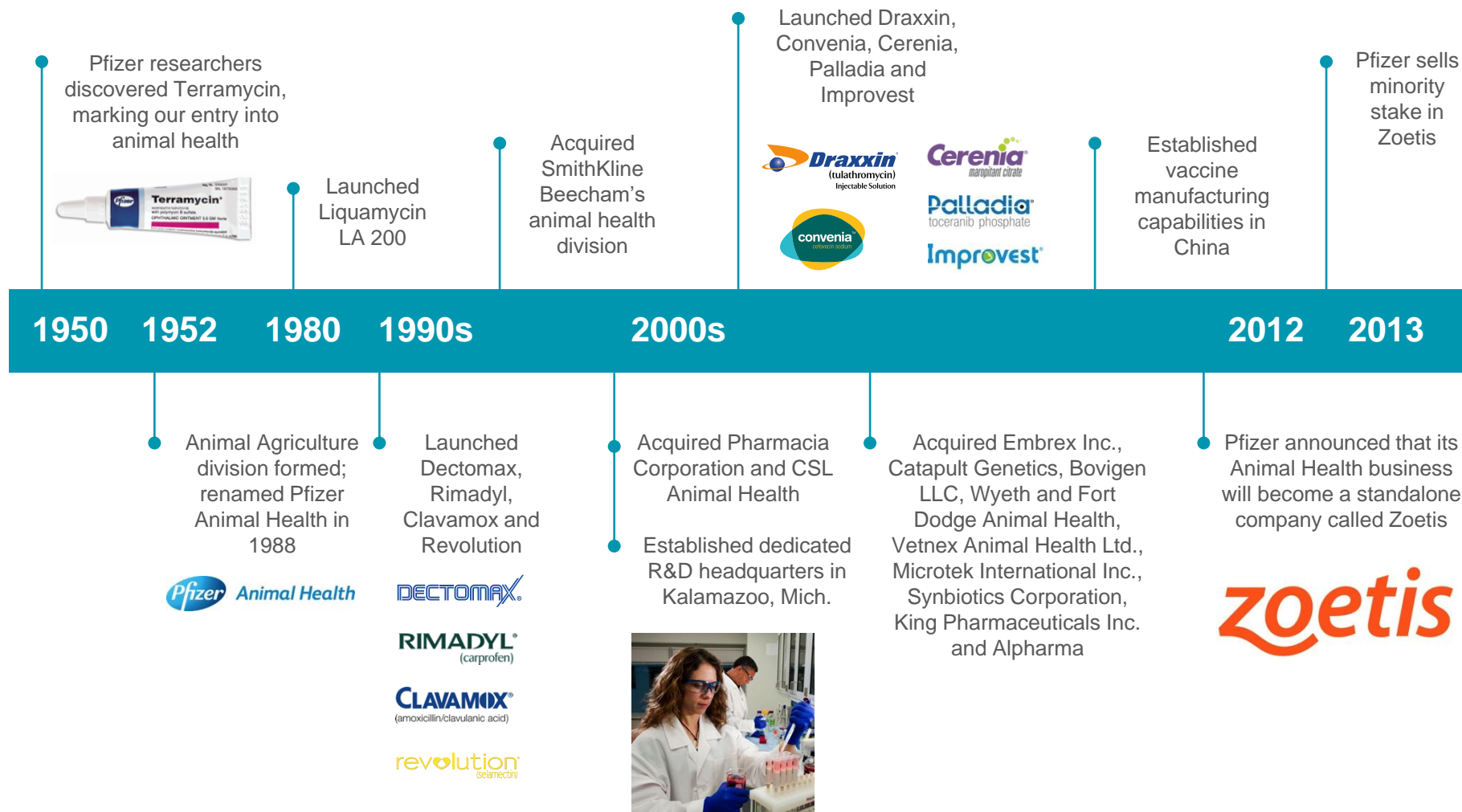


# Single Use-based Flexible Antigen Facility for Veterinary Vaccine Development and Production

Verhoeve Francis

BioProduction, Dublin, 20<sup>th</sup> October 2016

# OUR HISTORY AND HERITAGE

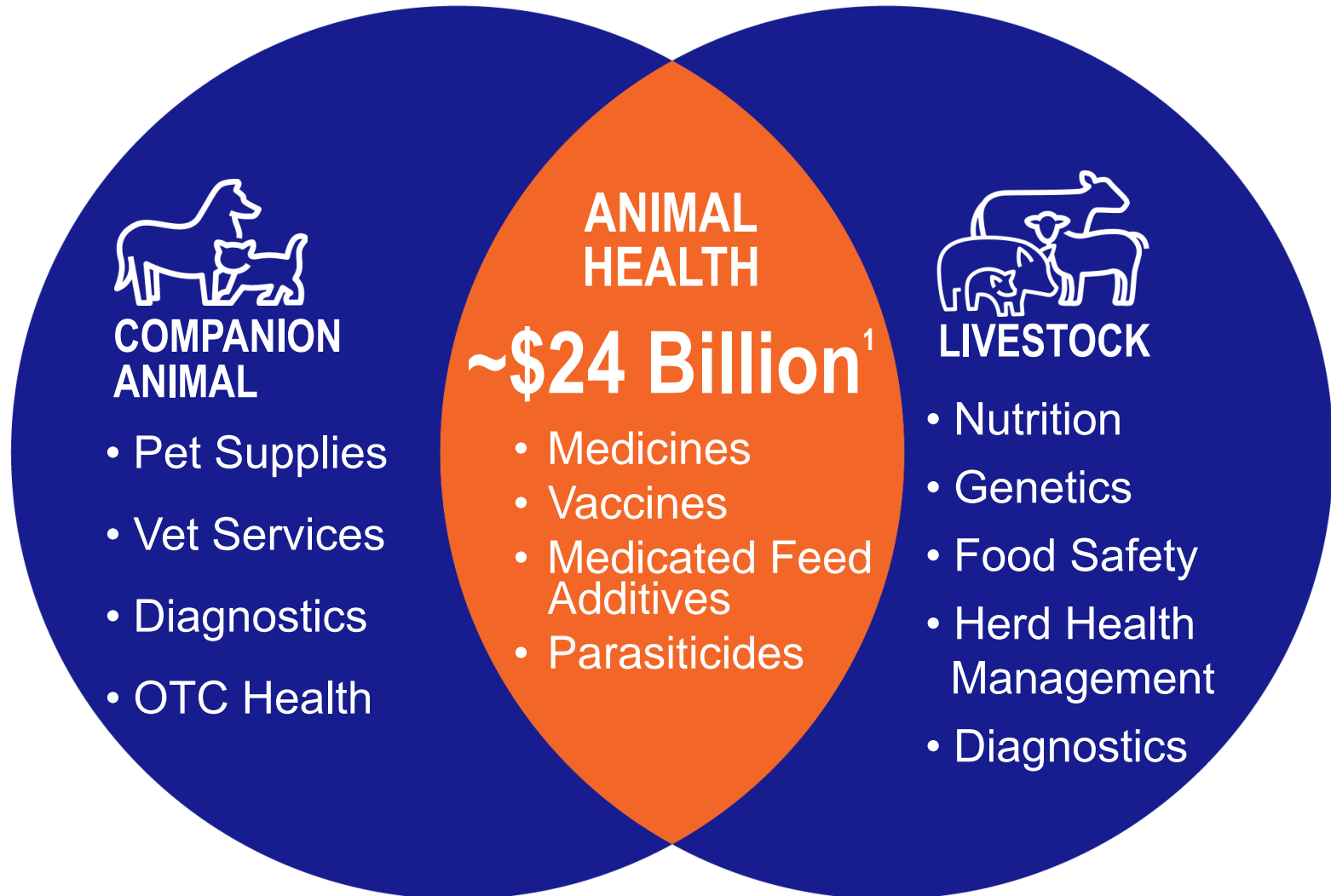


**zoetis**

**zoetis**

# AT THE CORE OF A \$100+ BILLION INDUSTRY

~\$24B GLOBAL ANIMAL HEALTH MARKET EXPECTED TO EXCEED \$33B BY 2020<sup>2</sup>



<sup>1</sup> Vetnosis Review 2014

<sup>2</sup> Vetnosis STORM FORECASTS: 2014-2023

27

MANUFACTURING  
SITES

8

CORE  
ANIMAL  
SPECIES



\$4.8  
BILLION

ANNUAL  
REVENUE

R&D COLLEAGUES

1,100+

300+

PRODUCT  
LINES

WE PROVIDE

MEDICINES  
VACCINES  
DIAGNOSTICS  
GENETIC TESTS  
SERVICES

5

MAJOR PRODUCT  
CATEGORIES

60+

YEARS  
OF  
EXPERIENCE

MARKET PRESENCE IN

120+

COUNTRIES

APPROXIMATE COLLEAGUES  
WORLDWIDE

10,000

OUR FOCUS

34%<sup>1</sup>

COMPANION  
ANIMAL HEALTH

65%<sup>1</sup>

LIVESTOCK  
HEALTH

3,600+

MEMBER ZOETIS  
FIELD FORCE

Note: 2014 facts and figures shown

<sup>1</sup>Excludes revenue associated with Client Supply Services, which represented 1% of total 2014 revenue.

# CONTEXT

## Why going disposable:

- **Animal health sector complexity**

- Large number of species and diseases (numerous production processes)
- Increasing number of product transfers
- Need for rapid production shifts with minimum footprint.

- **Emerging diseases are a global risk**

- Increasing global travel
- Increasing world food trade
- Appearance of new treats
- Rapid disease spreading



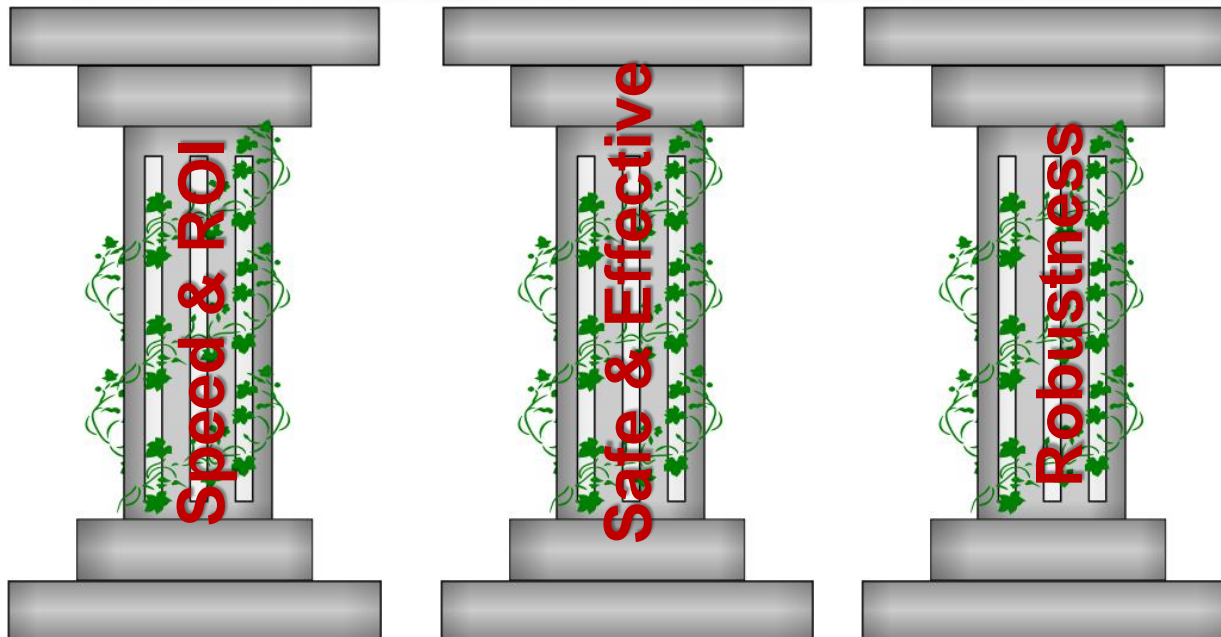
**1 billion people  
travel by air annually;  
50 million of these travel  
to the developing  
world**

- **Building of a flexible antigen production facility**

- Rapid response unit with a flexible capacity to handle various viral vaccines.
- Capacity to handle viral organisms with different levels of risks (up to BSL3)



# The basic tenets of product development



# Concept: Disposable BSL-3 Factory

## Key aspects:

- Single zone that with transportable equipment
- Adaptable between BSL-2 and BSL-3
- Fully flexible
  - For MVS-WVS production:
  - For Antigen production
- Suitable for:
  - Modified live vaccines
  - Inactivated killed vaccines



- Whole new building – Invest >22 million euros
- Location: Louvain-la-Neuve, Belgium

# Disposable facility design





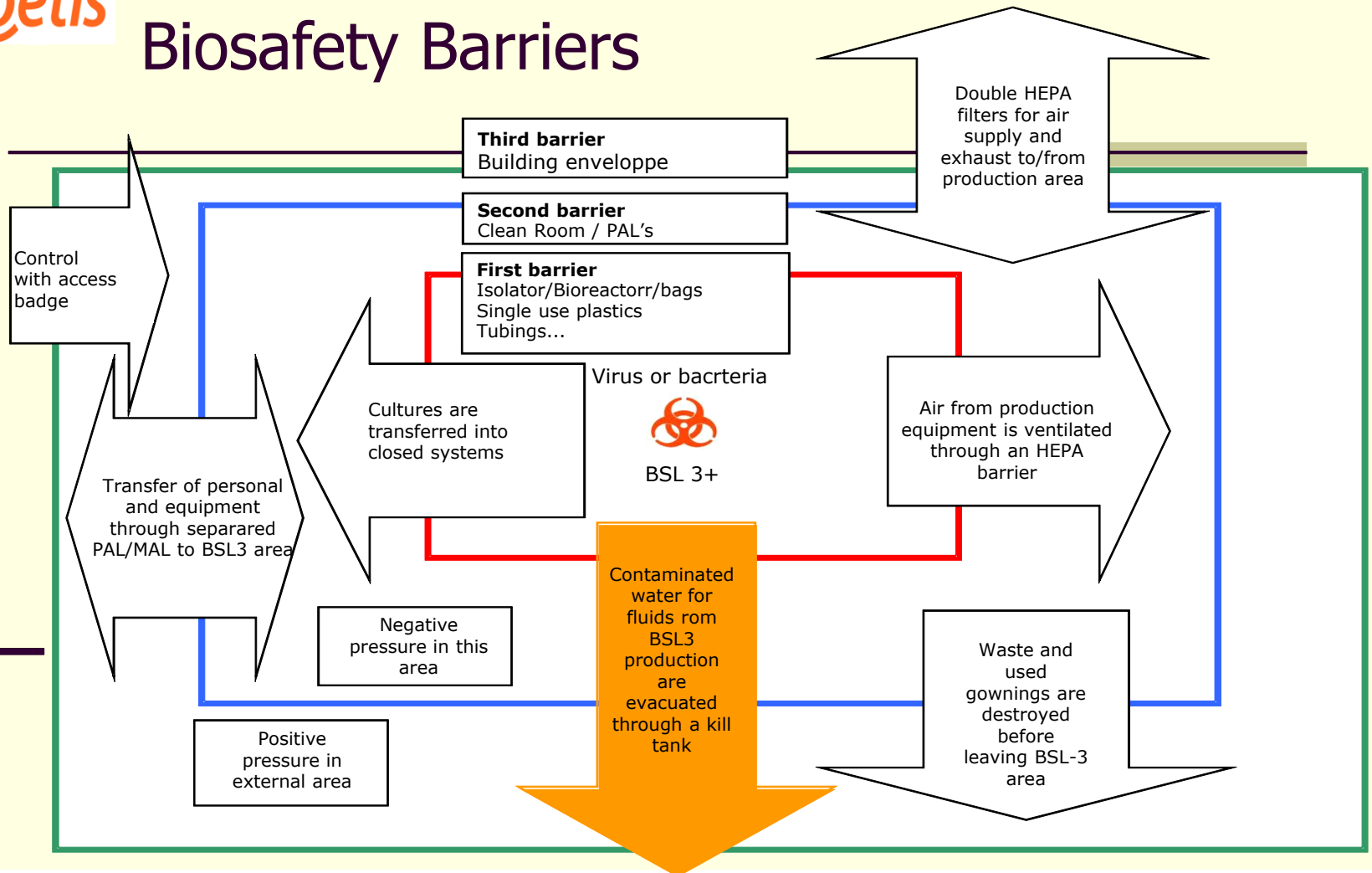
# Flexible factory with flexible strategy

- **Principles of the flexible disposable facility**
  - Absence of CIP/SIP and limited use of utilities
  - General process performed in closed system
    - Upstream (single use bioreactors)
    - Downstream (Inactivation-single use TFF system)
  - Inoculum strategy
    - Limited open phase approach (seed manipulation in isolator)
- **Campaign strategy**
  - For BSL1/ BSL2: multi-product campaigns
  - For BSL3: mono-campaign approach
- **Production of batches with variable levels of quality**
  - Non GMP technical batches
  - GMP pilot batches
  - GMP commercial batches

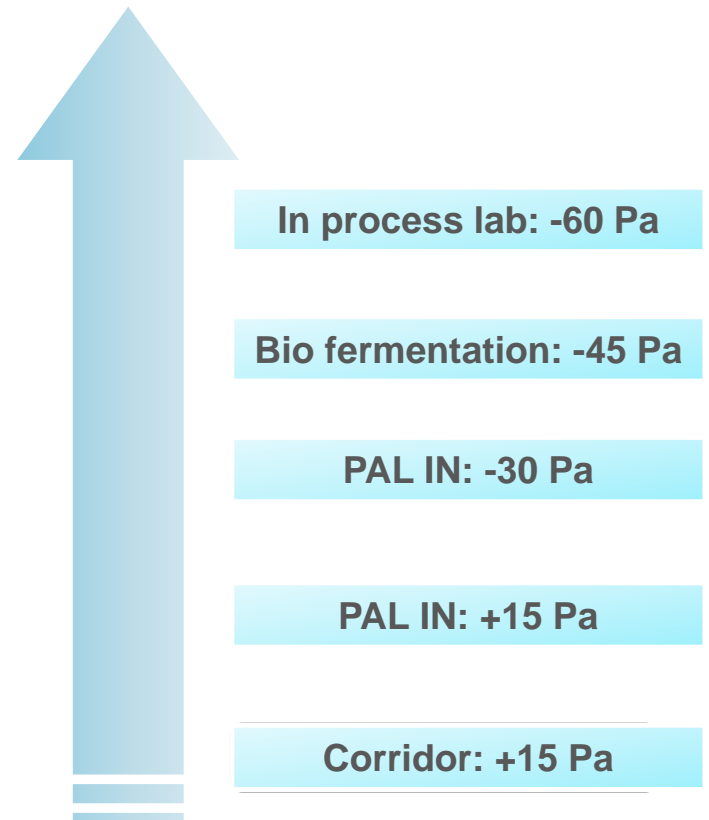
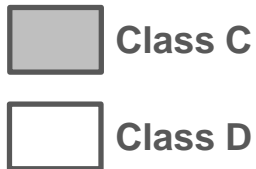
# BSL-2/BSL-3 Containment



## Biosafety Barriers



# Cleanroom management



# BSL-2/BSL-3 Impact

- **Personel impact:**
  - Disposable clothes (single use followed by decontamination)
  - Reusable (if BSL-2 campaign).
- **Material impact:**
  - Presence of double exhaust filters on SUB and wave bioreactors
  - VHP decontamination for antigen bag exit
- **Seed impact:**
  - Use of specific bio-carrier boxes from warehouse
- **Equipment impact:**
  - Isolator operating either in negative or positive pressure modes
- **Spills and wastes:**
  - If BSL3 spill, VHP treatment before cleaning operations (and risk analysis)
  - Waste management:
    - Autoclaving for all components in contact with contaminated products
    - Effluent management through BSL-3 operating kill tank



# Antigen control: IPC lab

**Mission:** In Process Testing of the antigens for BSL-3 viruses

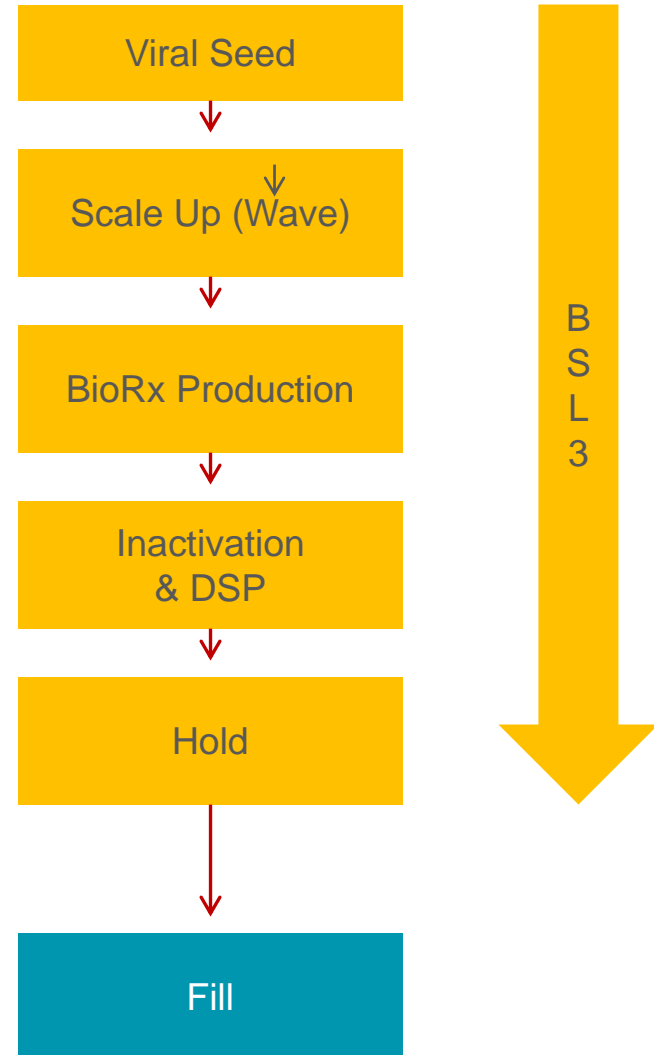
- Sterility testing
- Inactivation (validation) testing
- Viral titration (potency)
- Filter integrity testing
- Incubation for monitoring plates





# Basic Process Flow

- Viral seeds are introduced to the lab through a VHP Pass Box.
- Seeds are opened in an Isolator and transferred to a small volume wave tank.
- Wave tanks go from 0,5L to 50L
- Direct transfer to a 250 L SUB for low volume processes
- Transfer from 250L SUB to 1000 L SUB for high volume processes
- Inactivation (single or double inactivation, bottom to bottom transfer)
- DSP (concentration/diafiltration)
- Hold 4°C until QC data confirm inactivation and sterility are SAT



# Starting operations: isolator



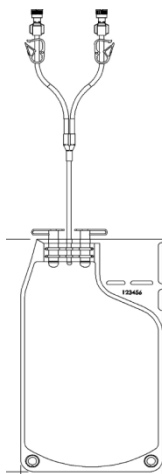
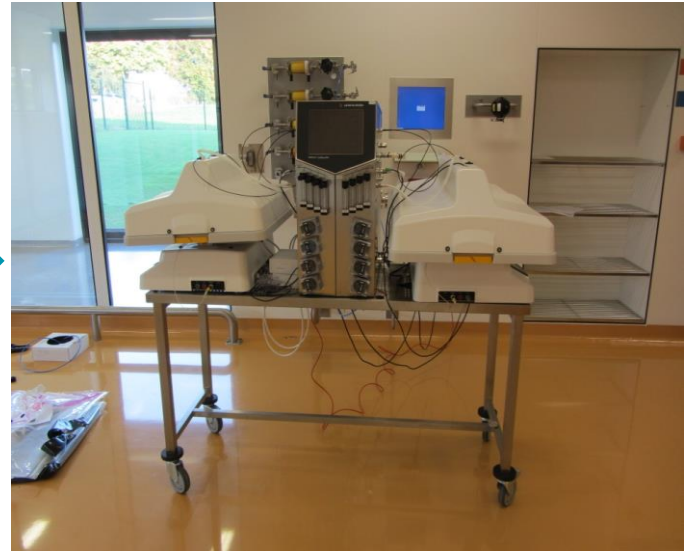
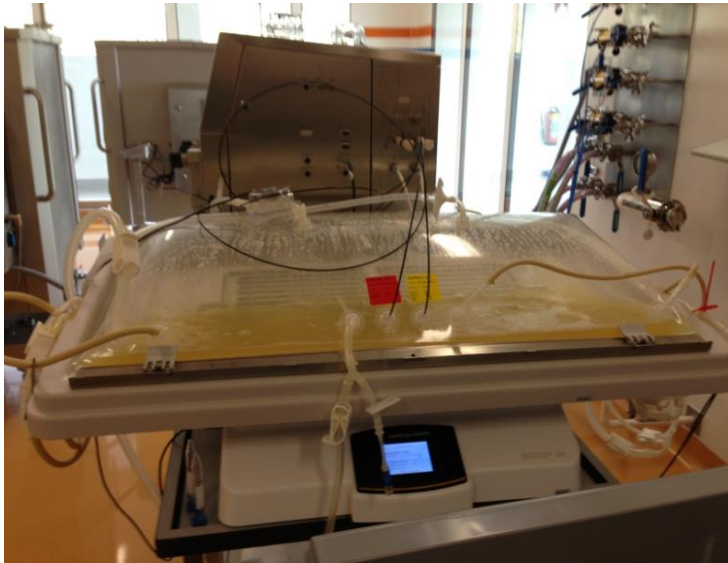
## Single open phase

- Inoculum phase (vial thawing)
- Infection phase
- Master/Working Seed filling

- Class A in C area
- Qualified equipment (validated VHP treatment)
- Challenge cross contamination
  - Handling of several strains/cells in the same area
- Cell counting can be performed in room or in isolator (Nucleocounter)
- All operations documented (one batch record per product + logbooks)



# Cell expansion in single use bioreactors



- Inoculum thawed in isolator or inoculum thawed in bag
- Transfer into bottle with closed system connexions
- Aseptic connexion to Wave tank (2L/10L cultibag RM)
- Transfer and dilution in Wave tank (20L/50L cultibag RM)

# Cell expansion and infection in SUB

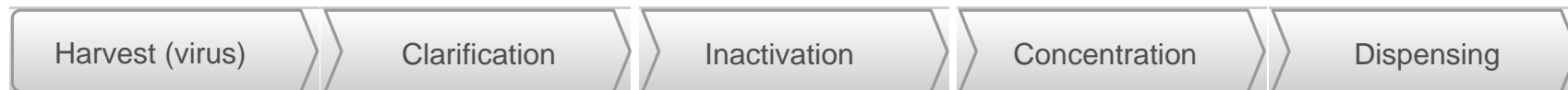


- Inoculation of a 250L Hyclone SUB
- Inoculation of a 1000L Hyclone SUB
- Total capacity: 4 x 1000L Hyclone SUB
- Finesse controller
- Aseptic sampling

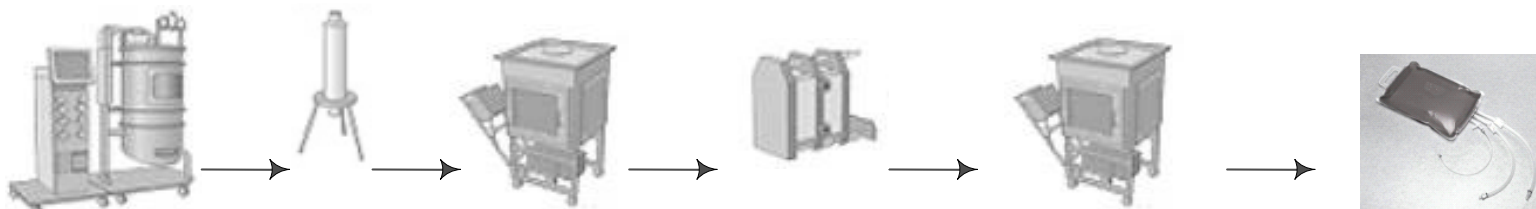




# Down Stream : inactivation and concentration



Downstream



Two vessels: 1000L



Vessel: 100L capacity



# Disposable facility: single-use everywhere

## Connexions:

Welding

Aseptic connectors

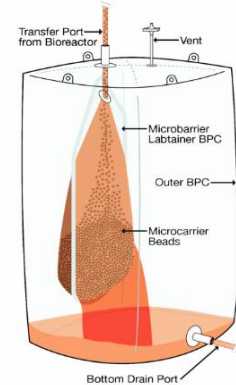


How to connect  
disposable  
system to  
others?

Test integrity?

By design of **Key  
manifolds** to be  
able to connect  
two systems  
together!

## BPC:



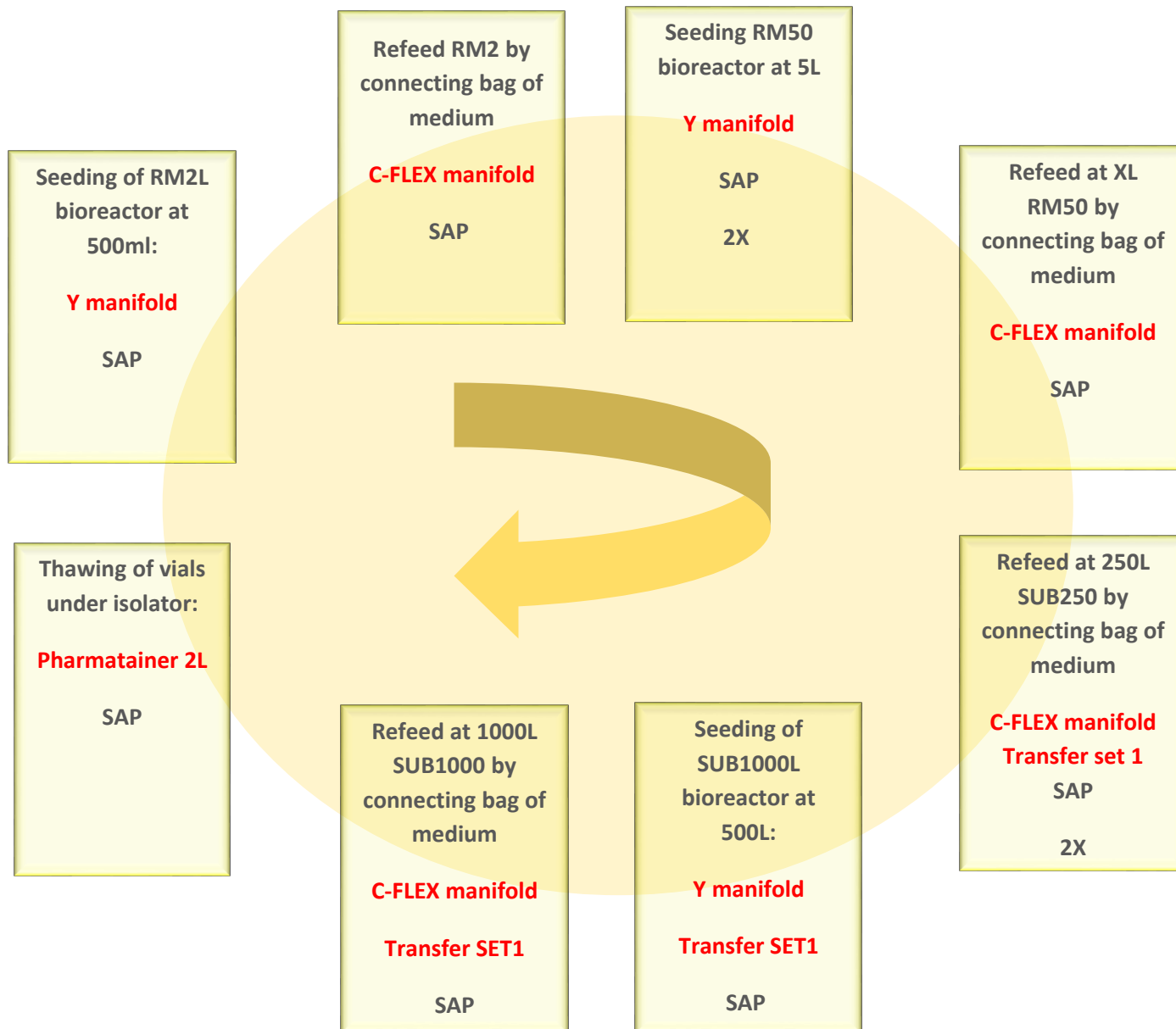
## Equipment:

SUB-WAVE

DF-TFF

Inactivation

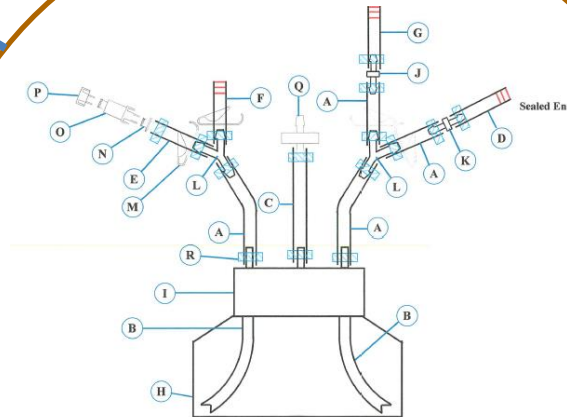
# Component Flow and mapping



# Single-use components

For sedimentation  
of cells in small  
bioreactor

For thawing vials  
under isolator



For adding seed under  
isolator

For sampling on  
bioreactor and  
dispensing vials  
under isolator

For adding medium  
with additives in small  
bioreactor

**Sterile 2L bottle**

# Initial process (BSL-2): flow diagram

- Cell and viral seeds are opened in a biosafety cabinet with laminar airflow .
- Expansion in roller bottles (incubator)
- Direct transfer to a 250 L Stainless steel bioreactor
- Transfer from 250L SS to 1000 L SS for production phase (500L)
- Infection phase of 9 days (MOI 0,01)
- Inactivation: chemical process with bottom to bottom transfer from vessel 1 to vessel 2
- Concentration (reusable TFF module)
- Dispensing in 20L bottles



# Process transfer: Upstream

Step	Initial process	Single-use process
<b>Thawing</b>	Biosafety cabinet Vial thawing Transfer to 1 roller bottle	Isolator Vial thawing Transfer to Wave RM (250 ml)
<b>Expansion 1</b>	Expansion in roller bottles Dilution to 3000 ml	Culture in Wave RM 2L Dilute to 500 ml
<b>Expansion 2</b>	Expansion in roller bottles Dilution to 15000 ml	Transfer to Wave RM 50L Dilute to 6000 ml
<b>BR 250L</b>	Transfer to SS BR 250L Dilution to 200L	Transfert to SUB 250L Dilution to 120L
<b>BR1000L</b>	Transfer to SS BR 1000L Dilution to 475L	Transfert to SUB 1000L Dilution to 500L
<b>Infection</b>	Cell density: 2,79 cells/ml MOI: 0,01 Temperature shift	Cell density: 3,69 cells/ml MOI:0,01 Temperature shift
<b>Harvest:D+9</b>	Cell density: 1,18 E6/ml (77%) Titre: 7,28	Cell density: 3,0 E6/ml (77%) Titre: 7,65



# Process transfer: downstream

Step	Initial process	Single-use process
<b>Clarification</b>	SIP clarification filters 20 µm – 5 µm	Single use irradiated clarification filters (20 µm – 5 µm)
<b>Inactivation</b>	Stainless steel vessels 500L	Single use bags (stirred) 1000L
<b>Concentration</b>	CIP/SIP TFF vessel with steam sterilizable cartridges	Disposable TFF module (3,5 m <sup>2</sup> cartridges)
<b>Dispensing</b>	Transfer glass bottles (autoclaved)	Transfer to plastic bags (closed system)



# Disposable initiative

## Mission:

Provide guidance for design, development, and delivery of new and/or improved flexible technologies with supporting data and documentation for increased efficiencies and yield on new and existing projects.

## Charter:

- Build database with equipment inventory among sites
- Investigate opportunities for shifting from standard to SU platform
- Identify problems among processes and sites and provide or expand SU solutions
- Explore and integrate new technologies (supplier network)
- Standardize equipment and components among Zoetis
- Open to innovation (no bad ideas)

**QUESTIONS?**

