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Henriette Schubert / Karin H.Wassard

Case Story
Facility for Large Scale BSL2/GMO2 GMP Vaccine Production

Challenges, Choices & Design Drivers

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Focused pharma engineering

The Challenges of the New Pharma Reality

Increasing demand for agility:

- AGILE AND FLEXIBLE OPERATIONS
- SEAMLESS GMP COMPLIANCE
- FUTURE PROOF SOLUTIONS

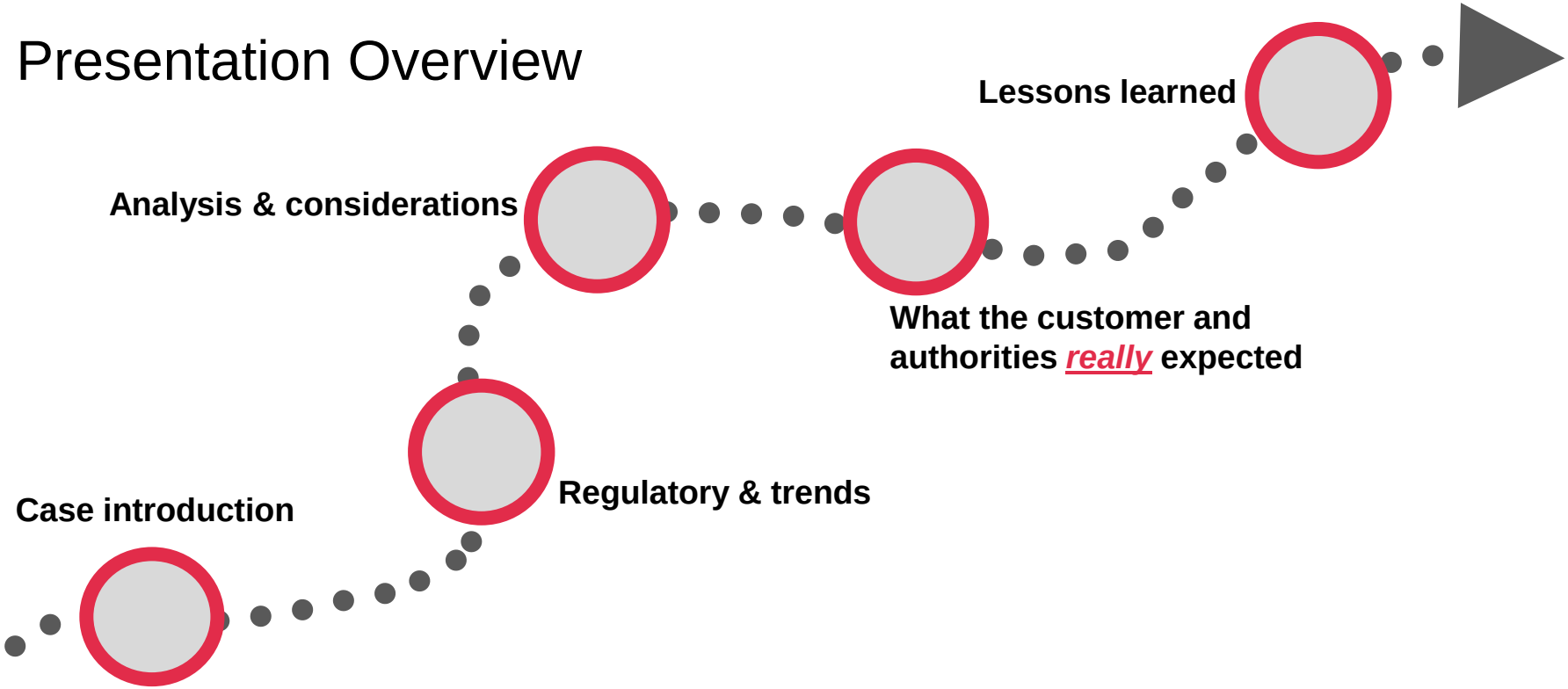
EXTERNAL DRIVERS

- Healthcare costs are growing
- Increased regulatory pressure
- Increased competition
- Products running out of patent
- New drug categories emerging

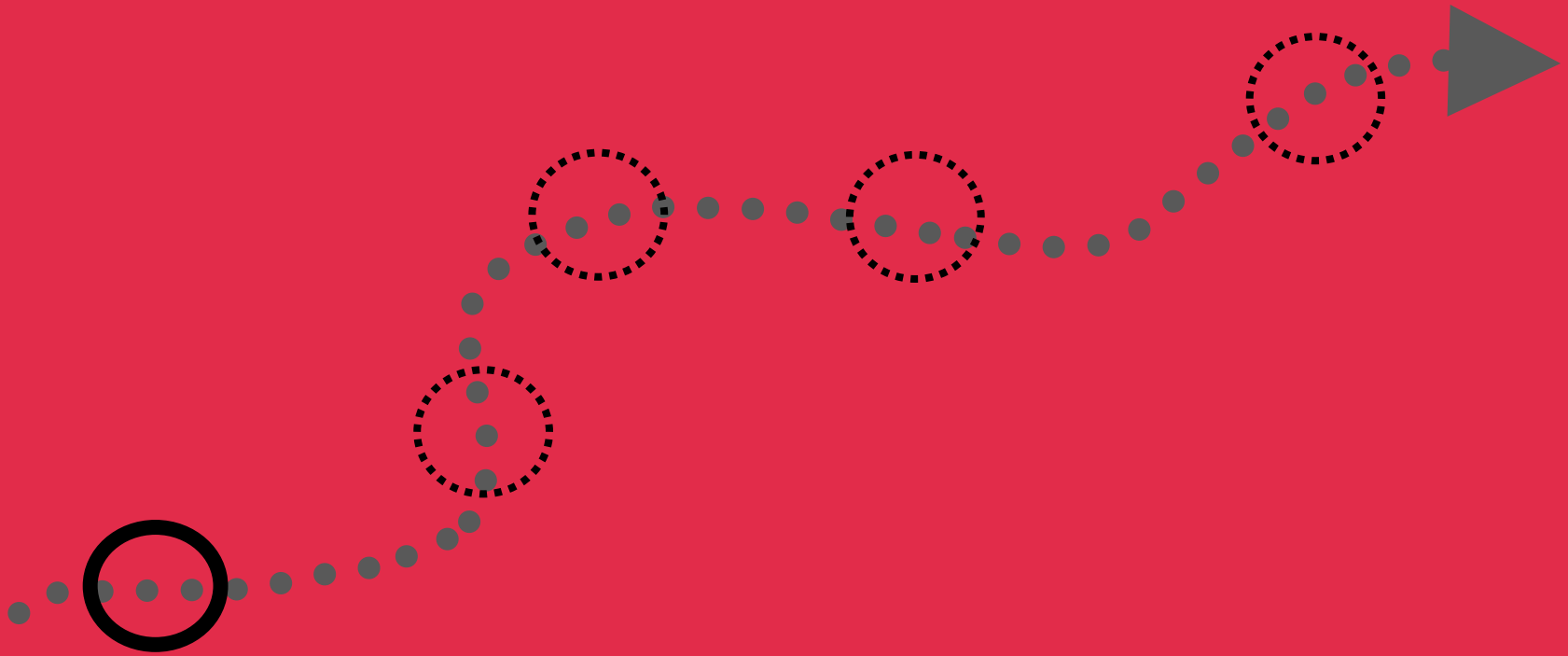
INTERNAL DRIVERS

- Cost pressure
- Changing R&D strategy
- Global production
- Standardisation
- Quest for key differentiators

Presentation Overview



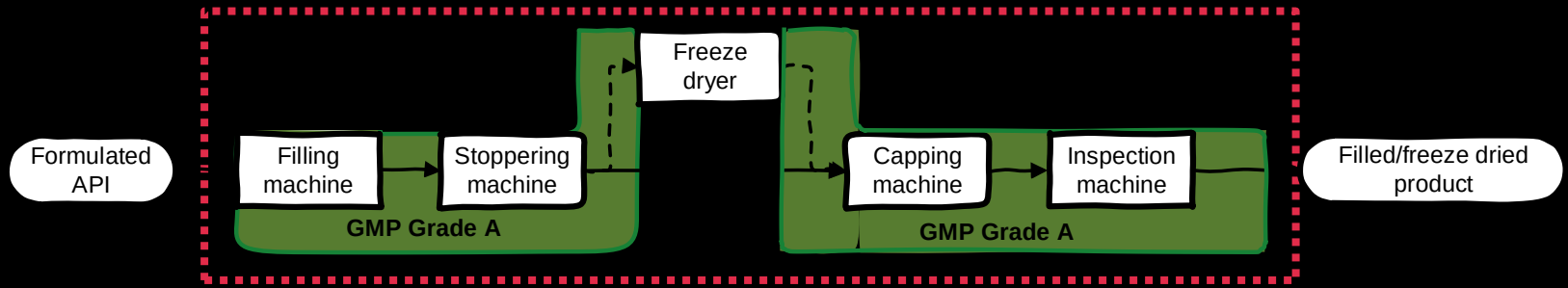
CASE INTRODUCTION



Case based on an undisclosed Case from Northern Europe

Case Introduction – Main Design Drivers

- Large scale fill & finish facility, live vaccines
- High level of GMP (aseptic production), Grade A/B (ISO 5)
- Moderate level of biocontainment (BSL2/GMO2)
- Flexibility for new products, similar to existing in pathogenicity/characteristics
- Frequent fumigation zones
- High capacity within limited footprint



Case: Assumptions for Future Products

Biological agent assumptions

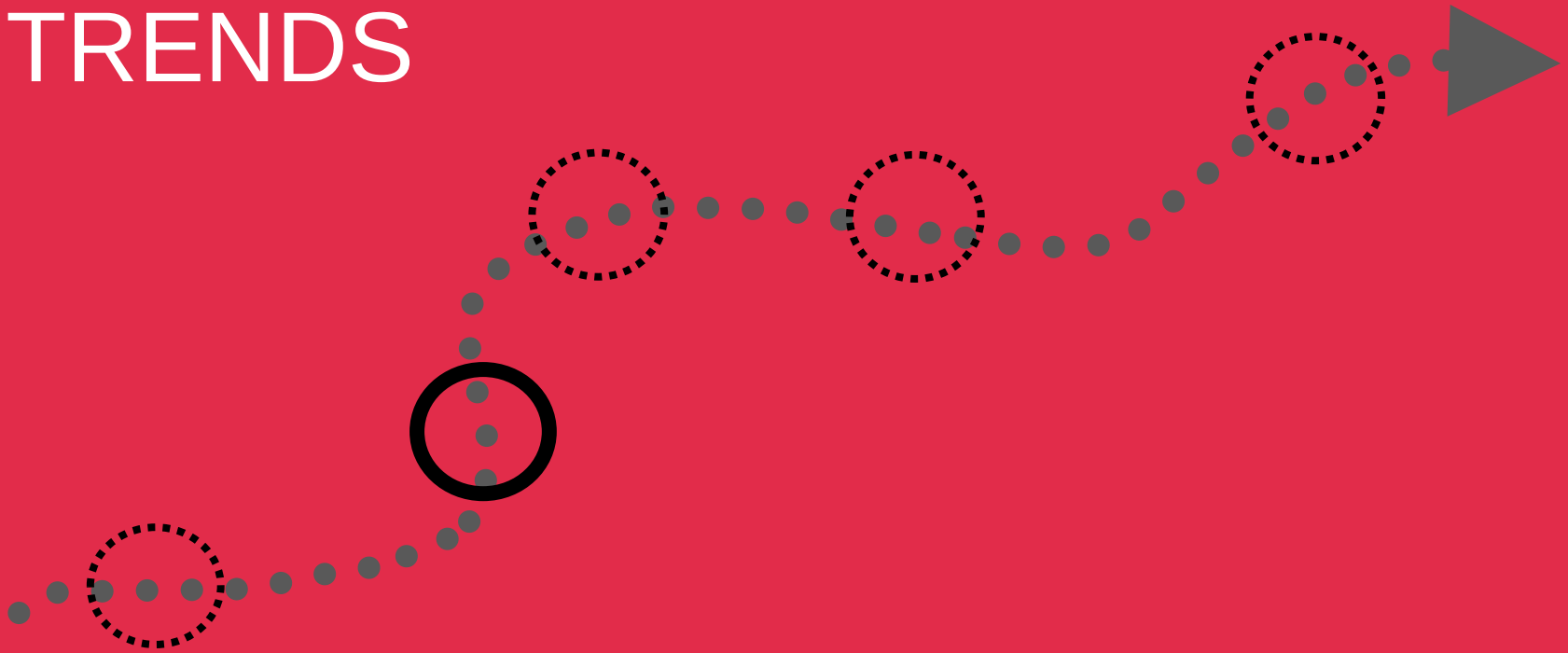
- The future products (up to GMO2) are assumed to be within similar characteristics:
  - Same vectors
  - Same immunological response type
  - Same implication, transmission and survival, if exposed to workers and the external environment

Humans
Vaccination effect
(Stimulate immune system)

Environment
May survive shortly
Sensible to UV light
No known effect related to plants

Animals
Vaccination effect
May replicate shortly

REGULATORY EXPECTATIONS & TRENDS



Regulatory Framework and Focus

GMP Requirements and focus (aseptic products)

- **Aseptic products** cannot be terminally sterilized and contamination cannot be accepted
- Manufacturing of pharmaceutical products is all about **"Risk for the patient"** – ensure the product is safe for the end-user
- **Minimise operator impact on product** (operators are considered the biggest risk of product contamination)
- **Prevention of cross contamination** and ensure product and flow segregation, use of unidirectional flow principle (multi-product facilities)
- **Risk based** approach

Biocontainment Requirements and focus (class 2)

- **Minimise dissemination** of the GMO
- **Minimise release of the biological agent** to the external environment
- **Minimise product impact on operator** (low risk activities but *can* cause human disease
- **Waste handling** / Inactivation using validated methods
- Viable micro-organisms to be contained in a system which **separates the process from the environment**
- **Risk based** approach

”Conventional cleanrooms are on the borderline of compliance” **

Filling = Open Process – Barrier System Requirements

cGMP

US FDA:

- The regulatory authorities are expecting more and more barrier systems to eliminate direct operator impact to critical processes

EU*:

- “The transfer of materials into the aseptic processing zone and the **role of people** in the process are key concerns”
- “Use of isolators for aseptic processing is therefore to be supported but ultimately it is for **industry to select and justify the technologies** it uses”

Filling process

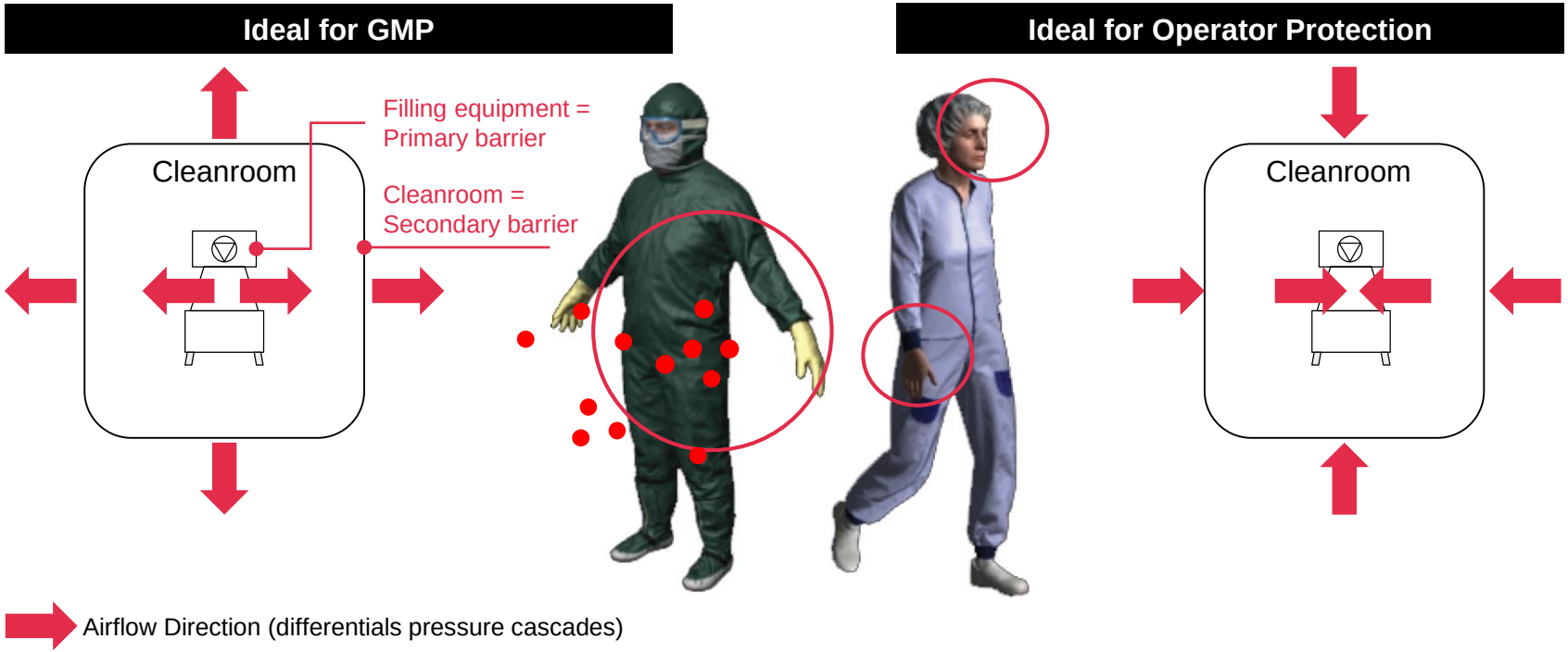
BSL2/GMO2 LS

- Viable micro-organisms should be contained in a system which separates the process from the environment (closed system) **GMO2**
- Viable organisms should be handled in a system which physically separates the process from the environment **BSL2**
- “Minimise dissemination”
- “Closed systems should be located within a controlled area”

** ISPE Barrier Isolation Technology Conference Berlin, September 2007 Presentation by Ian Thrussell, MHRA*

*** US-FDA – Rick Friedman comment, March 2013*

Open Process – “Barrier System”
Pressure Regimes - Conflict of GMP vs. Operator Protection



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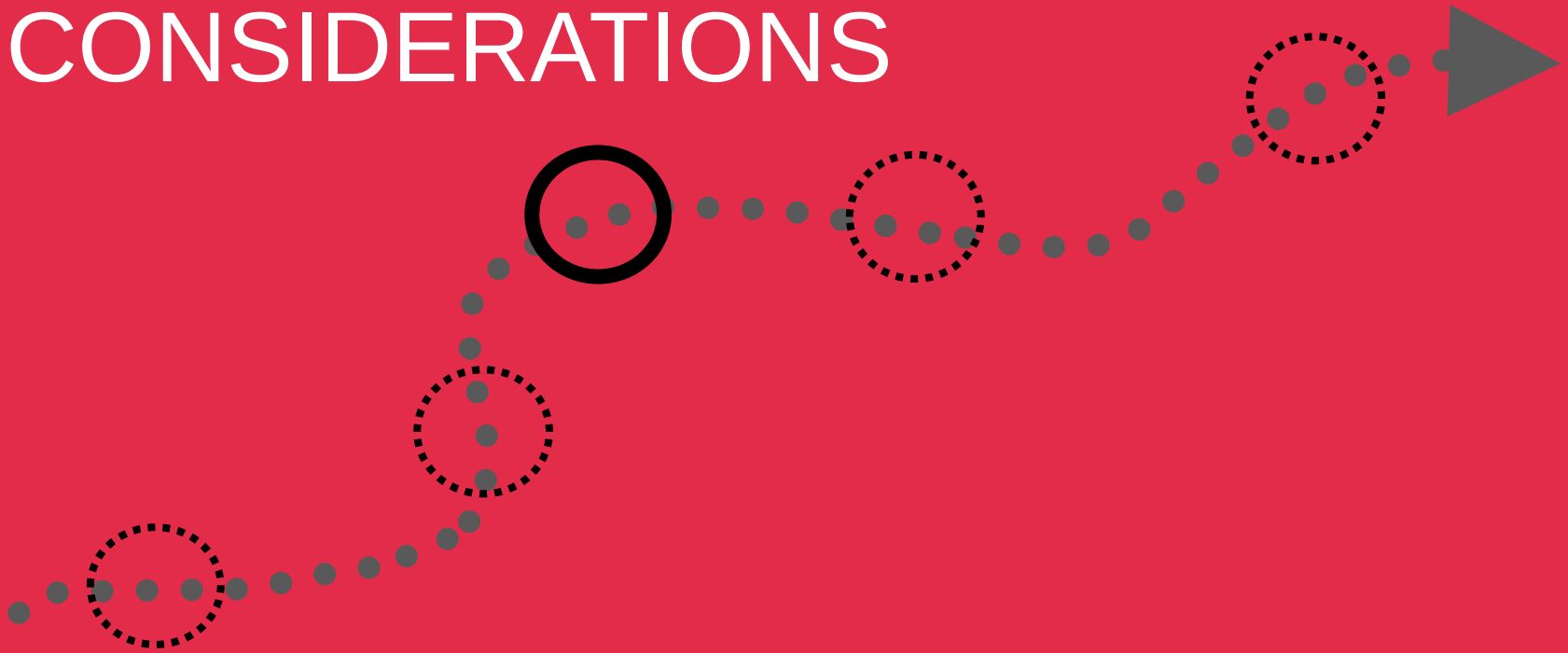
Different Purpose and Definitions
- however, they have to go together hand in hand

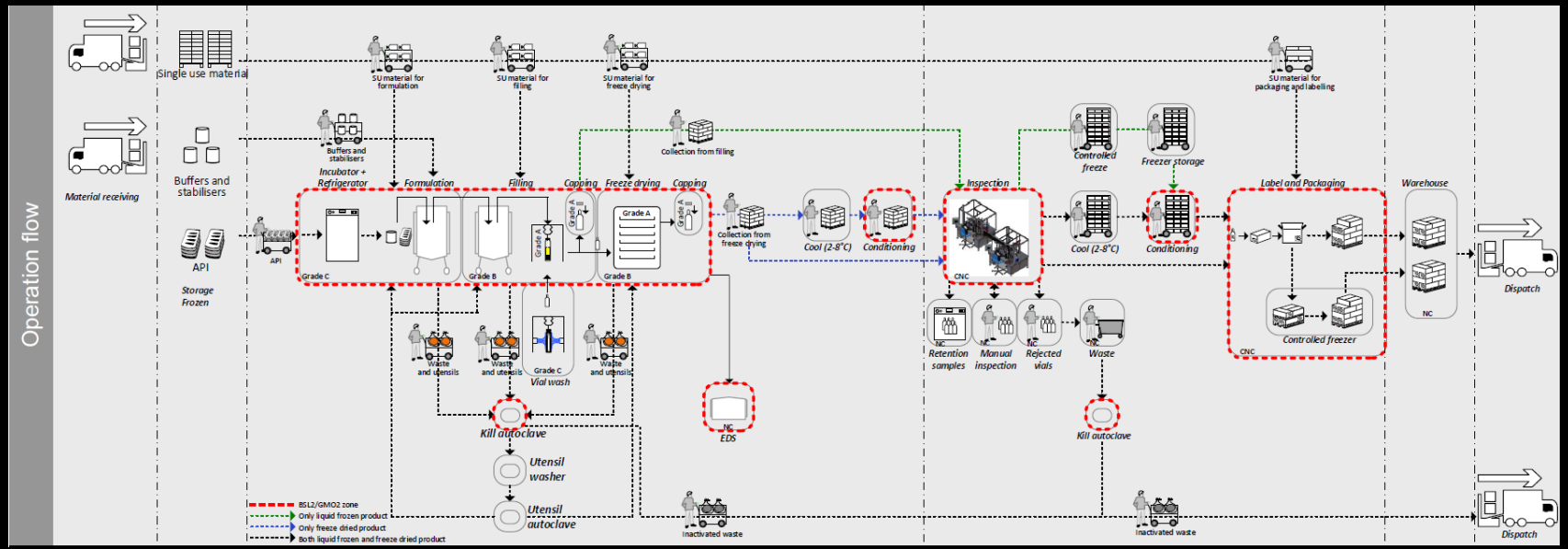
Regulatory Expectations &Trends

Risk assessments (product and process risk)	Risk assessments (bio-risk)
Open processes in closed barrier systems	System that physically separates the process from operator + environment
Huge focus on separating operator from product	High focus on operator safety and minimise release

ANALYSIS AND CONSIDERATIONS



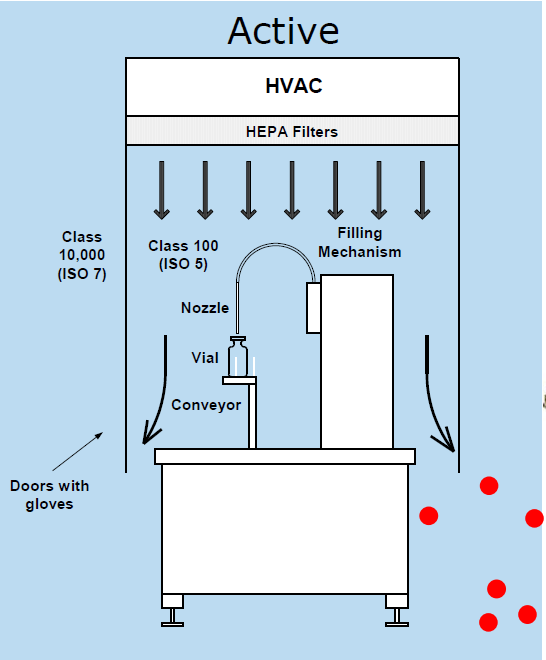
Operational Workflow Diagram used for Analysis



Risk assessment for individual equipment, process steps, workflow, operations and operator impact

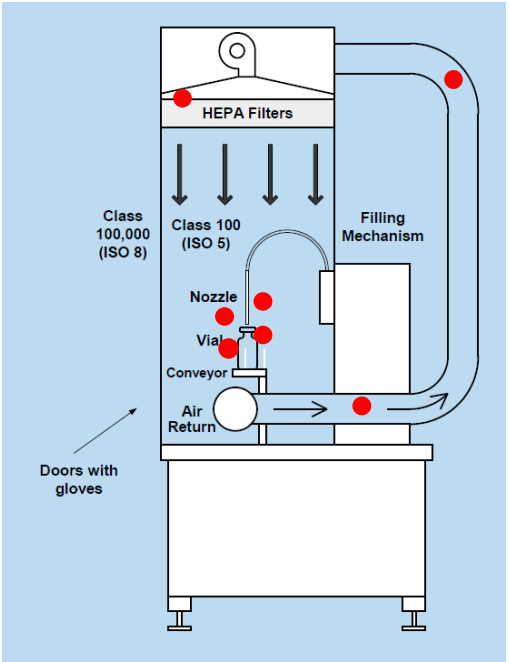
Barrier Systems

Product exposure to room & outside of clothing



GMP A/B
GMO2

GMP C
GMO2



RABS RESTRICTED ACCESS BARRIER SYSTEM

ISOLATOR

Functional Layout – RABS

RABS technology

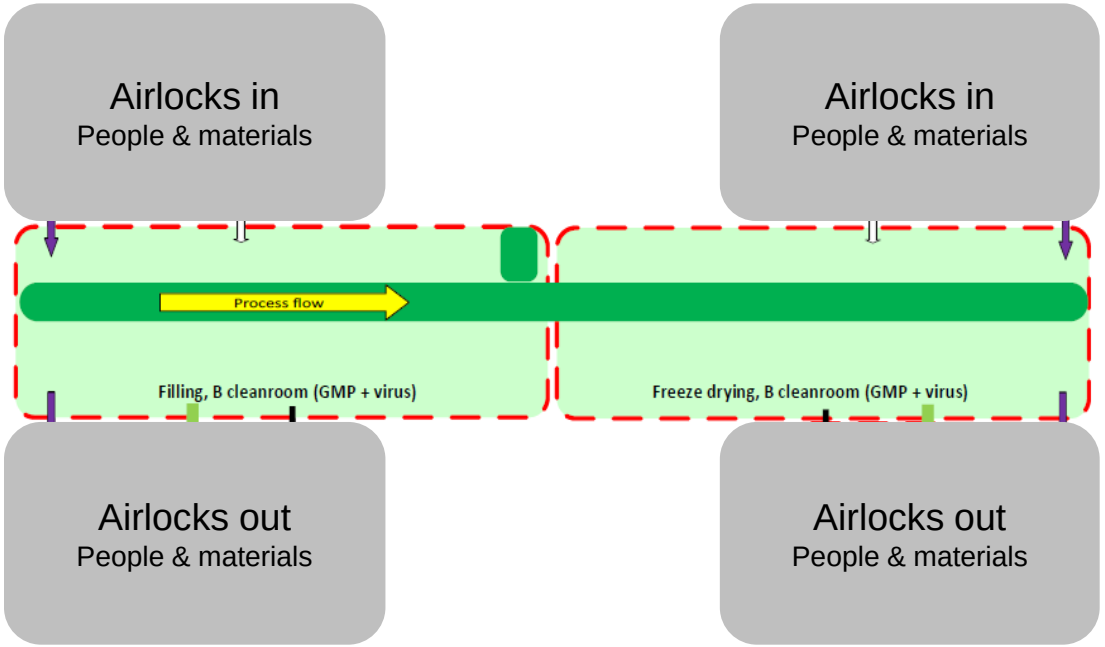
- High cleanroom class (A/B)
- Unidirectional flow
- Airlock complexity/m^2 high

- TIC cost ~ medium
- Operating cost high
  (GMP B ~ 23$/person/entry)

- Primary GMO barrier = room
- Operator risk medium?

- H2O2 zones/m^2 high
- Batch change over time high

- HVAC energy high



Functional Layout – Isolator

ISOLATOR technology

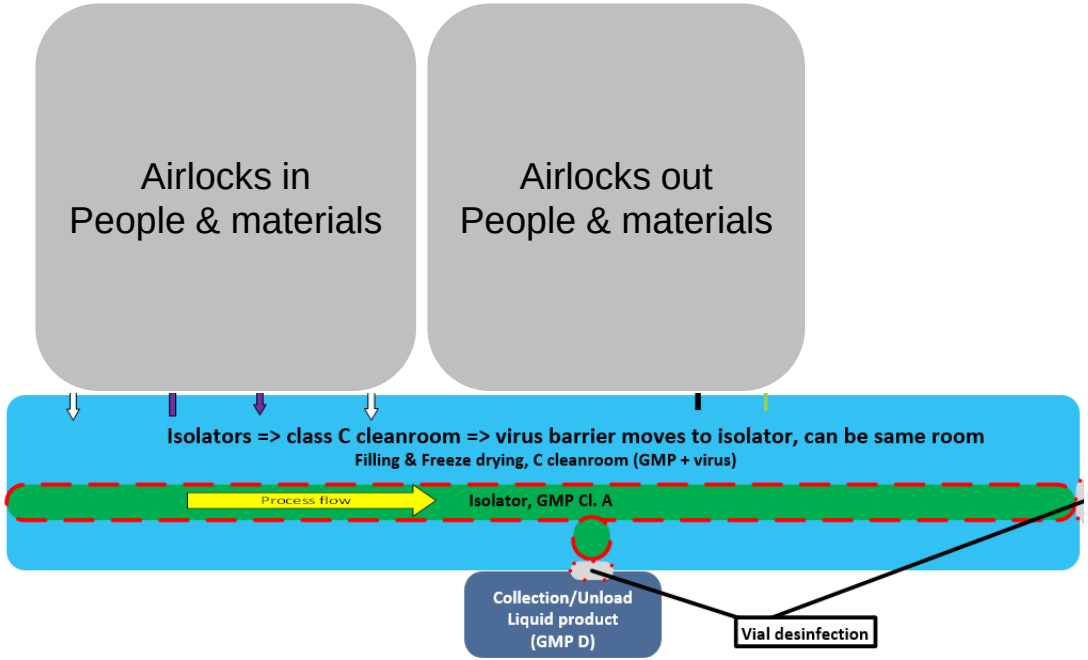
- Medium cleanroom class (C)
- Unidirectional flow
- Airlock complexity/m^2 low

- TIC cost ~ high (isolator)
- Operating cost medium

- Primary GMO barrier = isolator
- Operator risk low

- H2O2 zones/m^2 low
- Batch change over time low

- HVAC energy lower



Initial Barrier System Decision - RABS

Picture courtesy: Inova

Based on initial analyses & evaluation

- **RABS** solution chosen
- Decision based on **very low effect** (vaccination effect) for operators, if exposed, due to **known future products**
- **Economy beneficial** (driven by Total Investment Cost)
- Deriving GMP class B room background and extensive airlock systems

WHAT THE CUSTOMER AND AUTHORITIES *REALLY* EXPECTED

The Game Changer - Consolidation and Dialogue Meetings

I expect to be able to work with <u>any</u> biological agent / GMO2 at large scale in the future……..

Not limited to the characteristics of the known products

Gee…!

We require that there a <u>no impact</u> whatsoever on operators from the product…….

Customer **Authorities**

Expectations & Mutual Understanding

GMO2-2.5 → **GMO2.99**

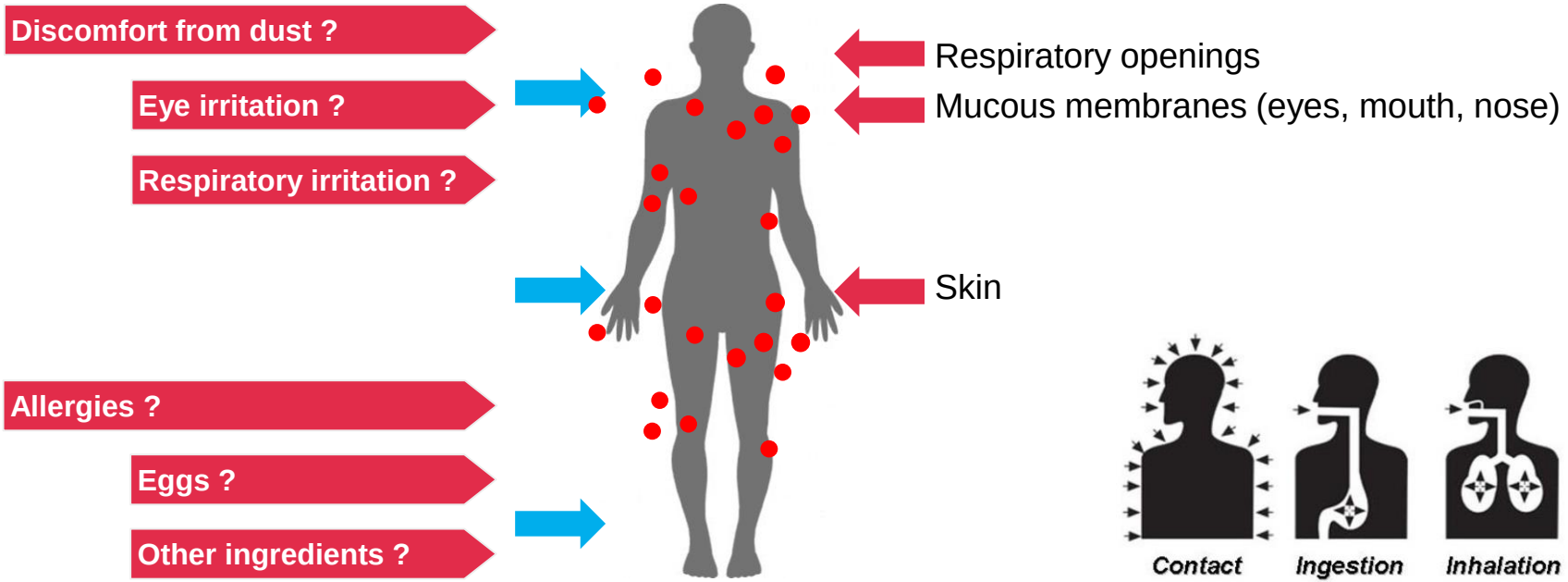
Basis for the design until consolidation

- **Known biological agents/GMO's** and their known characteristics (low risk activities)
- Future products with the **similar characteristics and risk level**
- **Worst case consequence of exposure** considered to be a vaccination effect

Actual expectations after alignment

- **Unknown biological agents/GMO's** where not all characteristics are known
- **Future products could involve any agent** within BSL2/GMO2 (full flexibility)
- **Consequence of exposure not known** and authority expectation is **"no impact whatsoever"**

What is the Impact – of **“No Operator Impact”?**



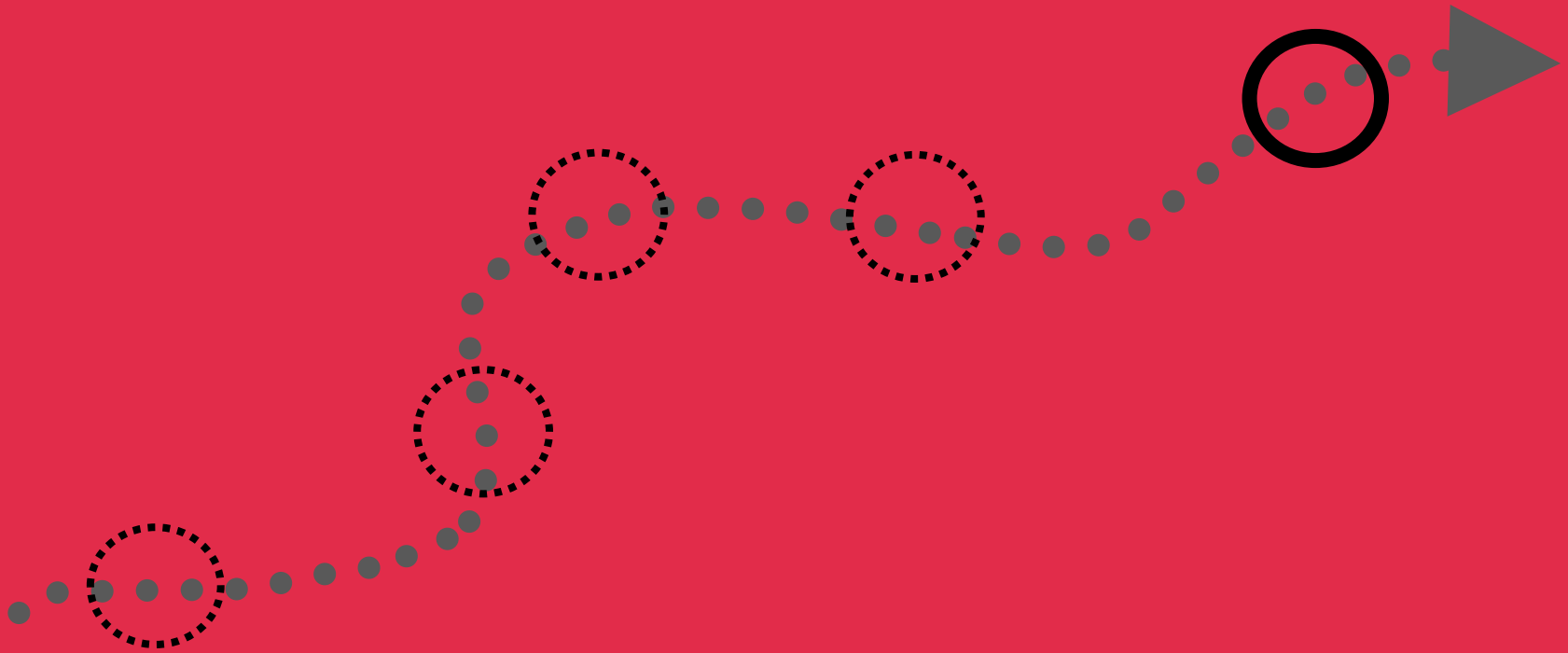
Impact on the Project
Re-visiting the Analyses and Technology Choices

Initial technology choice and concept needed re-evaluation when it was clear what was ***really*** expected….

RABS would have worked, HOWEVER…..
Authorities reserved the right to disqualify

In the end: It is all about risk - Isolator technology is the state-of-art

LESSONS LEARNED



Case Story – Lessons Learned

Lessons Learned

- **High complexity**: GMP and GMO2, multiproduct and future flexibility drives the design
- Focus on operations and using a **risk based and analytic approach** before initiation of concepts / design
- Mutual **understanding of open-closed systems and barriers**, GMO vs GMP – as a solid basis for technology choice
- **Biological agent clarification** and customer commitment is essential – upfront
- **Timely dialogue with relevant authorities** (outcome may influence the project to a great extent)
- Crucial to **ensure challenges / constrains** are highlighted and addressed timely
- With the final design drivers in place – **isolator technology would be the 'state-of-the-art' solution** for product and operator safety (including vials surface disinfection)

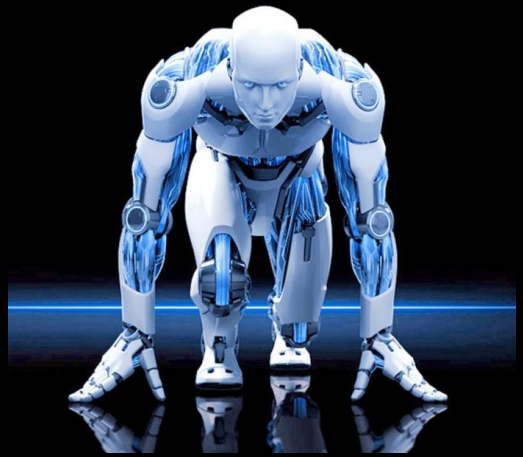
Food for Thought – and where are we heading?

Food for thought

If a high level of containment i
the real expectation from
authorities at BSL2/GMO2 LS
– what can then be expected
the next level BSL3/GMO3?

Future

Robots in
isolators?



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Henriette Schubert

Global Technology Partner
hsbt@nnepharmaplan.com
Mobile phone: +45 30 79 42 93

Karin Hedebo Wassard, PhD

Principal Consultant
khw@nnepharmaplan.com
Mobile phone: +45 30 79 39 96