#sharing challenges
and solutions in practice

Closed Systems in CNC Ballroom

A Risk Based Approach

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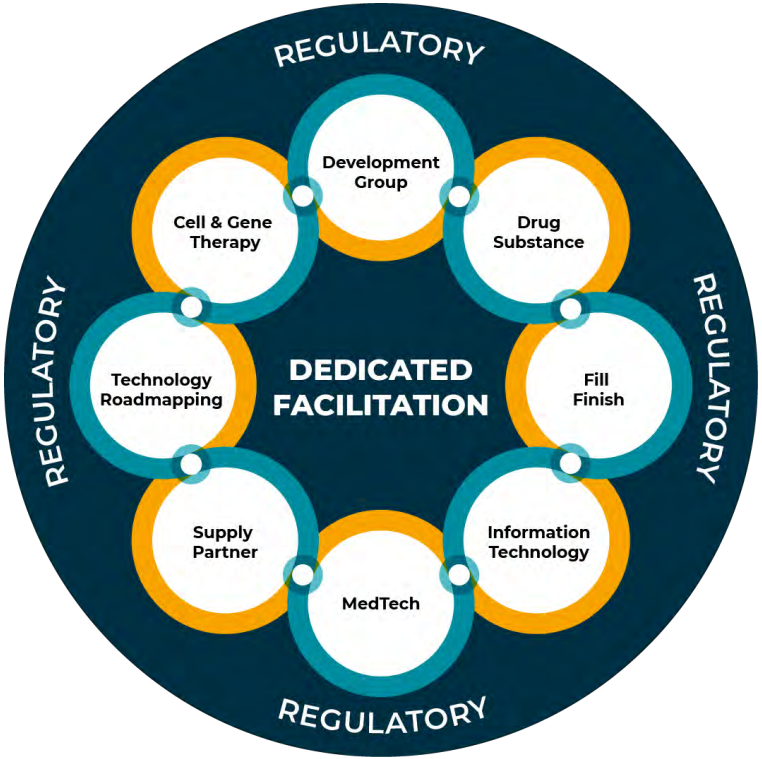
- Biophorum (formerly BPOG) Closed Systems in CNC workstream
- **Process Closure Playbook 2022 (BioPhorum)**
- **Risk-Based Selection of Environmental Classifications for Biopharmaceutical Operations (PDA journal 2021)**
- Quality Risk Management facilitator for Product protection/Closed Systems
- More than 20 of year experience with QC, Upstream/ downstream processes and process engineering
- Based in Bagsvaerd, Denmark

Who is Biophorum?

- Cross industry collaboration with the aim of:
- Accelerating the rate at which the biopharma industry attains a mature and lean state, benefitting patients and stakeholders alike.

  - Best practice sharing
  - Benchmarking
  - Joint-solution development to common challenges
  - Definition of standard requirements
  - Formation of collective perspectives to regulatory guidelines.



Membership includes most of the top biopharma manufacturers

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Agenda

- Regulatory guidance
- Understanding closure
- Risk Assessment
- Facility impact
- Conclusion

Regulatory guidance encourage utilizing closed systems

European Medicines Agency

U.S. FOOD & DRUG ADMINISTRATION

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-13 (Part II)
1 January 2017

ICH harmonisation for better health

4 Buildings and Facilities

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

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Understanding closure

- **ISPE definitions**
  - Closed system (equipment)
  - Functionally closed (equipment)
  - Briefly exposed process
  - Open process

Method of closure

Something we do before operating the system

Closed

Not exposed to the production environment
E. g. Pre sterilized single use bioreactor

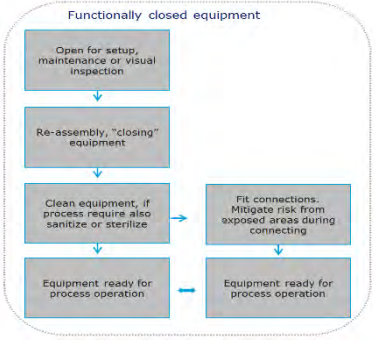
Functionally closed

Exposed to the production environment and then closed by
e. g. CIP or CIP/SIP

BPOG study in cooperation with BTEC

Functionally closed by CIP using industry solvents
Opened temporarily to connect
Functionally closed using WFI or industry solvents

BTEC = Biomanufacturing Training and Education Center



Operation of system

Operated Closed

Both Closed SUS and functionally closed

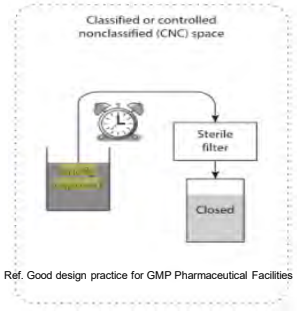
Protected from the production environment at all time.
Room classification not required

Briefly exposed process

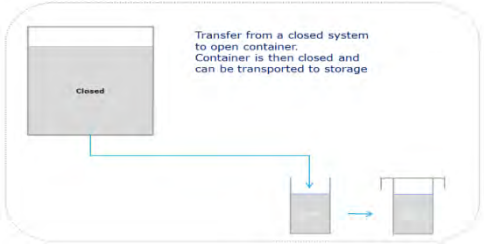
Product exposed to the Production environment followed by mitigation.
Room classification maybe not required

Open process

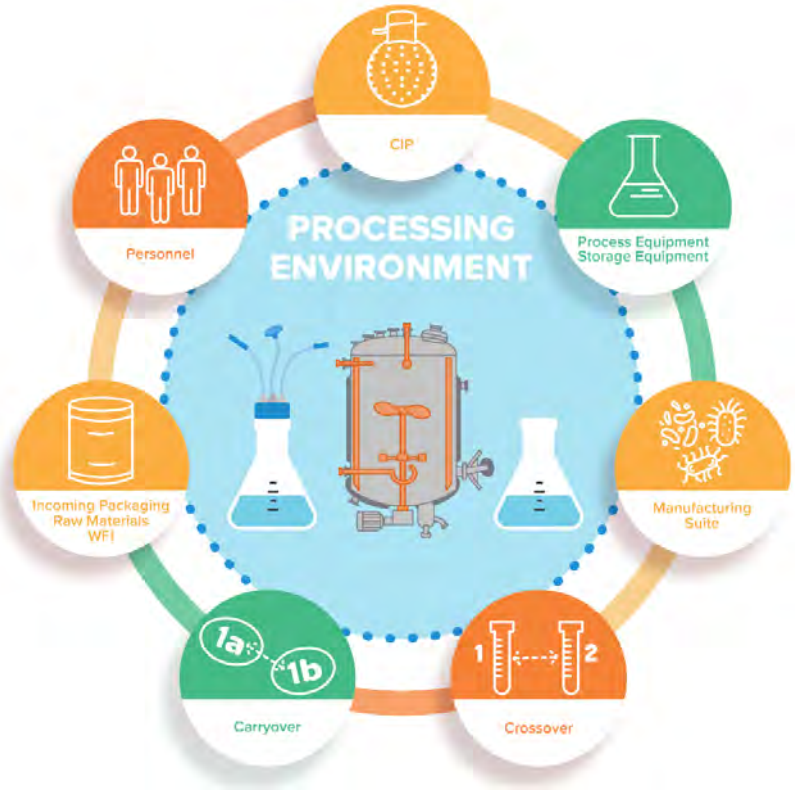
Product exposed to production environment must be protected by appropriate room classification



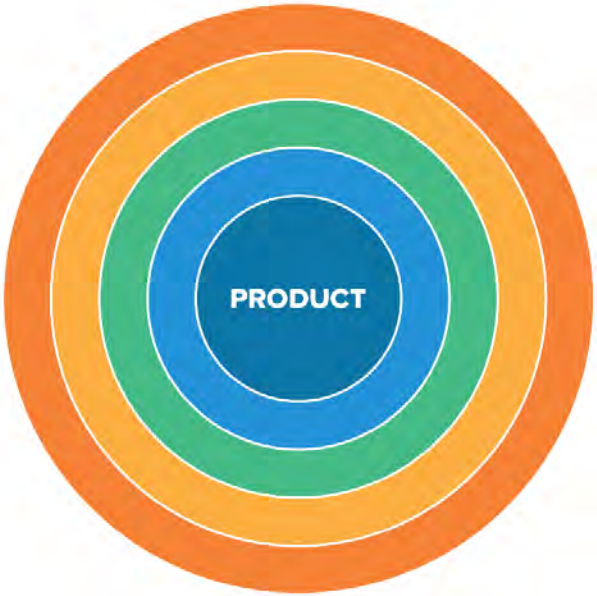
Ref. Good design practice for GMP Pharmaceutical Facilities



Potential Sources of Contamination



Operational Philosophy



Closed Single-Use System for Aseptic Process (e.g. cell culture)

Components and Equipment

- Integral
- Sterile

System Assembly

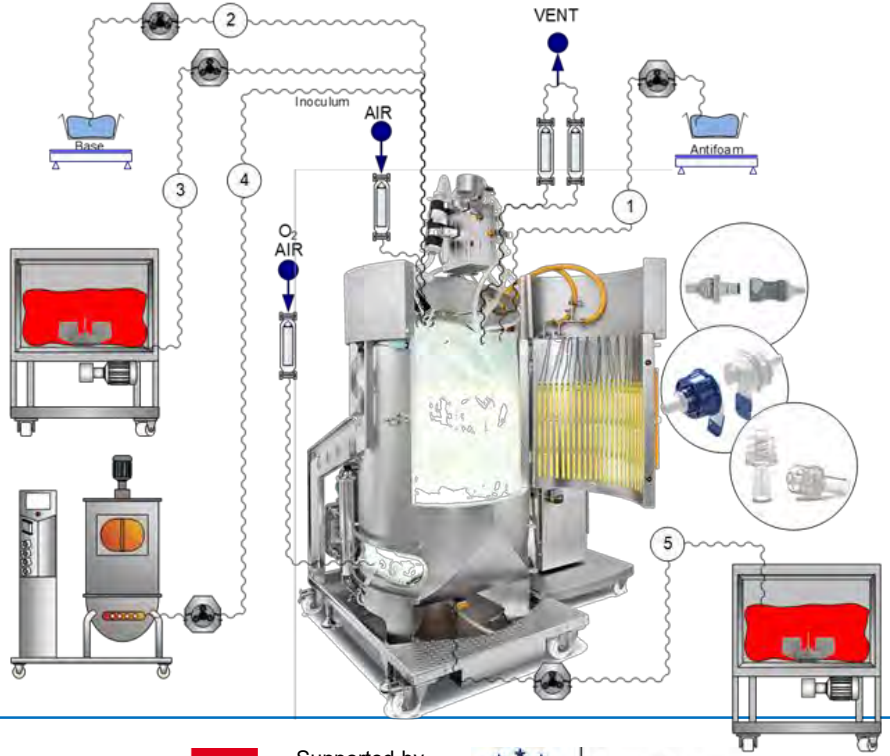
- Performed aseptically
- Never expose product contact surfaces

All Additions

- Sterile
- Goal is axenic inoculum & production culture

Integrity of System

- Maintained until clearance of product



Functionally Closed Single-Use or Multi-Use System for Low Bioburden Process

Components and Equipment
- Cleanable/ Sanitizable

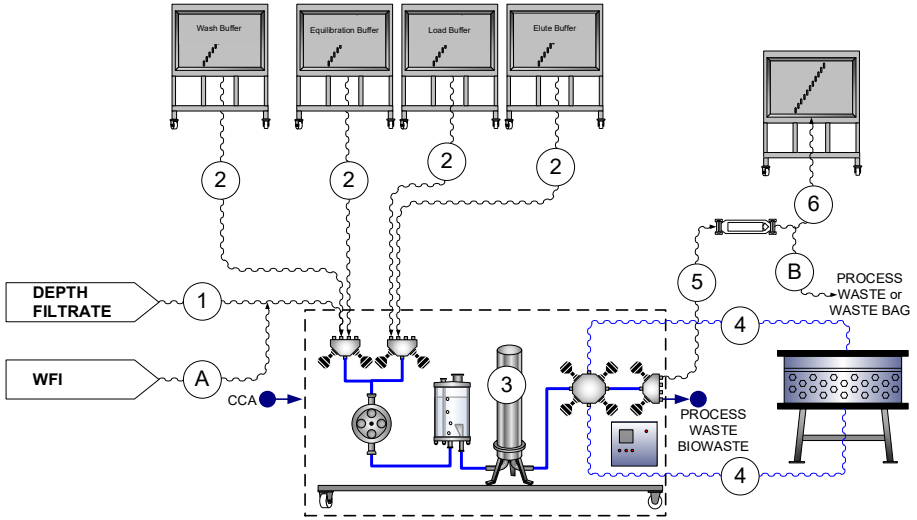
System Assembly
- CIP required

System Integrity
- Maintained post-CIP until clearance of product

Connections (post CIP)
- Functionally closure:
  - ⇨ Flush, Sanitized or aseptic

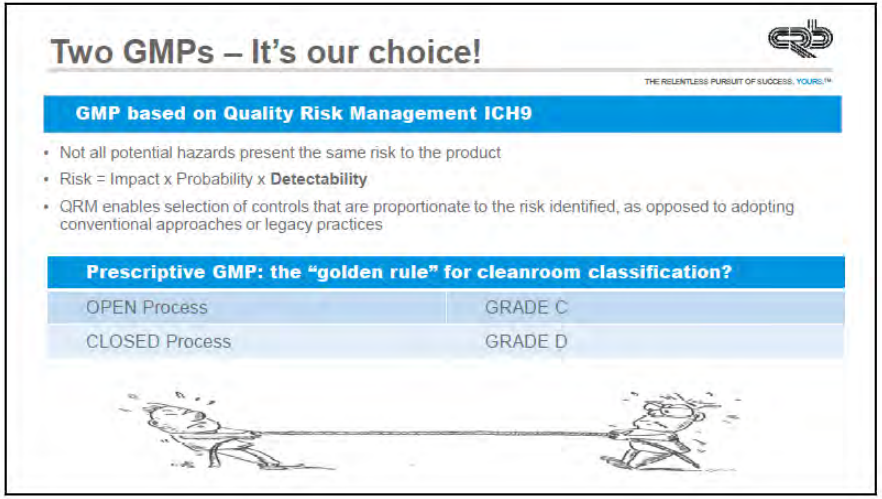
Additions
- Bioburden control/sterile prior to and during process

Maintenance of bacteriostatic state is critical



CNC or Classified area

- Structural thinking for a classical problem…
- How to initially determine room classification for a given process step when I don't have enough information for a detailed risk assessment / analysis e.g. during concept design?



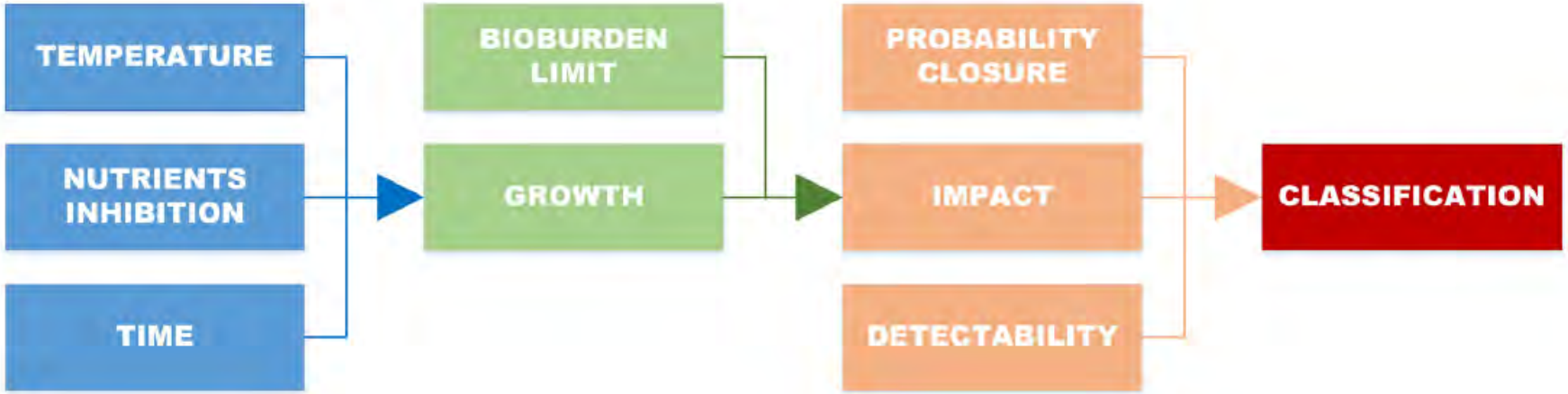
Risk Assessment

- Evaluate the risk that a contamination from the surrounding air causes a bioburden contamination.
- Set the cleanroom classification based on that risk (cleanroom is a risk mitigation measure)
- Use a ‘theoretical’ method, i.e. assign scores to the risk factors and determine the cleanroom classification

Classification = f(risk left over)
= Impact x Probability x Detectability

Impact = f(Bioburden Limit, Growth Potential)
Probability = Mitigation = f(Closure)
Detectability = f(Detection)

The room classification model



Step 1 - Growth potential – 3 dimensions

$$\frac{dx}{dt} = \exp\left(\mu_{max} \cdot T_{effect} \cdot N_{effect} \cdot t\right) \qquad (2)$$

Where:

1. **μmax** (in 1/h) is the maximum growth rate.
2. **T effect** is a factor between 0 and 100% to account on the temperature effect on the growth.
3. **N effect** is a factor between 0 and 100% to account on the growth promotion characteristics (i.e. nutrients) of the product/process solution.
4. **t** (in h) is the processing time where the contamination can grow. The processing time t can be seen as the time between when contamination occurs and when the next bioburden reduction step take place. For a buffer preparation it could be just a few hours whereas for an inoculum preparation can be for an extended period of multiple weeks.

Temperature	Optimum	Room temperature	Low temperature
Range	30–36°C	20–25°C	2–8°C
Rating	1.00	0.50	0.05

Nutrients/Inhibition	Optimum	Limited	None
Range	Medium	C-source only	Water/Inhibition
Rating	1.00	0.50	0.10

Time	Short	Medium	Long
Range	<8h	8–24h	>24h
Rating	8	24	48

Nutrients - Ferm. Media / rating = 1				
Temp	30-36°C	1.00	6.6E+04	2.8E+14	7.9E+28
	RT	0.50	2.6E+02	1.7E+07	2.8E+14
	2-8°C	0.05	1.7E+00	5.3E+00	2.8E+01
		rating	8	24	48
			<8h	8-24h	>24h
			(proliferation) Time		

Nutrients - C-source only / rating = 0.5				
Temp	30-36°C	1.00	2.6E+02	1.7E+07	2.8E+14
	RT	0.50	1.6E+01	9.1E+03	1.7E+07
	2-8°C	0.05	1.3E+00	2.3E+00	5.3E+00
		rating	8	24	48
			<8h	8-24h	>24h
			(proliferation) Time		

Nutrients - water, inhibition / rating = 0.10				
Temp	30-36°C	1.00	3.0E+00	2.8E+01	7.8E+02
	RT	0.50	1.7E+00	5.3E+00	2.8E+01
	2-8°C	0.05	1.1E+00	1.2E+00	1.4E+00
		rating	8	24	48
			<8h	8-24h	>24h
			(proliferation) Time		

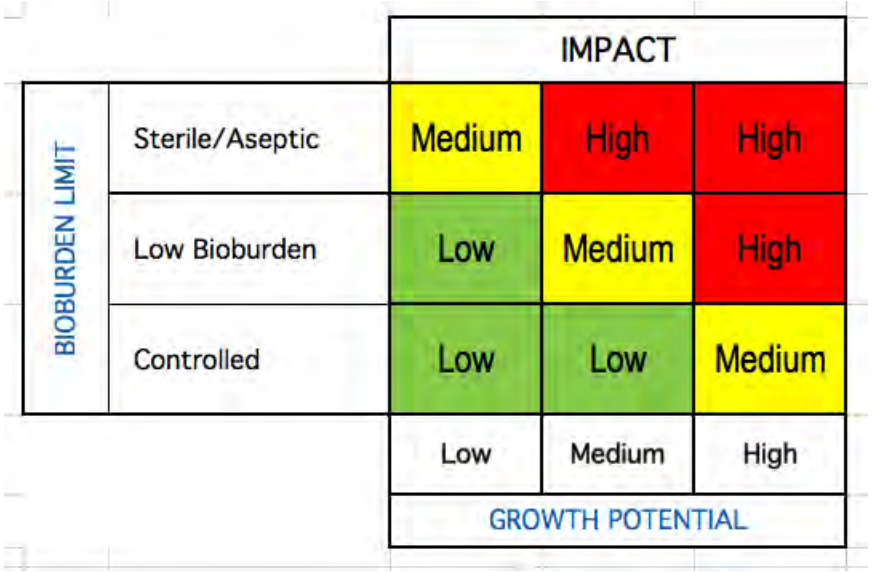
Step 2 – Impact calculation

- Function of growth potential and the process's Bioburden limit

Table 1. Growth Potential and Bioburden Limit definitions and rating

Growth Potential	
Rating	Description
Low	Process characteristic (e.g. temperature, time etc.) does not facilitate growth
Medium	Growth is supported but partially limited by no perfect condition (e.g. limited nutrients, etc.)
High	Perfect condition for growth (e.g. like in a bioreactor)
Bioburden Limit	
Rating	Description
Low	Controlled bioburden
Medium	Low bioburden
High	Aseptic or sterile like conditions

Step 2 - Impact evaluation



BIOBURDEN LIMIT	IMPACT: Low	IMPACT: Medium	IMPACT: High
Sterile/Aseptic	Medium	High	High
Low Bioburden	Low	Medium	High
Controlled	Low	Low	Medium
GROWTH POTENTIAL	Low	Medium	High

Probability

- ***Probability = Mitigation = f(Closure)***

Table 2. Probability definition and rating

Probability	
Rating	Description
Low	Closed systems: maximum process/product protection
High	Open systems: contamination is likely

- The model is designed to be applied in situations such as early design phases e.g. concept design, and then you would define how the system is to be validated and operated closed via a further detailed assessment, as that level of detail would not be known at this stage.
- Basic assumptions:
  - Equipment is cleaned, sanitized and/or sterilized based on the intended use.

Detectability

Detectability	
Rating	Description
Easy	In-line, i.e. higher degree of confidence that the contamination will be detected in real time
Moderate	Off-line, i.e. contamination is detected but its assessment is limited (due to testing time lag)
Difficult	Not detectable, i.e. contamination will probably not be detected

- This is logical thinking for a truly risk-based approach.
- Unfortunately, following traditional GMP principles, use of detection is not accepted as a control measure as it is seen as not having a robust system/process. Nonetheless, a lower environmental classification is not synonymous with failure

Step 3 - Room Classification determination

- Classification = f(risk left over)
  = Impact x Probability x Detectability

BIOBURDEN LIMIT	IMPACT: Low	IMPACT: Medium	IMPACT: High
Sterile/Aseptic	Medium	High	High
Low Bioburden	Low	Medium	High
Controlled	Low	Low	Medium
GROWTH POTENTIAL	Low	Medium	High

CLOSED System/Process	IMPACT: Low	IMPACT: Medium	IMPACT: High
DETECTABILITY: Difficult	CNC	CNC	CNC
DETECTABILITY: Moderate	CNC	CNC	CNC
DETECTABILITY: Easy	CNC	CNC	CNC

OPEN System/Process	IMPACT: Low	IMPACT: Medium	IMPACT: High
DETECTABILITY: Difficult	C	A/C	A/B
DETECTABILITY: Moderate	D	C	A/C
DETECTABILITY: Easy	CNC	D	C

- Closed process = CNC - Full Stop!

Risk evaluation examples

Application	Growth Promotion	Temperature	Time to Next Bioburden Reduction Step	Growth Potential	Bioburden Limit	Impact	Probability Closure	Detectability	Area Classification
Media preparation	High	RT[b]	<8 h	Medium	Controlled	Low	Open	Moderate	D
Inoculum	High	Optimum	>24 h	High	Sterile/aseptic	High	Open	Easy	C
Bioreactor	High	Optimum	>24 h	High	Sterile/aseptic	High	Closed	Easy	CNC
Cell factories	High	Optimum	>24 h	High	Sterile/aseptic	High	Open	Easy	C
Harvest	High	Low	<8 h	Low	Low bioburden	Low	Open	Easy	CNC
Harvest	High	RT	<8 h	Medium	Low bioburden	Medium	Open	Easy	D
Harvest	High	RT	<8 h	Medium	Low bioburden	Medium	Open	Moderate	C
Buffer preparation	Medium	RT	<8 h	Low	Controlled	Low	Open	Moderate	D
Buffer preparation	Medium	RT	<8 h	Low	Controlled	Low	Open	Moderate	D
Protein A	High	RT	<8 h	Medium	Low bioburden	Medium	Open	Easy	D
Chromatography	Medium	RT	<8 h	Low	Low bioburden	Low	Open	Easy	CNC
Chromatography	Medium	RT	<8 h	Low	Low bioburden	Low	Open	Moderate	D
Column packing	Low	RT	<8 h	Low	Low bioburden	Low	Open	Easy	CNC
Column packing	Low	RT	<8 h	Low	Low bioburden	Low	Open	Moderate	D
UF/DF[c]	Medium	RT	<8 h	Low	Low bioburden	Low	Open	Moderate	D
UF/DF	Medium	RT	<8 h	Low	Low bioburden	Low	Open	Difficult	C

[a]Classifications: A = EU Grade A; C = EU Grade C; D = EU Grade D; and CNC = control not classified.
[b]RT = room temperature.
[c]Ultra-Filtration/Dia-Filtration.

Bioreactor

- Impact (High)
  - Bioburden limit => Axenic condition = aseptic or sterile
  - Growth potential => growth media, optimal temperature and long process time
- Probability (Closed)
  - Sterilised equipment and operated as closed process
- Detectability (EASY)
  - probability that a contamination from the environment is detected is high
  - CNC space is appropriate

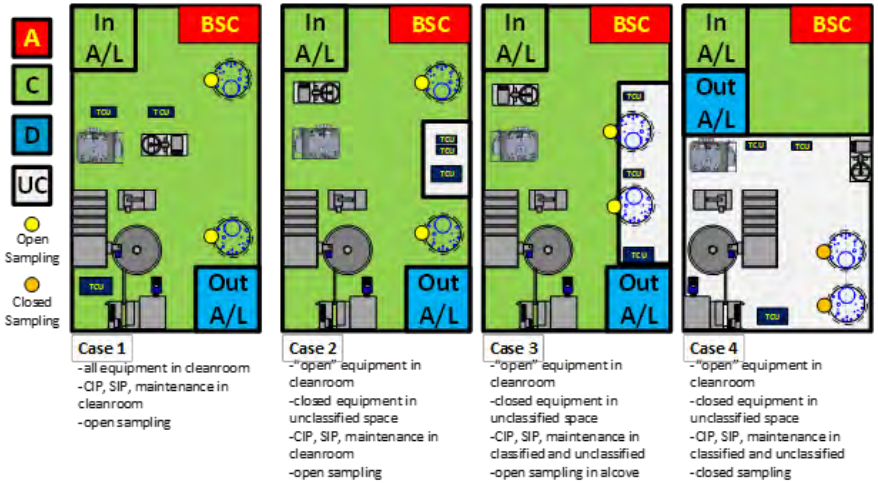
Buffer preparation

- Impact (Low)
  - Bioburden limit => Controlled bioburden
  - Growth potential => medium growth potential, room temperature and short process time
- Probability (Open)
  - CIP'ed equipment and open operation during preparation
- Detectability (Moderate)
  - If probability that a contamination from the environment is detected is medium
  - Grade D space is appropriate, but if detection can be increased then CNC would be okay
  - With closed addition CNC would be appropriate

Chromatography

- Impact (Low)
  - Low Bioburden limit
  - Growth potential => medium in solvents, Room temperature and short process time
- Probability (Open due to preparation)
  - CIP or manual cleaning of equipment and operated as closed process
- Detectability (Moderate/Easy)
  - probability that a contamination from the environment is detected depend on process step
  - Grade D if Moderate detection otherwise CNC space is appropriate

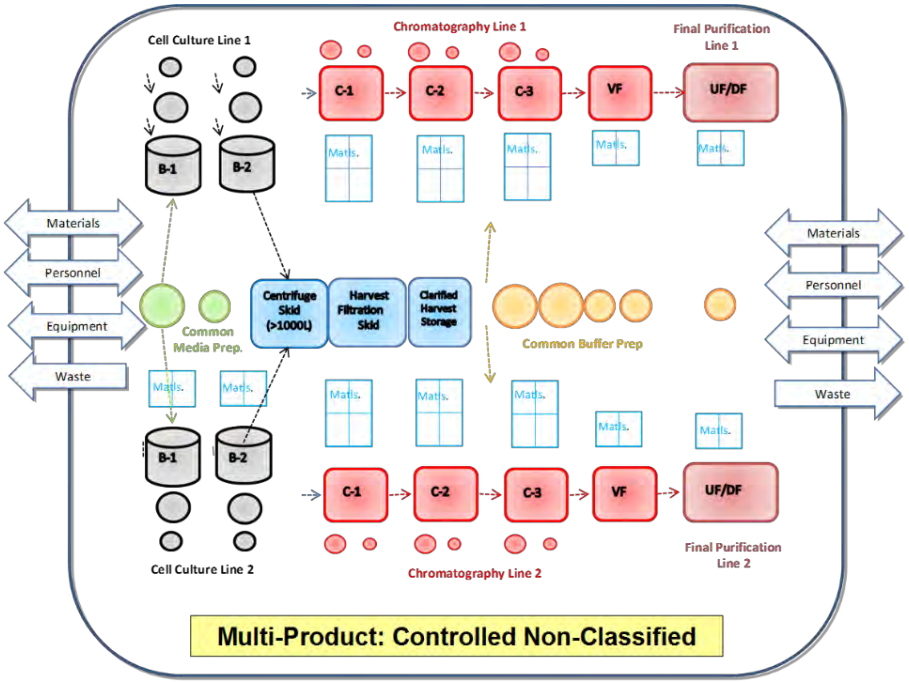
Facility impact – How do we build it?



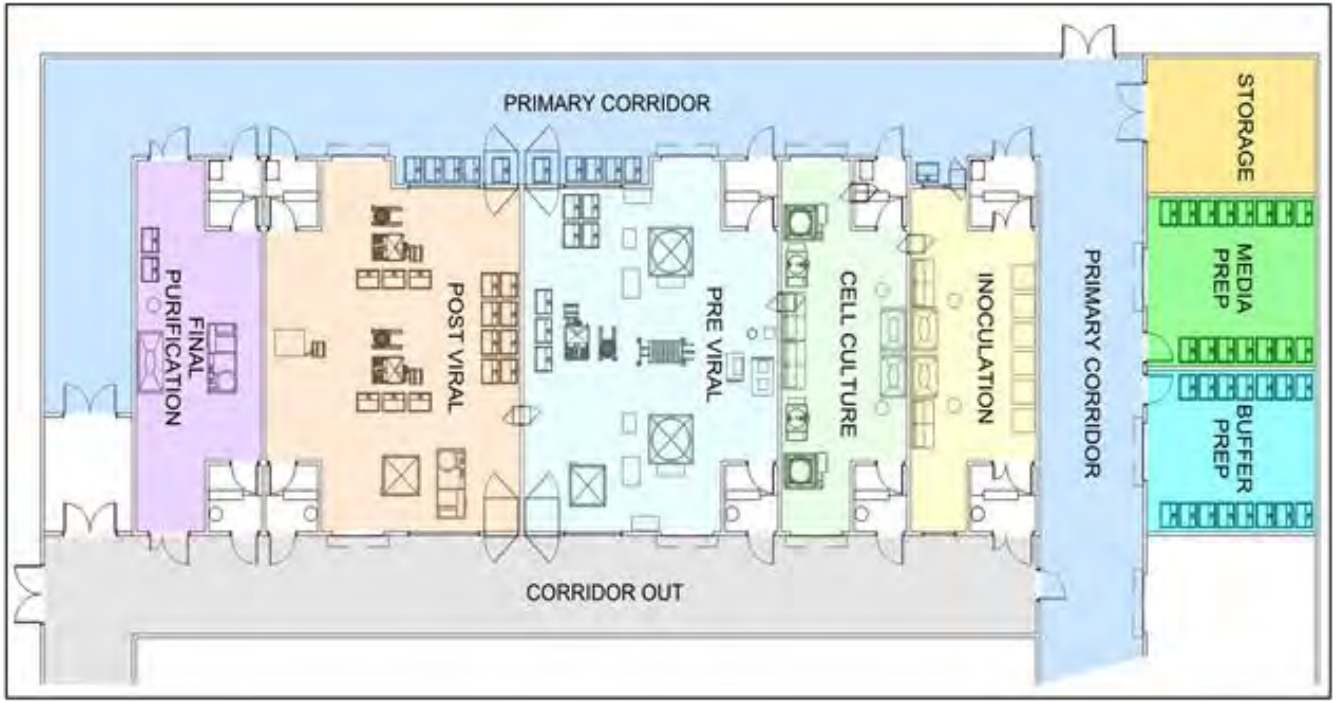
- Drives facility simplification
  - Classified space reduction
  - Simplify segregation
  - Promote flexibility
  - Enhancing product protection
  - Reduces risk
  - Reduce CAPEX and OPEX

Evaluating appropriate bioprocessing environments

- Closure Risk Assessment
- Assess Room classification
- Operational strategy
- Contamination/Cross contamination Risk Assessment
- Convenience/flexibility
- Segregation
- Single Use/Hybrid/Stainless steel



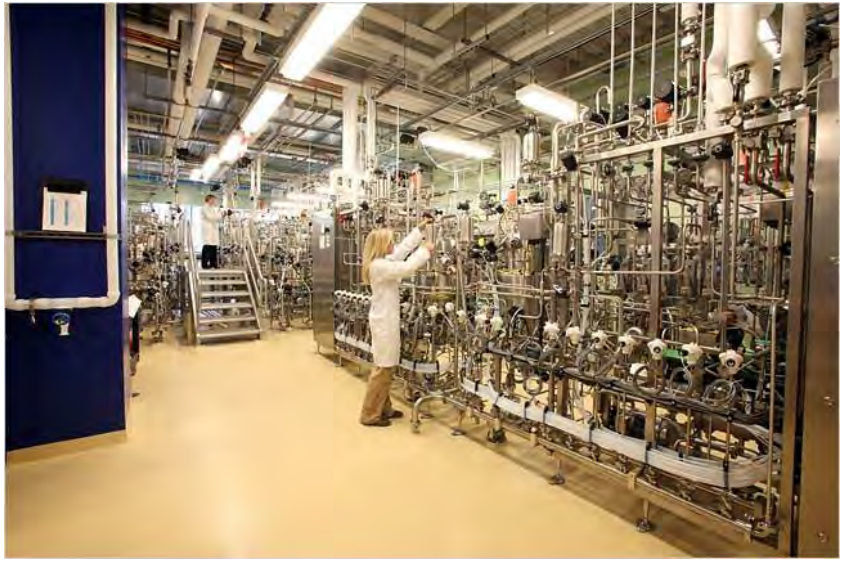
More segregated layout configuration



Which Grade are these rooms?

Both CNC!

Pictures provided by CRB



Pictures provided by CRB

Grade D and CNC spaces in Drug Substance facility

- Grade D:
  - 100% Pharma finish

- CNC Space:
  - 61% Pharma finish
  - 39% Clean Industrial finish

- Communication & transfers between areas
- “Pleasing” the regulatory inspectors
- Aesthetics for clients, visitors and auditors

Pictures provided by CRB

Conclusion

With closed system it is possible to:

- Simplify & harmonise selection of room classification
- Meet regulatory requirements
- Justify ballroom facility
- Introduce lower room classification

Benefits

- Improving product quality and patient access to products
- Simplified design
- Reduction of capital and operational costs
- Reduced Cost of Quality
- Flexibility in facility operation

Thank you for your attention

QUESTIONS ?

References and Relevant Literature

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