How can the new Annex 1 leverage technology innovation in Pharma?

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Innovation

- Historical background
- Engineering
- Sterilization
- Barrier systems
- Robotics
- Emerging technologies
- Key takeaways

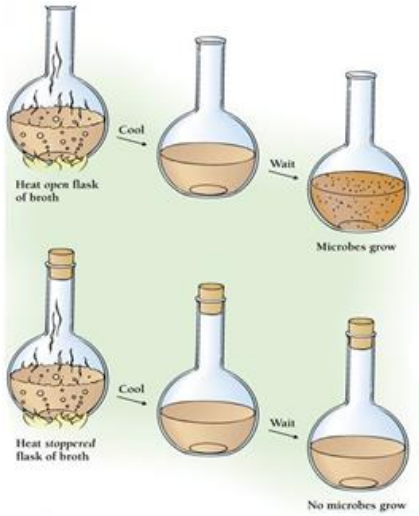
Historical background

Enlightenment Age in Pavia - Alessandro Volta

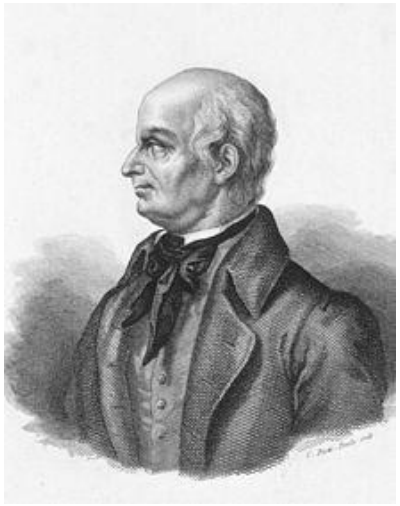
Denis Papin “Digester”
Museum for the History of the University of Pavia
(Object from the collection of Alessandro Volta)

Alessandro Volta (1745 - 1827)

Enlightenment Age in Pavia - Lazzaro Spallanzani



Experience on spontaneous generation (1765 ca.)



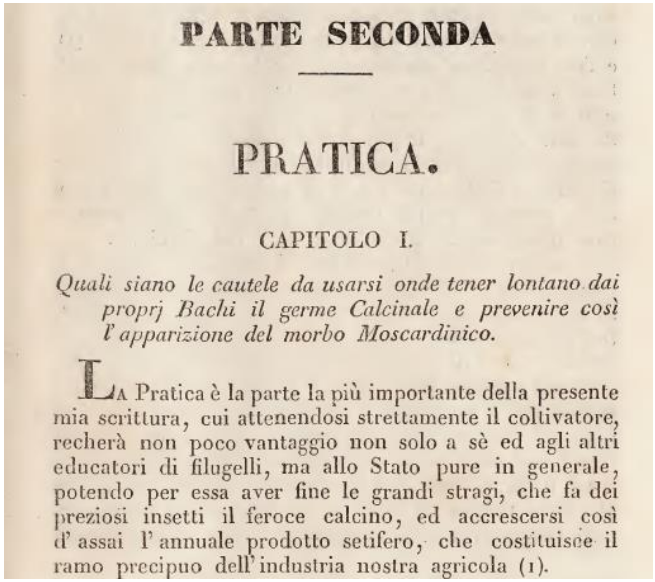
Lazzaro Spallanzani (1729 - 1799)

«le meilleur observateur de l'Europe»
- Voltaire

Microbiological origin of infectious diseases – Agostino Bassi

Agostino Bassi (1773 – 1856)

Microbiological origin of infectious diseases – Agostino Bassi



PARTE SECONDA

PRATICA.

CAPITOLO I.

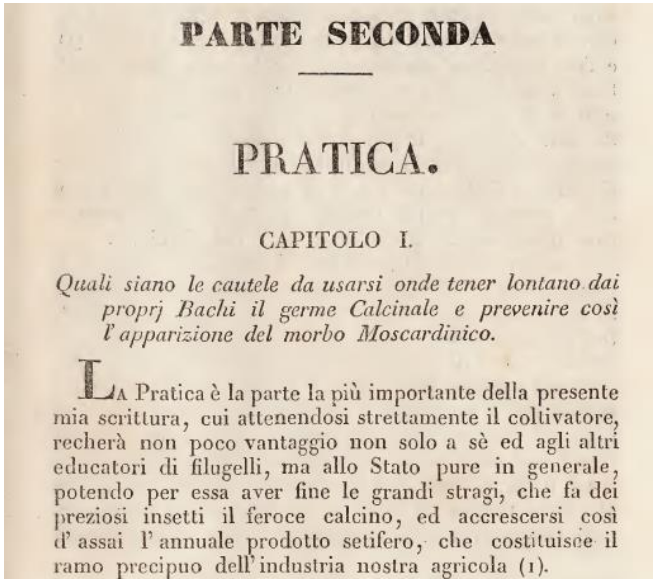
Quali siano le cautele da usarsi onde tener lontano dai proprj Bachi il germe Calcinale e prevenire così l'apparizione del morbo Moscardinico.

La Pratica è la parte la più importante della presente mia scrittura, cui attenendosi strettamente il coltivatore, recherà non poco vantaggio non solo a sè ed agli altri educatori di filugelli, ma allo Stato pure in generale, potendo per essa aver fine le grandi stragi, che fa dei preziosi insetti il feroce calcino, ed accrescersi così d'assai l'annuale prodotto setifero, che costituisce il ramo precipuo dell'industria nostra agricola (1).

"Del mal del segno, calcinaccio o moscardino" (Edizione 1836, Tipografia Orcesi, Lodi) - Agostino Bassi

> *What are the precautions to be used to keep the "Calcino" germ away from Silkworms and thus prevent the appearance of the "Moscardino" disease.*
>
> ***The practice is the most important part of my text** and the farmer, strictly adhering to it, will bring advantages not only to himself and to the other silkworm growers but also to the State, being able with this to put an end to the great slaughters caused by the ferocious "calcino" to the precious insects and greatly increase the annual silk production that constitutes the main sector of our agricultural industry.*

Microbiological origin of infectious diseases – Agostino Bassi



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‘’Del mal del segno, calcinaccio o moscardino’’ (Edizione 1836, Tipografia Orcesi, Lodi) - Agostino Bassi

- *Segregation*
- *Cleaning*
- *Disinfection*

Microbiological origin of infectious diseases – Agostino Bassi

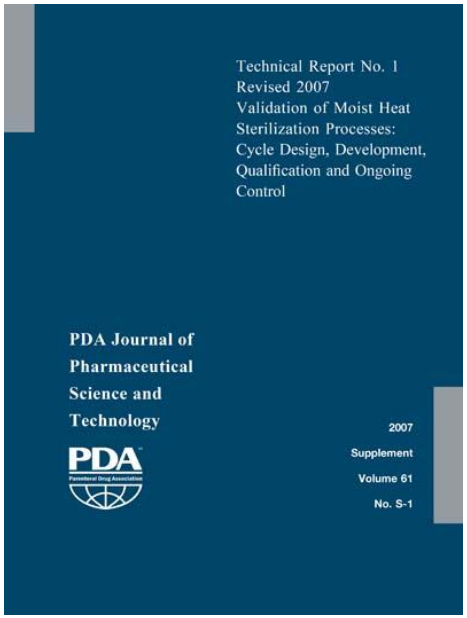
Il disinfettamento col mezzo del vapore, può farsi, collocando i graticci in uno stanzino disposti in modo che l'uno sia un po' più discosto dall'altro, ed introducendo in questo il vapore dall'esterno col mezzo di un cannone che comunichi col coperchio di una gran caldaja piena d' acqua in ebolizione.

"The "disinfection" with steam can be done by placing the racks in a small room arranged so that one is a little distant from the other and introducing the steam into this from the outside by means of a big pipe that communicates with the lid of a large boiler full of boiling water."

1978 - PDA Technical Monograph N°1 Validation of Steam Sterilization Cycles

Dario Pistolesi

Vittorio Mascherpa

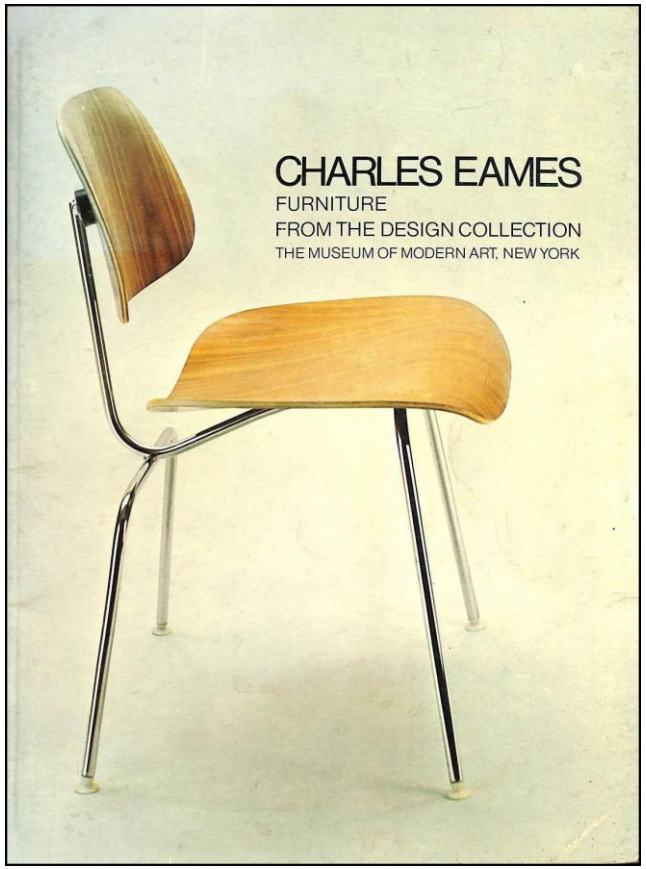


Technical Report No 1, rev. 2007

Engineering

Old design, innovative design (1930 ca.)

Charles Eames (1940 ca.)



Dieter Rams

1958

2001

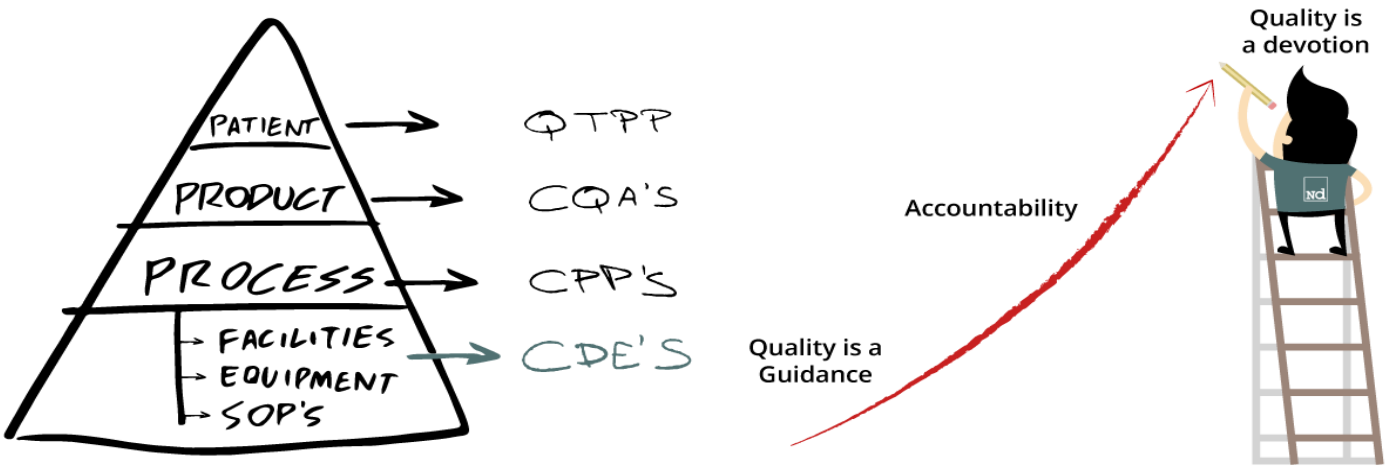
Dieter Rams

1. Good design is innovative
2. Good design makes a product useful
3. Good design is aesthetic
4. Good design makes a product understandable
5. Good design is unobtrusive
6. Good design is honest
7. Good design is long lasting
8. Good design is thorough down to the last detail
9. Good design is environmentally friendly
10. Good design is as little design as possible

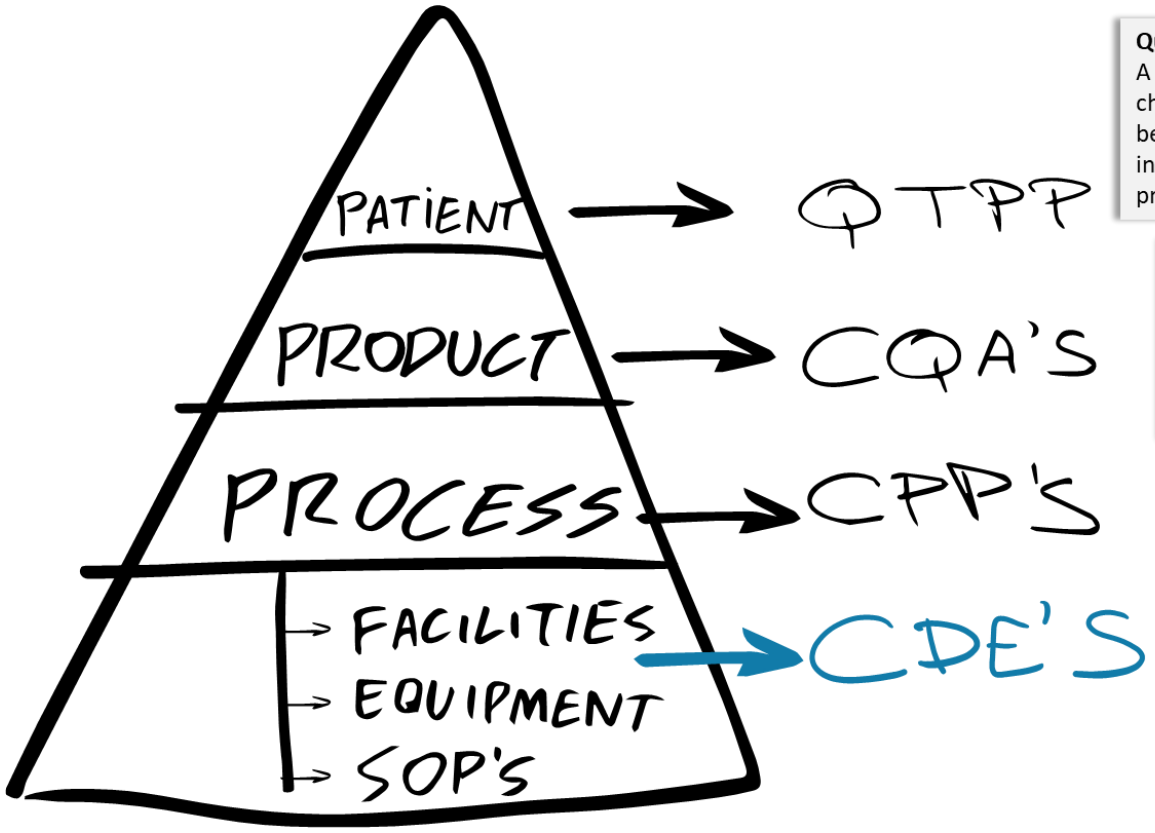
Dieter Rams

Quality by Design

A **systematic approach** to development that begins with predefined objectives and emphasizes product and **process understanding** and **process control**, based on sound science and **quality risk management**.



Quality by design



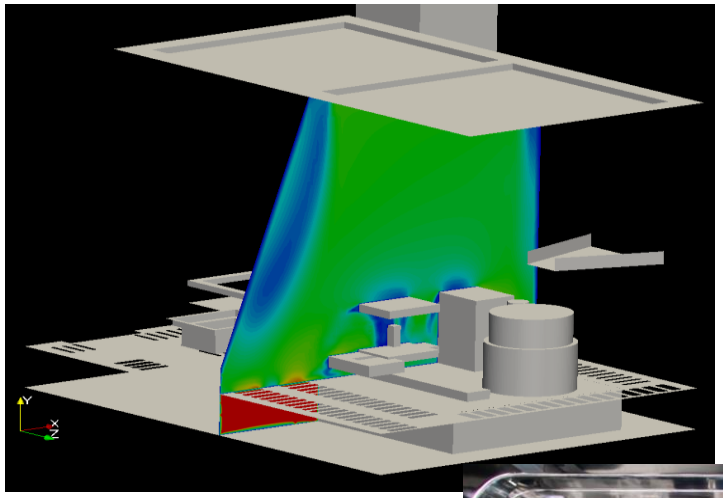
Quality Target Product Profile (QTPP):
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

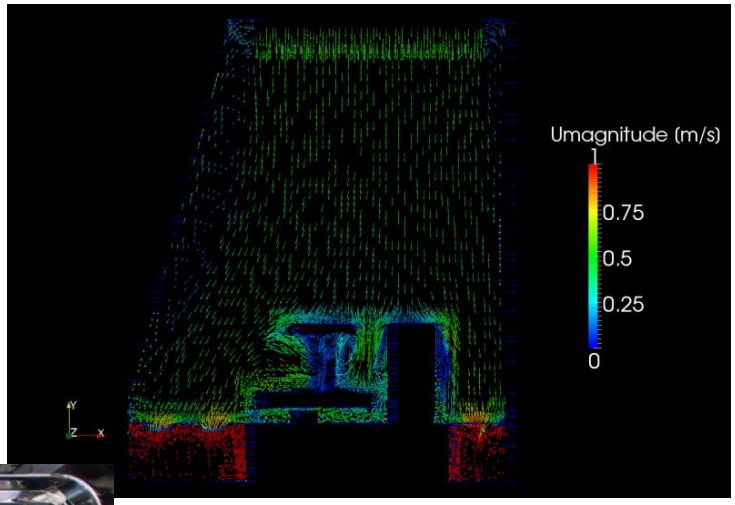
Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Process Parameter (CPP):
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Design Element (CDE):
System functions and features identified as having the potential to control risks to product quality and therefore patient safety.

Computational Fluid Dynamics predictive tool to investigate the CDE of a system

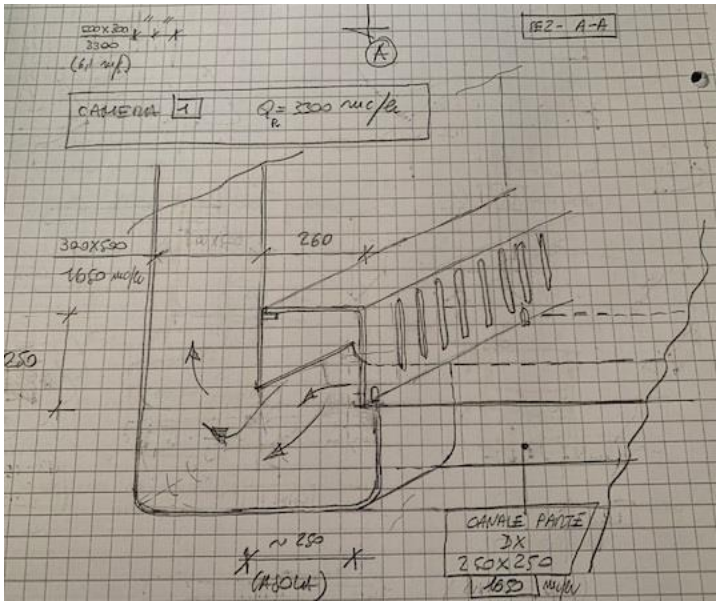


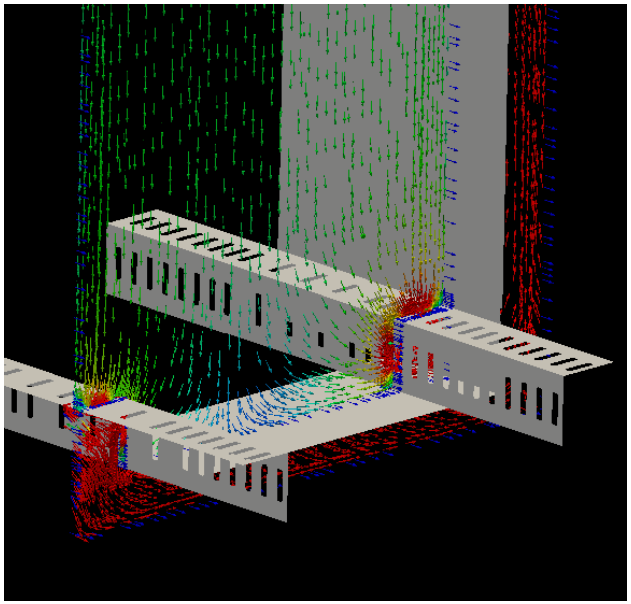


CFD advantages

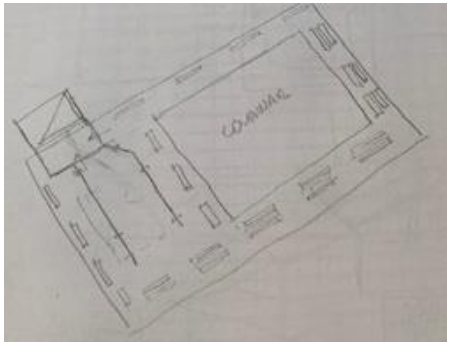
- Qualitative and quantitative indications of the trend of the air motion field (direction, speed)
- Identification of potential criticalities: vortex, stagnation areas
- Optimization of the air diffusion / intake areas, in order to optimize fluid dynamics performance
- Preliminary evaluation of an idea
- Computer as a virtual laboratory / wind tunnel
- Quick project optimization

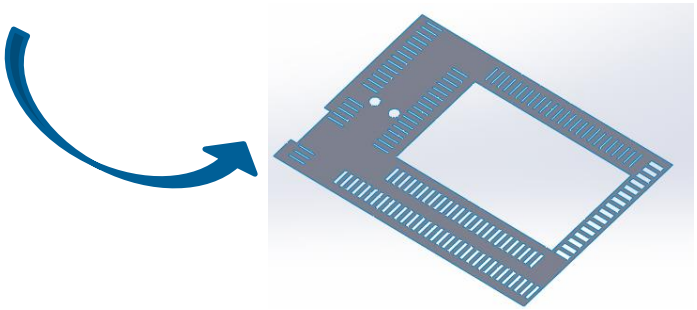
CFD, from scratch to simulation

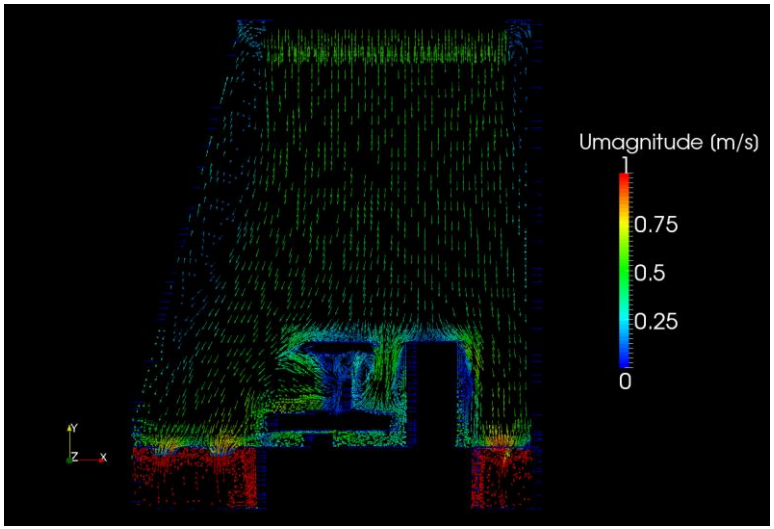




CFD, from scratch to simulation

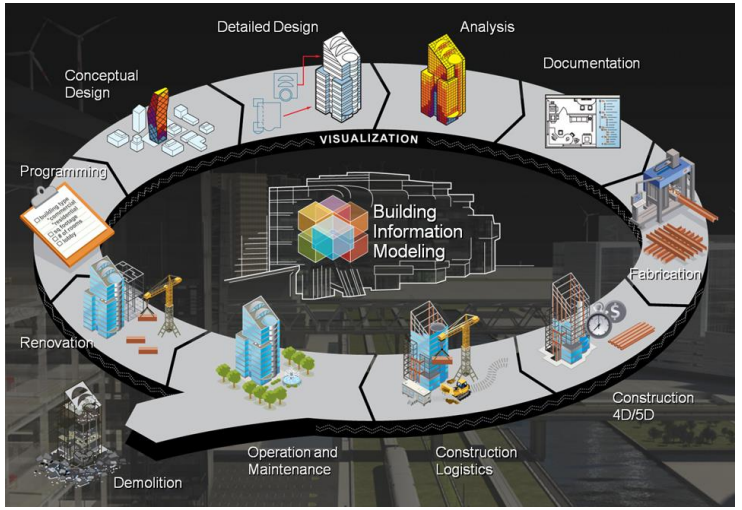






Building Information Modeling

- Planning
- Engineering
- Construction
- Building management
- De-commissioning

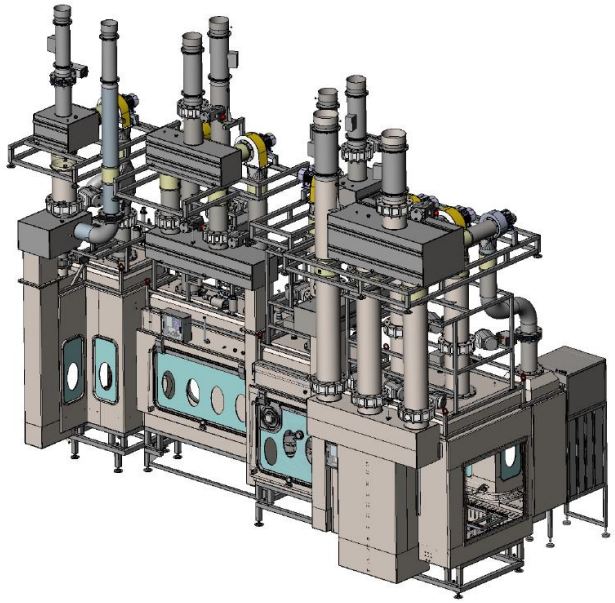


Building Information Modeling

Digital parametric model containing all the information regarding the entire **life cycle of the work.**

All the professionals involved work on a **shared environment**.

Updated information accessible to all designers in **real time**.



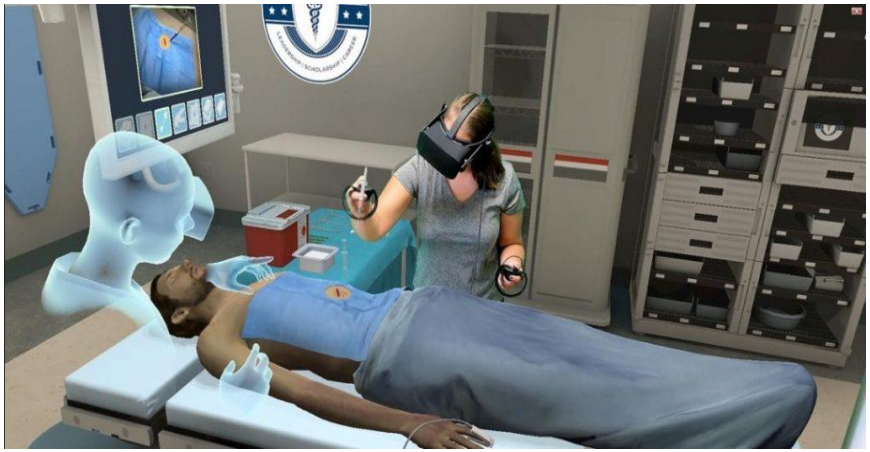
Augmented Reality

Augmented reality is an **interactive experience** of a real-world environment where the objects are enhanced by **computer-generated perceptual information**

Augmented Reality

- Allows the access to complementary information in real time without having to search for it
- Real time update, synchronization with central server
- Improved communication capabilities
- Allow a constant connection between employees and a remote support

Virtual Reality



Virtual Reality

Clean Room Challenges

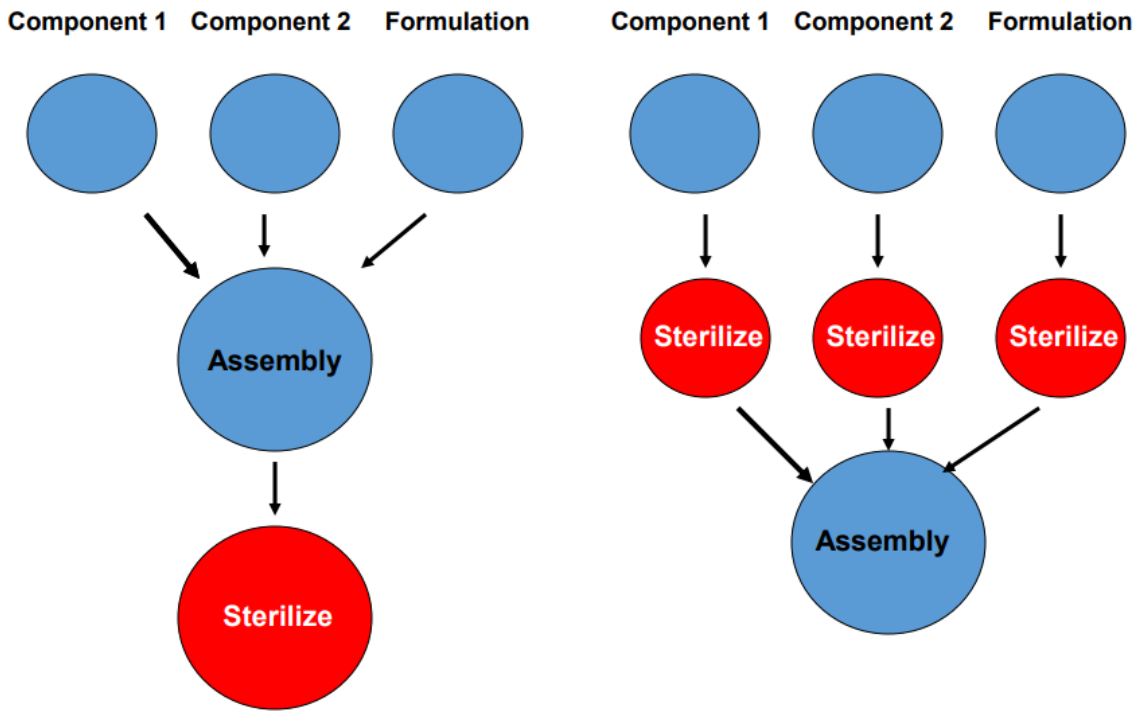
- Real training not always possible
- No accurate behaviour mesurement system for human errors
- Worst cases hard to be replicated (i.e. recovery actions)

VR simulation Solutions

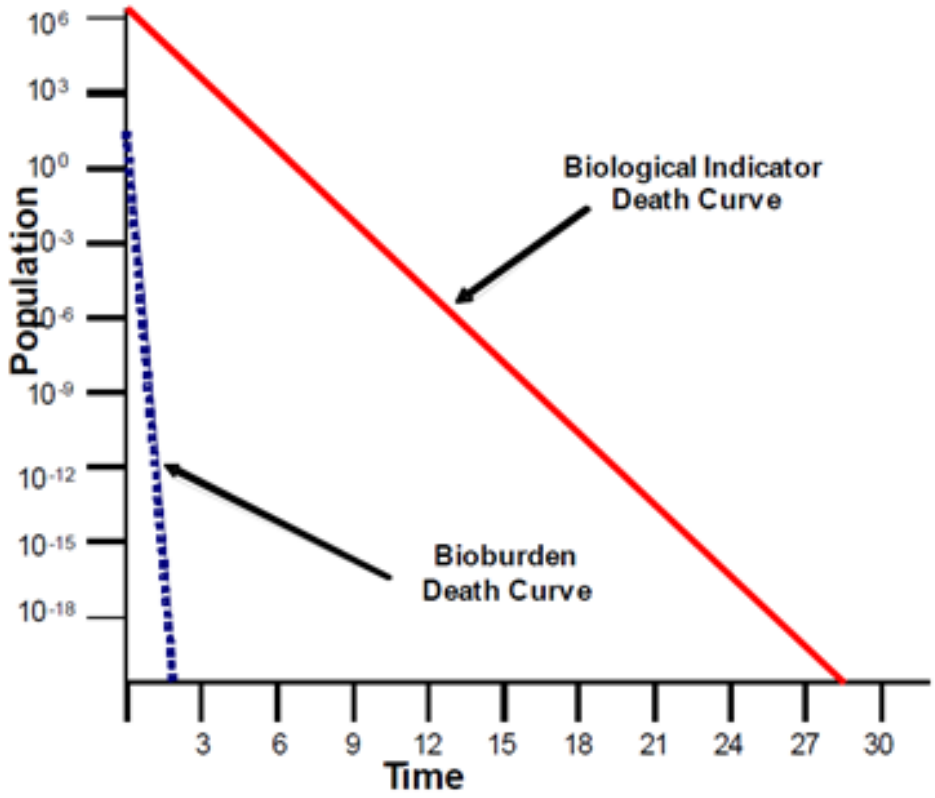
- Environements and scenarios simulation
- Higher level of training retention

Sterilization

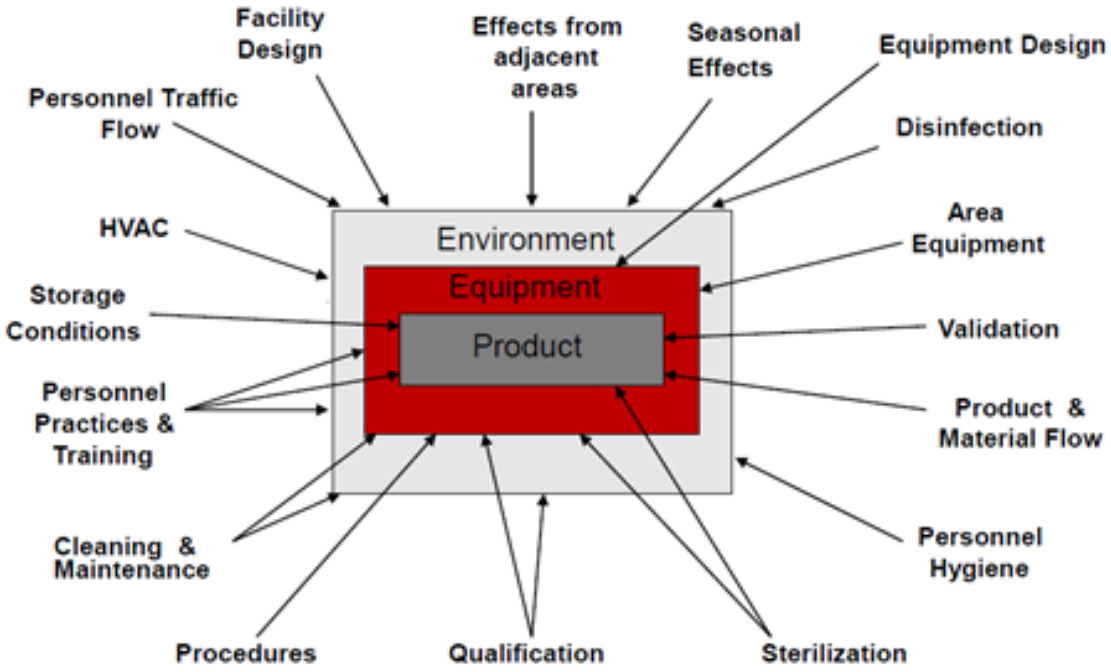
Terminal Sterilization and Aseptic Processing



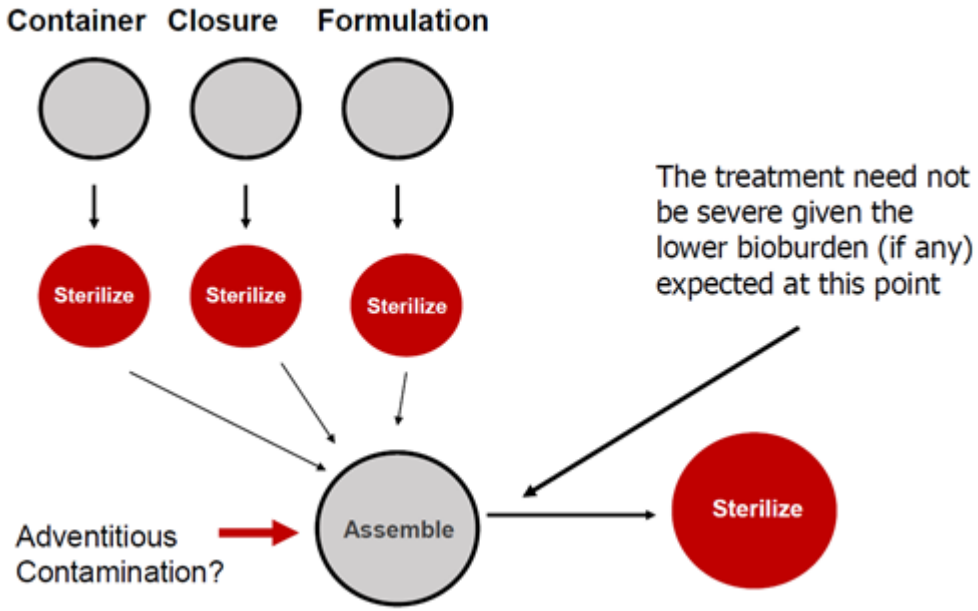
Reference BI and relative bioburden resistance

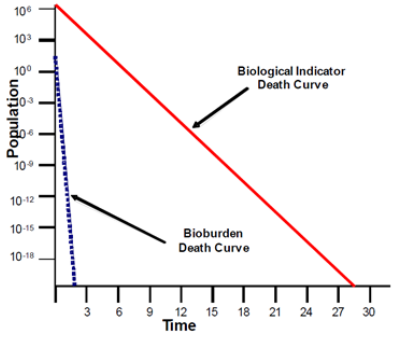


Aseptic processing challenges



Aseptic Processing and Terminal Sterilization





Barrier Systems

Manned Clean Room

CHALLENGES

- Sterile gowning – operator comfort
- Training, requalification
- High quality background air needed
- Environmental monitoring
- Personnel monitoring

Open RABS

CHALLENGES

- High quality background air needed
- Low level improvements in contamination control
- Decontamination of filling machine (VHP) usually combined with room, low process control

Isolators

REAL TECHNICAL IMPROVEMENT

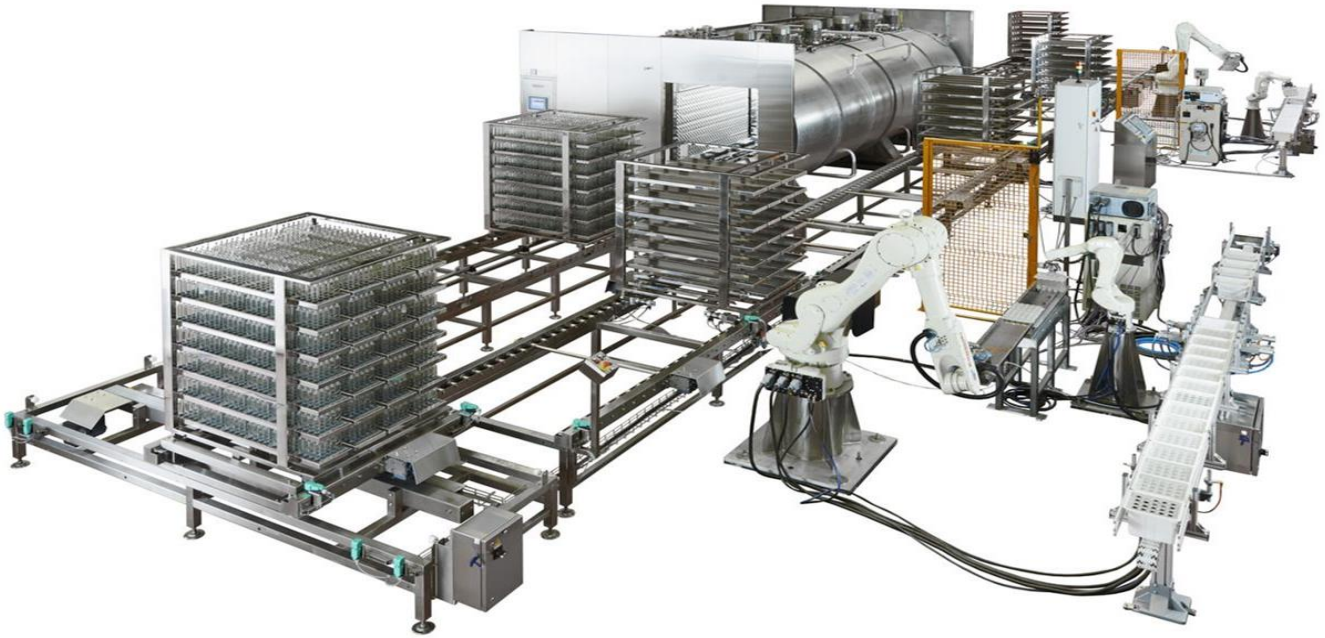
- Highest level of containement
- Medium quality background air
- Simplified gowning
- Fast training and qualification of personnel
- VHP automatic decontamination, high process control
- Costs

Robotics

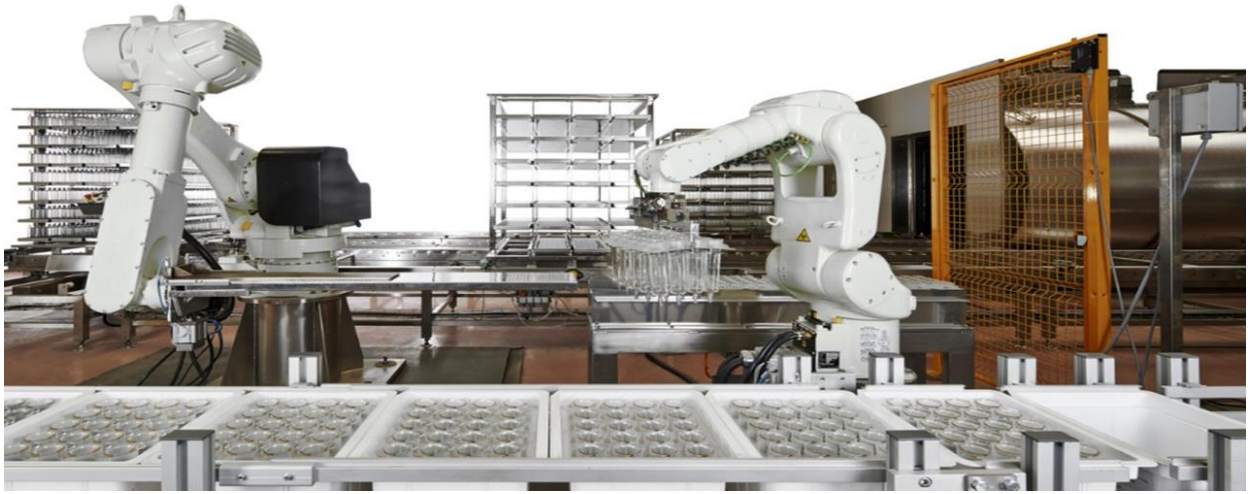
Robot

Class A	• Filling, isolators and RABS inner chambers • Chemical decontamination (VHP)	Robots with the highest standard in design, materials and components
Class C	• Background area for isolators • Chemical/alcohol disinfection	Robots with high standard in design, materials and components
Class D	• Terminally sterilized product handling • Final packaging	Clean robots

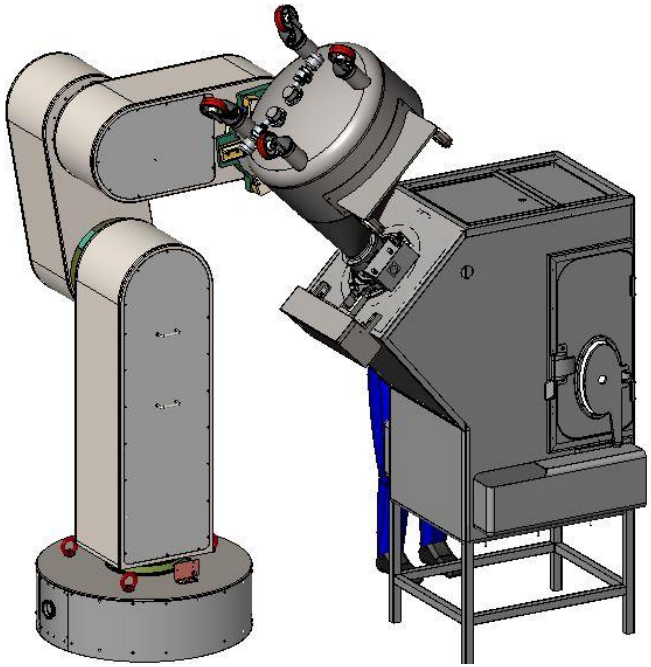
Class D



Class D



Class C

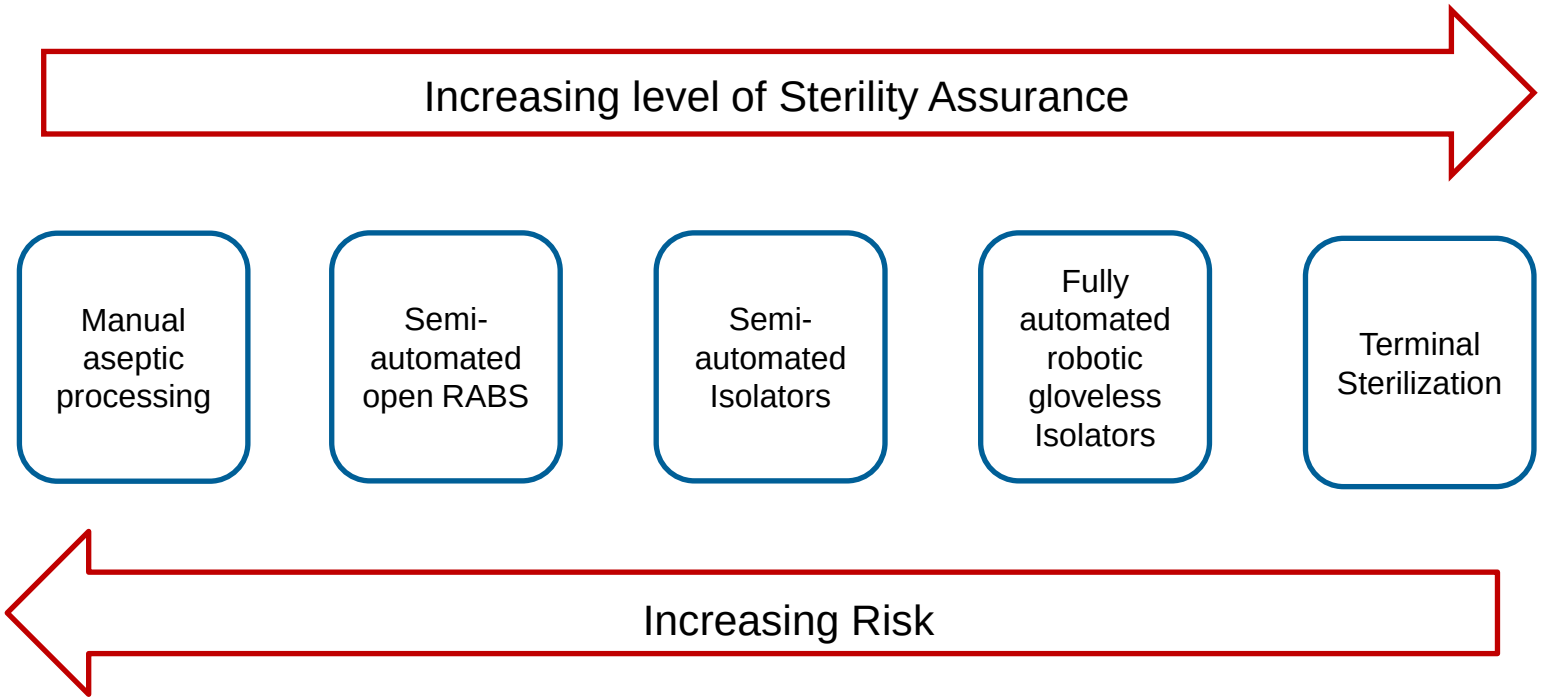


Class A

Gloveless Isolator

Emerging Technologies

Sterile Manufacturing



Challenges of new drugs

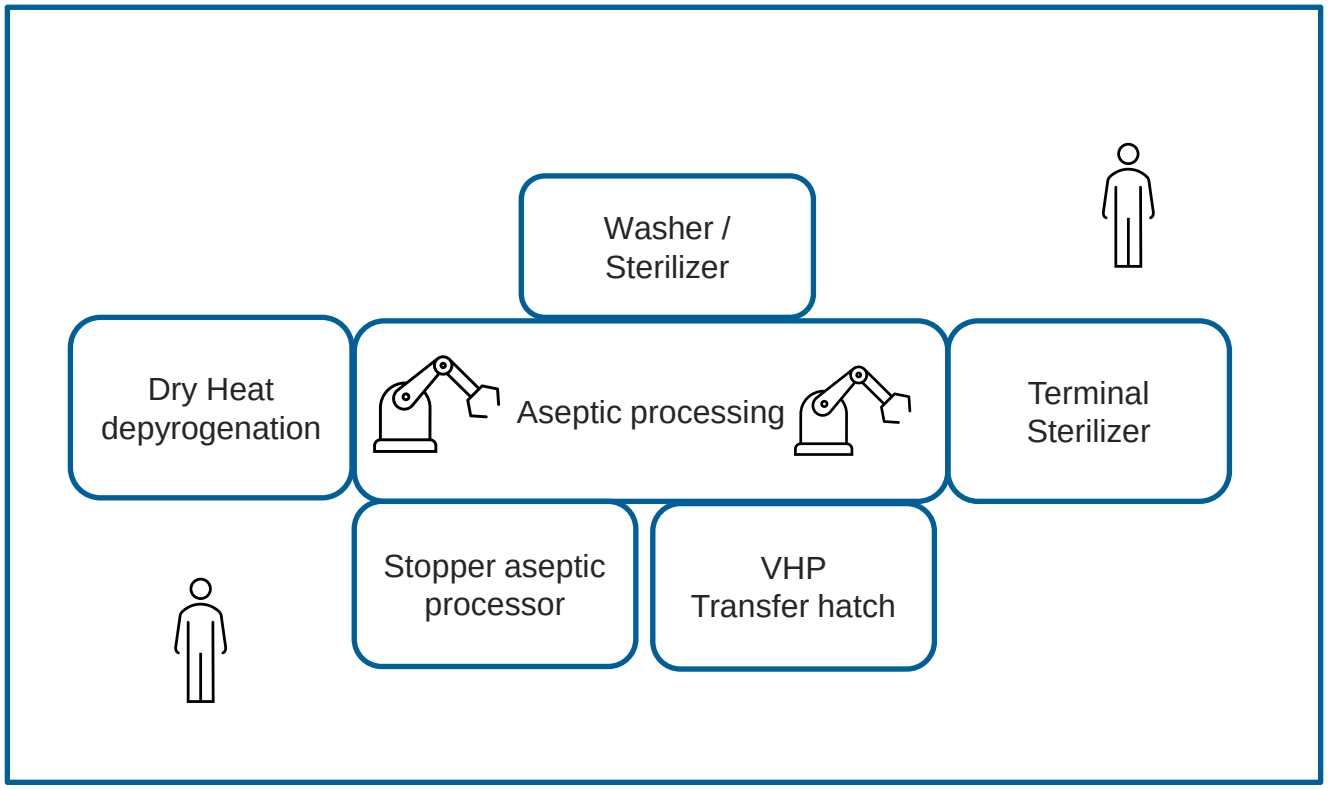
- Short time between R&D and production
- New generation drugs
- Cell & Gene therapies
- Orphan drugs & customized therapies

- Process flexibility
- Greater manufacturing complexity
- Increasing quality expectations
- Easy scale up

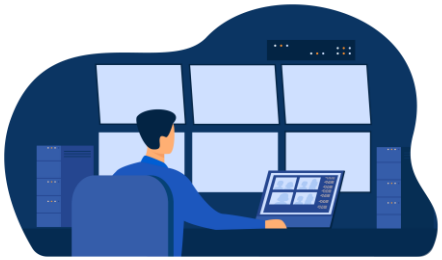
- High output manufacturing not adequate
- New flexible manufacturing model required

Integrated Cluster Unit

Robotized Cluster Unit



Humanless Environment



Washer / Sterilizer

Dry Heat depyrogenation

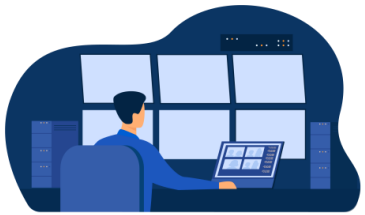
Aseptic processing

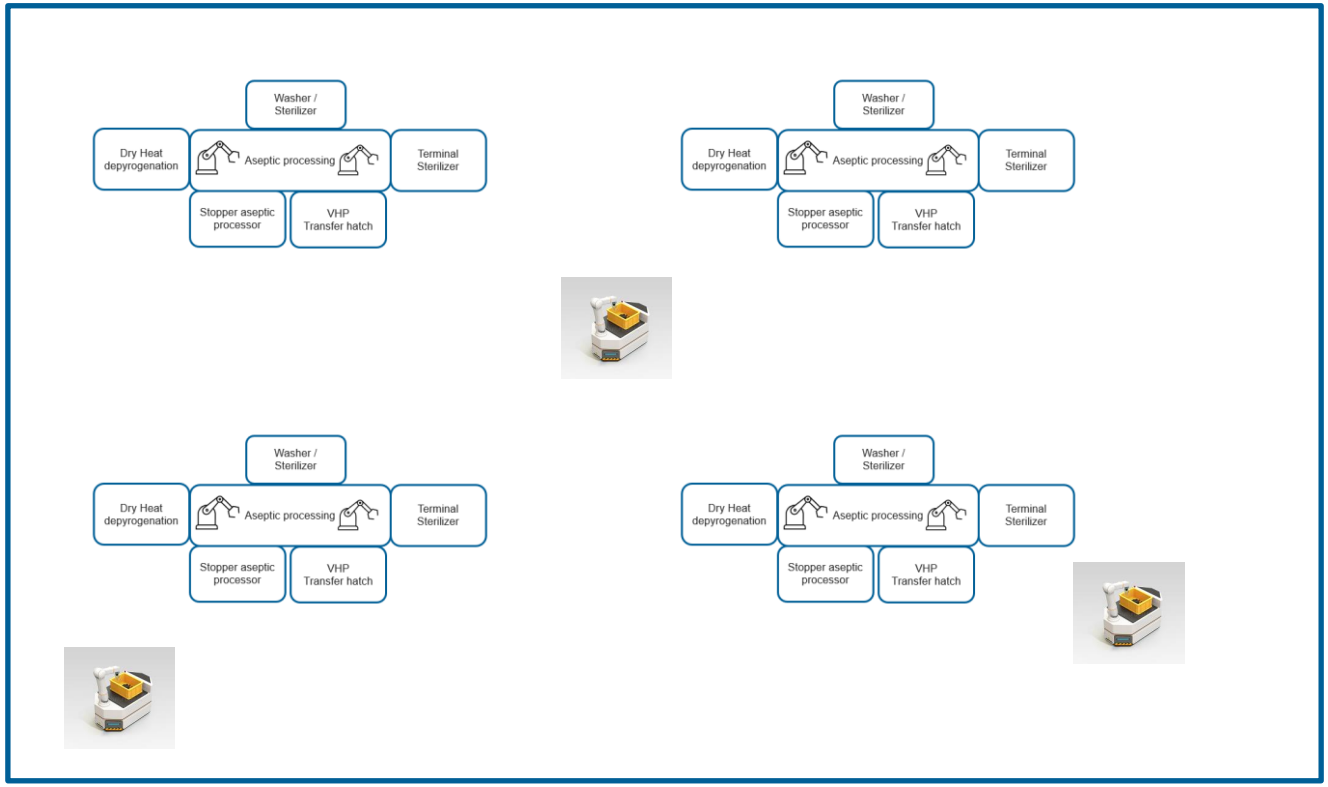
Terminal Sterilizer

Stopper aseptic processor

VHP Transfer hatch

Humanless Factory





Key takeaways

Key takeaways

- Innovation is a mindset
- Technology will allow a stronger CCS
- Predictive tools for a widespread application of QbD principles
- Advanced terminal sterilization methods to increase quality assurance
- Isolators and robotics are the basic elements for new challenging drugs
- Cluster concept for the factories of the future

References

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Thank you

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