POINTS TO CONSIDER FOR THE COMMERCIAL MANUFACTURING OF ATMPS

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- Studied Mechanical Engineering, GMP, Quality Control, Auditing, Hygienic Design, Pharmaceutical Engineering, Qualification/Validation
- PDA: Preventing Contamination and Cross Contamination
- PDA Isolator Expert Group
- PDA Program Committee for the EU ATMP
- PDA Advisory Board for ATMPs
- ISPE Chair CoP Containment and Chair Future Robotics
- ISPE Annex 1 Commenting Group

Your Presenter: Richard Denk, Nick Name Mr. Containment

- ISPE CoP SPP Sterile Product Processing
- ISPE Chair Containment Guide
- PICs/Annex 2 – 2A ISPE Comments Team
- ISO TC 198 Aseptic Processing and Isolators

The Commercial Manufacturing of ATMPs is a challenge to the Industry. Guidance is needed.

Introduction of the PDA Points to Consider Document for the Commercial Manufacturing of ATMPs. In the view of EU-GMP Annex1- PIC/s Annex 1 and PIC/s Annex 2A

Why a PtC for the Manufacturing of ATMPs?

EUROPEAN
COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

EUROPEAN
COMMISSION

Brussels, 22.8.2022
C(2022) 5938 final

GUIDELINES

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use

ANNEX 2A

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

ıethods employed in the manufacture of Advanced Therapy Medicinal Products
Ps) are a critical factor in shaping the appropriate regulatory control. ATMPs can
ined therefore largely by reference to their method of manufacture. For example,
ne therapy ATMPs, genetic modifications can be obtained through a variety of
ıds (e.g. viral & non-viral vectors, mRNA, genome editing tools). The genetically
ed cells can be of human origin (autologous or allogeneic) or animal origin
geneic cells), either primary or established cell lines. Genetically modified cells
terial origin are excluded from the scope of this annex. In a medicinal product,
enetically modified cells can be presented alone or combined with medical
s. This annex provides additional and specific guidance on the full range (as
d in the glossary) of ATMPs and the active substances that are used in their
facture. Although one of the objectives of this present revision was to prepare a
nent that would stand for several years the field is quickly changing; it is
nised that amendments may be necessary to accommodate technological

Contributors of the PtC for the Manufacturing of ATMPs

- Wide range of stakeholders
  - Various countries – Asia, Europe, Middle East, Americas, Australia
  - End users, equipment vendors, consumable vendors, etc.
  - Engineer, Quality, Product Manager, etc.
- Probably the first PtC with a good number of contributors from Asia

Points to Consider for the Manufacturing of ATMPs

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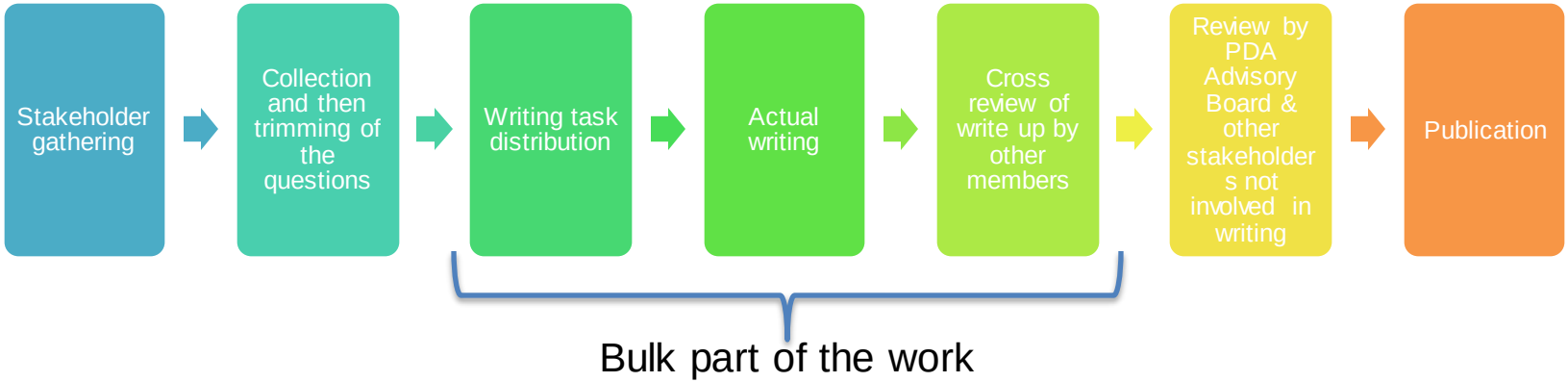
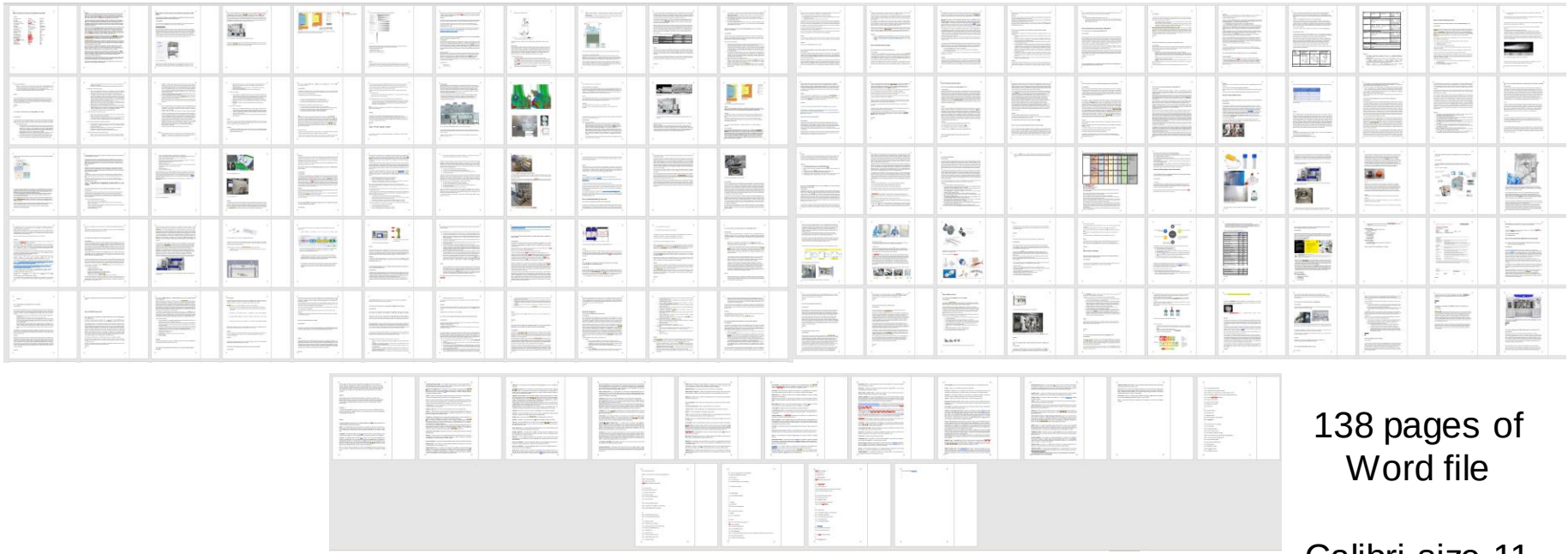
The process of actually writing this PtC



Content of the PtC for the Manufacturing of ATMPs

Topic 1: What are important aspects to be considered while designing an ATMP facility?	Topic 9: Disinfection & Decontamination
Topic 2: Pressure Concepts / Cascades	Topic 10: Cleaning and Hygienic Design
Topic 3: Design differences during project execution between BSC and Isolators	Topic 11: Transfer Technology / Closed Processes System
Topic 4: ATMP GMP (Manufacturing) requirements	Topic 12: Single Use Technology
Topic 5: Risk Management	Topic 13: Scale out approach for ATMP facility vs Scale Up Challenges
Topic 6: Contamination Control Strategy	Topic 14: ATMP Fill & Finish
Topic 7: Prevention of Cross contamination/ Product Mix Up	Topic 15: Sterility Test
Topic 8: Occupational Safety Requirements	Topic 16: Upcoming Technologies with Robots, Cobots (Sustainability)

Content of the PtC for the Manufacturing of ATMPs



138 pages of Word file

Calibri size 11

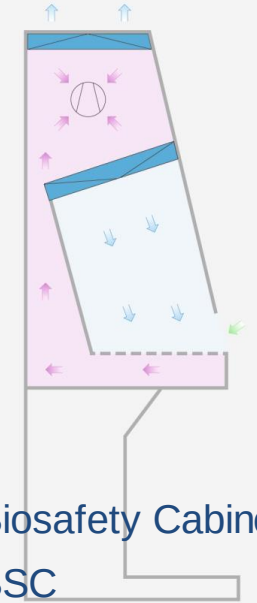
Topic 1: Important Points to Consider Manufacturing of ATMPs

- Which primary Containment Control can be used for your process?
  ATMPs often require very complex process structures.
  - Closed Single Use System
  - BSC Bio Safety Cabinets
  - BSC in combination with Single Use System
  - Isolators

- The primary Containment Control decides about your secondary Containment Control.

Topic 1: Important Points to Consider Manufacturing of ATMPs

Single Use System



Biosafety Cabinet

BSC

Isolator

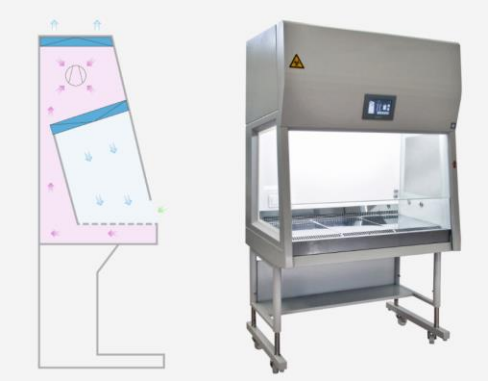
Topic 1: Important Points to Consider Manufacturing of ATMPs

- Pros.
  - Less investment Cost
  - No Cleaning after use

Courtesy Sartorius

- Cons.
  - Assembly could become very complex.
  - Integrity can`t be tested with all connectors, bags etc. before use.
  - Disassembly could become a contamination risk.
  - Waste handling and the inactivation of waste is critical.

Topic 1: Important Points to Consider Manufacturing of ATMPs



- Pros.
  - Less investment Cost
  - Operator Friendly

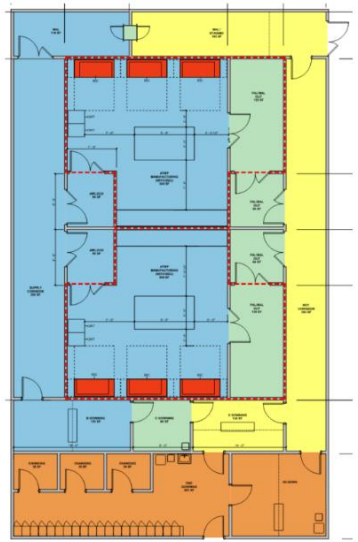
- Cons.
  - Operator gets in contact of aseptic-sterile operations
  - Not considered as a Barrier (According Annex 1)
  - Contamination from outside to inside and inside to outside most likely.
  - Contamination and Cross Contamination Risk.
  - Higher demand on the secondary containment
  - GMP and Occupational Safety (Many ATMPs requires BSL2 facility)

Topic 1: Important Points to Consider Manufacturing of ATMPs

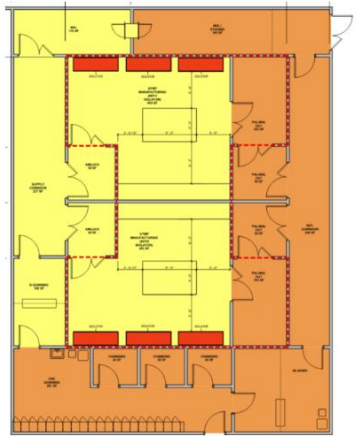
- Pros.
  - Validated Aseptic Conditions inside
  - Highest Protection of the Product and Operators
  - Lower demand on the secondary containment
  - Investment cost are compensated with the lower Secondary Cleanroom Level
  - Fast Decontamination times with vaporized Hydrogen-Peroxide possible.
- Cons.
  - Higher investment cost
  - Operator works through a Barrier
  - Contact with vaporized Hydrogen-Peroxide

Topic 1: Important Points to Consider Manufacturing of ATMPs

- Secondary Containment Control



BSC Option



Isolator Option

Annex 1 allows Grade D background for fully closed isolators.

Courtesy IPS

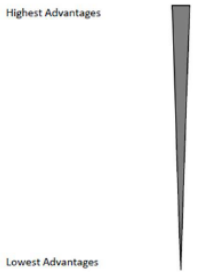
	Savings Over BSC Option
Facility SF	30%
Construction (Incl. Indirects)	44%

Topic 1: Important Points to Consider Manufacturing of ATMPs

- Secondary Containment Control

Further Comparison between BSC and Isolator for the facility Design:

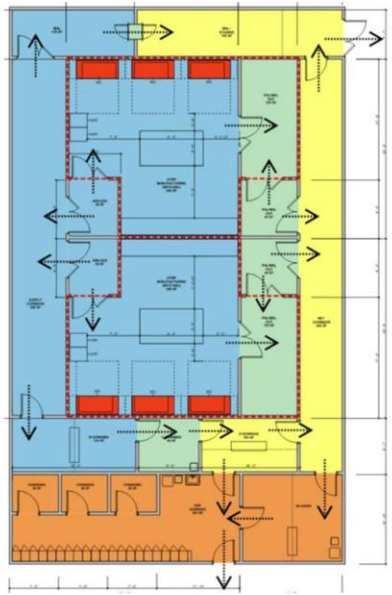
	Bio Safety Cabinet	Isolator
Quick time to market (short lead time)		
Capital expenditure savings (low initial invest)		
Low volume product: Operational costs		
Medium/large volume product: Operational costs		
Consumable savings, e.g. for Monitoring, Gowning, HVAC		
Contamination control		
Workers' safety		
Sustainability		
GMP Annex 1 Compliance		



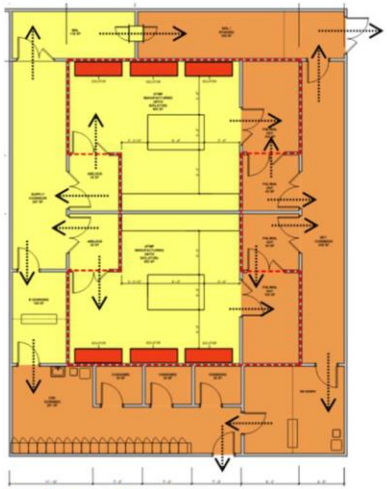
The capital expenditure (CAPEX) and operational expenditure (OPEX) costs for Bio Safety Cabinets and Isolators need to be evaluated considering the individual circumstances like:

- Manufacturing time (short or long)
- Complexity of the process
- Degree of automation (like robotics)
- Global Location of facilities (hourly rate)

Topic 2: Pressure Concepts



BSC Option



Isolator Option

Courtesy IPS

Topic 7: Prevention of Cross Contamination

- What are the Cross Contamination Risks.
  - Primary Containment isn`t good enough. Airborne Contamination- Contact Contamination- Waste Contamination.
- What else could be the risk of Cross Contamination
  - Potency of the material in multi product facilities.
  - Cells from the patient could be contaminated.
  - Working with Viral Vectors – higher Bio Safety Level

Topic 7: Prevention of Cross Contamination

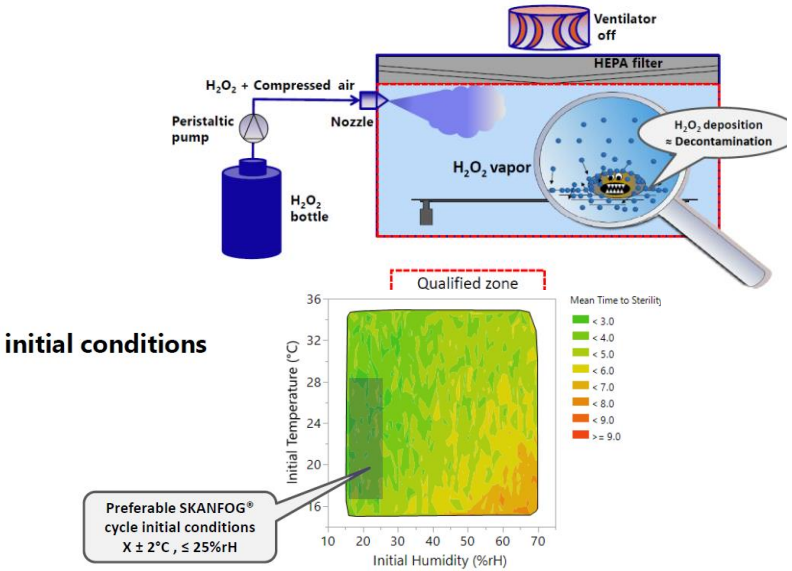
- What means Bio-Safety Level 2 during Manufacturing.

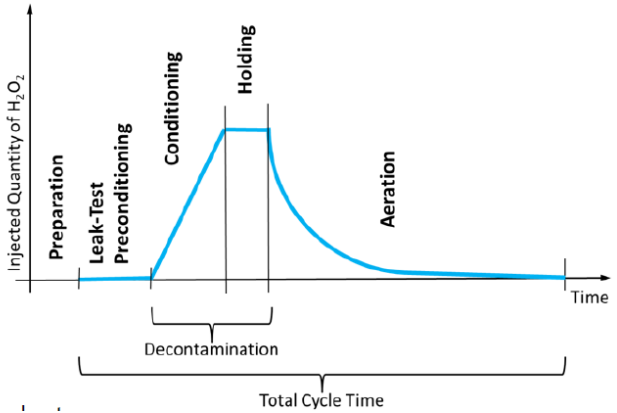
Considerations during Manufacturing.

- Spreading inside of the Barrier
- Risk of Spreading outside the Barrier
- Surface Contamination
- Occupational Safety Risk
- Cleaning and Inactivation
- etc

Topic 7: Prevention of Cross Contamination

- Surface Inactivation with atomized H_2O_2

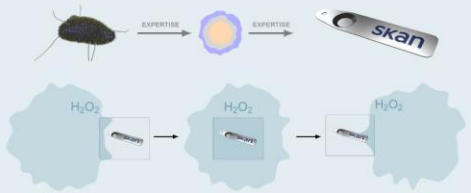




Topic 7: Prevention of Cross Contamination

BI`s for the proof of inactivation

Decontamination sensor ?



Smart Operations team

- Customer contact (order and information)
- Shipment managment (Parcel tracking, customs, GDP, cold chain)
- Lab. equipment management (Monitoring, qualification, calibration)
- Complaint management
- Material ordering process and stock management

Bioprocess team

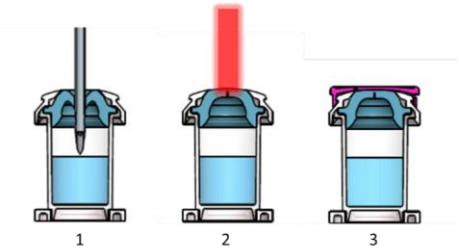
- In-house media preparation
- General pre-processing of materials
- Core production processes
- Ongoing R&D and technological watch on Bioprocess

Quality Control team

- Environmental monitoring program and hygiene control
- Material entry control program
- Change control and deviation management
- Certification
- Ongoing R&D and technological watch on QC methods

Topic 14: Fill & Finish

- Closed Vial Technology.



Pictures Courtesy AT Aseptic Technology

Topic 14: Fill & Finish

AT-Closed Vial® technology

Features

Easy to implement filling technology minimizing contamination risks and ensuring Container Closure Integrity at cryogenic temperatures.

- ⟶ Ready-to-fill closed vial
- ⟶ Scalable filling equipment
- ⟶ Full validation package
- ⟶ Excellent suitability for Cell and Gene therapies

Thank you