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2023 PDA ANNEX 1 WORKSHOP ATMP Part I

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#PDAannex1

Three Regulations:

EU GMP Annex 1: Manufacture of Sterile Medicinal Products (excludes ATMPs)

Part IV - GMP requirements for Advanced Therapy Medicinal Products (applicable to European Economic Area)

PIC/S Annex 2A: MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

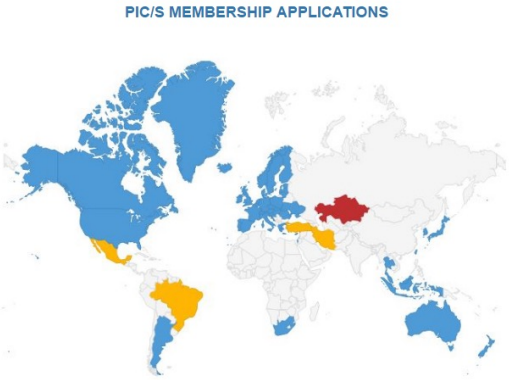
Applicability of Annex 1 to ATMPs:

PIC/S Annex 2A: Manufacture Of Advanced Therapy Medicinal Products For Human Use (Annex 1 in scope)

EEA: Part IV - GMP requirements for Advanced Therapy Medicinal Products
(Annex 1 not in scope)

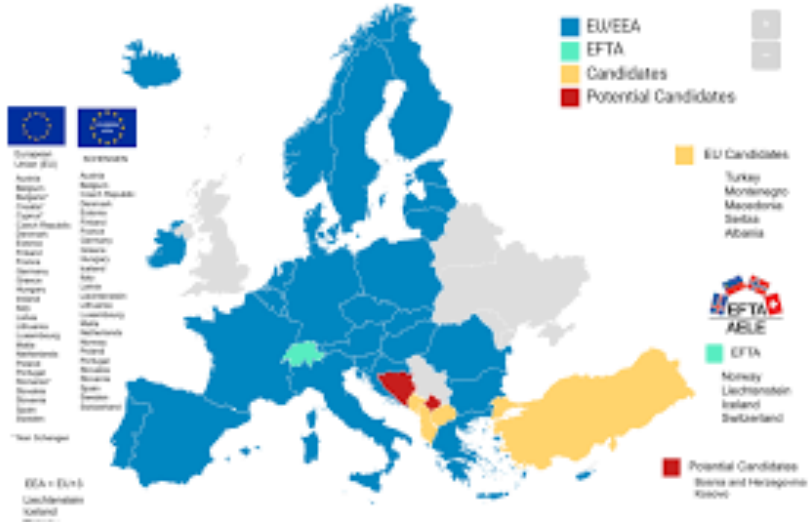
CH + UK:
Hybrid situation where both cases are true

Brief considerations on the reasons for divergences and introduction to the sensible approach:



Overview of PIC/S current 49 Members (blue); 5 Applicants (yellow); and 1 (Pre-) Applicants (red)

Applicants (5)	Pre-Applicants (1)
Brazil / ANVISA	
Iran / IFDA	
Italy (Vet) / DGSAF	
Mexico / COFEPRIS	Kazakhstan / CCMPA
Turkey / TMMDA	



Annex 1 relationships with EU GMP part IV and PIC/S Annex 2A:

- EU part IV, embeds an old draft of Annex 1 revision
- PIC/S Annex 2A, refers to Annex 1 adding, subtracting or modifying requirements where necessary

For MHRA unofficially yet, when the deficiency is found, reference is made to EU GMP Part I Chapters and annexes, followed by the corresponding Part IV reference.
There is a catch-all reference in the current Annex 1 that is used to link to Part IV
Processing
64. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.
Broadly the company has not done enough to protect the sterility of the product.
This is cited a lot.

Annex 1 relationships with EU GMP part IV and PIC/S Annex 2A:

For CH officially both EU and PIC/S versions of GMP are in force, when the deficiency is found, reference is made to EU GMP Part I Chapters and annexes, and by the corresponding Part IV reference. Or if is the case a deficiency will be cited only to the applicable code.
In practice, the preference of the inspector of the day…..

Content comparisons between PIC/S 2A, Part III and Part IV

ATMP Part IV	ATMP Part IV
1. Introduction Scope, Principle including PQS EudraLex Part 1 Chapter 1 / Part II ICH Q10	6. Documentation EudraLex Chapter 4, Annex 11 General principles, Specifications and Instructions, Records and reports, Other documentation, Retention of documentations, Traceability data
2. Risk Based approach EudraLex Part III / ICH Q9 PIC/S A2A 5.12 PIC/S A2A 1.2	7. Starting and Raw Materials (EudraLex Chapter 5, Part II) General principles, Raw materials, starting materials
3. Personnel EudraLex Part 1, Chapter 2, Annex 1 General principles, Training, Hygiene, Key Personnel	8. Seed lot and Cell Bank System (Detailed information)
4. Premises EudraLex Part 1, Chapter 3, Annex 1 PIC/S A2A Clauses 3.2 concurrent production; 3.12-3.14 adaptation principles for environmental monitoring General principles, Multi-products facility (Separation in place, time), Production Areas, Storage areas, QC Areas, Ancillary areas	9. Production EudraLex Chapter 5, Annex 1 PIC/S A2A 5.12 QRM and suitable premises grade General principles, Handling of incoming materials and Products, Utilities (water, medicinal gases, clean steam), Prevention of cross-contamination in Production, Aseptic Manufacturing, Other operating principles, Packaging, Finished products, Rejected, recovered and returned materials
5. Equipment EudraLex Chapter 3, 6, Annex 1 PIC/S A2A, 3.19 Bioinformatics General principles, Maintenance, cleaning and repair	10. Qualification and Validation Annex 11 and 15 PIC/S A2A 5.19 Qualification of premises and equipment (General principles, steps of the qualification process), Cleaning validation, Process Validation, Validation of test Methods, validation of transport conditions,

Content comparisons between PIC/S 2A, Part III and Part IV

ATMP Part IV	ATMP Part IV
11. QP and Batch release EudraLex and PIC/S Chapter 2, Annex 13, 16 PIC/S A2A 6.15 to 6.16 decentralized manufacturing release process and OOS General principles, QP, Batch release (Batch release process), Handling of unplanned deviation, Administration of OOS products	15. Environmental control measures for ATMPs containing or consisting of GMOs
12. Quality Control EudraLex Chapter 6, Annex 19 PIC/S A2A 6.14 short shelf-life products General principles, Sampling, testing, on-going stability program,	16. Reconstitution of product after batch release Reconstitution activities, Obligations of the ATMP manufacturer in connection with reconstitution activities,
13. Outsourced activities EudraLex Chapter 7 PIC/S A2A 7.1 outsourcing of collection and high specialized testing General principles, obligation of contract giver, obligation of contract acceptor,	17. Automated production of ATMPs General principles, Automated equipment, Personnel, Premises, Production and process validation, Qualified Person and Batch Certification
14. Quality defects and Product recalls EudraLex Chapter 8, Annex 13 PIC/S A2A 8.1 to 8.3 adaptations for short shelf-life products Quality defects, product recalls and other risk-reducing actions	18. Material Classification and applicable GMP PIC/S Annex 2A Introduction table and figures and 5.23 (PRP based)

ATMP Part IV	Comparisons
Pharmaceutical Quality Systems	Annex 1: refer to Chapter 1, detailed information what needs to be cover and who is responsible. Part IV: Mention Phase appropriate GMP concept. Lacking information regarding Risk Management, RCA, Management oversight etc. This document does indicate to assess effectiveness of QA systems and trend analysis as part of annual Quality review. Does not refer Q10.
Risk Based approach (RBA)	• Part IV: Allows risk-based approach to all types of ATMPs due to limited knowledge in early phase and nature of the product. **Informal RM** process is acceptable. Quality and Safety needs to be ensured from early phase. Good examples are given on RBA with benefits and limitations. • Alternate microbiological test method (e.g. Sterility test) is accepted. • Exceptions for appearance test including particulate test. Simulated samples: water runs accepted? • Waive stability program for short life ATMPs. • In early phase Grade A with C background is acceptable with RA. ***But it is not clear why agreement from competent authorities (agreement of both the assessors of the clinical trial and the inspectors of the site) are needed, who will receive it, how and what stage?*** • Allows less frequent calibration, PM based on RA, wider Spec during early phase etc.

Section by Section discussion

ATMP Part IV	Comparisons
3. Personnel General principles, Training, Hygiene, Key Personnel	• Need to have product knowledge and traceability of product: Good. Additional training requirement for GMOs to prevent cross-contamination and risk to environment. • Requirement of Biosafety officer by Sr management, when GMO present.
4. Premises General principles, Multi-products facility (Separation in place, time), Production Areas, Storage areas, QC Areas, Ancillary areas	• Provides clear instruction on multi-product facility including infectious virus: areas including HVAC segregation based on RA is required. Specific section on separation in place or time allowed (e.g. 100% air exhaustion for isolators in same room). • Specific information provided on QC areas and ancillary areas which is not clear in Annex 1. • No specific section Disinfection of cleanrooms as stated under Annex 1.
5. Equipment General principles, Maintenance, cleaning and repair	• Some good details are available including section 10.

ATMP Part IV	Comparisons
6. Documentation General principles, Specifications and Instructions, Records and reports, Other documentation, Retention of documentations, Traceability data	Great details of information available. Annex 13 can be referenced for more details on Product Specification File. Information on blinding requirement is clear. Chapter IV, Annex 11 has additional information that people will find helpful.
7. Starting and Raw Materials General principles, Raw materials, starting materials	There is an acknowledgement of use of research grade material but need to be risk assessed. Good discussion on critical RM. For details of supplier qualification, not much information provided including Quality agreement etc. Someone can also refer to Chapter 5.
8. Seed lot and Cell Bank System	Detailed information including GMP requirement for cell banks.
9. Production General principles, Handling of incoming materials and Products, Utilities (water, medicinal gases, clean steam), Prevention of cross-contamination in Production, Aseptic Manufacturing, Other operating principles, Packaging, Finished products, Rejected, recovered and returned materials	Good details. First time referencing other Annexes (1, 11) for sterilization and validation. The current version of Annex 1 has more details on Utilities compared to ATMP.

Section by Section discussion

ATMP Part IV	Comparisons
10. Qualification and Validation Qualification of premises and equipment (General principles, steps of the qualification process), Cleaning validation, Process Validation, Validation of test Methods, validation of transport conditions,	Good clarification on expectation when a facility needs requalification in case of new product introduction. Acknowledgement of FG variability due to variability of starting materials. Allows use of surrogate materials for PV. Concurrent validation is acceptable in some cases. Reference of Annex 11 for computer system validation. Some information / principles regarding QbD, concurrent validation etc. are not clear. Phase appropriate test method validation is acceptable other than safety related test, they must be fully validated from early phase.
11. QP and Batch release General principles, QP, Batch release (Batch release process), Handling of unplanned deviation, Administration of OOS products	Good examples are provided including testing outside EU and de-centralized manufacturing. Involving of QP for deviation as appropriate. Provision for OOS product is mentioned under certain conditions. Some details are lost compared to Annex 13 and Annex 16.
12. Quality Control General principles, Sampling, testing, on-going stability program,	Due to sample scarcity, in some cases 2X reference sample is not needed. Also, the storage condition can be different for reference sample than actual product to increase stability. Photo retain is acceptable. Good examples of sampling plan strategies (end to end). No discussion on OOS and documentation requirement.

ATMP Part IV	Comparisons
13. Outsourced activities General principles, obligation of contract giver, obligation of contract acceptor,	The "Contract" information compared to Chapter 7 is missing. Roles and Responsibilities in case of quality defects is required, this is good clarification.
14. Quality defects and Product recalls	Good details are present but at the same time Chapter 8 can be referenced for more information. Acknowledgement of mock recall in some cases not possible, due to short shelf life. Unclear guidance on adverse event reporting, contractual agreement for responsible parties compare to Chapter 7.
15. Environmental control measures for ATMPs containing or consisting of GMOs	New section emphasizing on risk to environment, containment requirement, flow of material, personnel and decontamination measures that must be in place.
16. Reconstitution of product after batch release	Important new section explaining the requirement on reconstitution, validation of the reconstitution process including impact to SISPQ, at the administration site for ATMPs only.
17. Automated production of ATMPs	New section with good details explaining how automated system can be utilized in ATMPs, APS, etc.

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2023 PDA ANNEX 1 WORKSHOP ATMP part II

with also considerations for low bioburden products

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Low Bioburden products

The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as:

- contamination control strategy
- design of premises
- cleanroom classification
- qualification, monitoring and personnel gowning

may be used to support the manufacture of other products that are not intended to be sterile such …… low bioburden biological intermediates but where the control and reduction of microbial, particulate and pyrogen contamination is considered important.

Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

IF THERE IS ONLY ONE TAKEWAY FROM THIS MESSAGE WOULD BE:

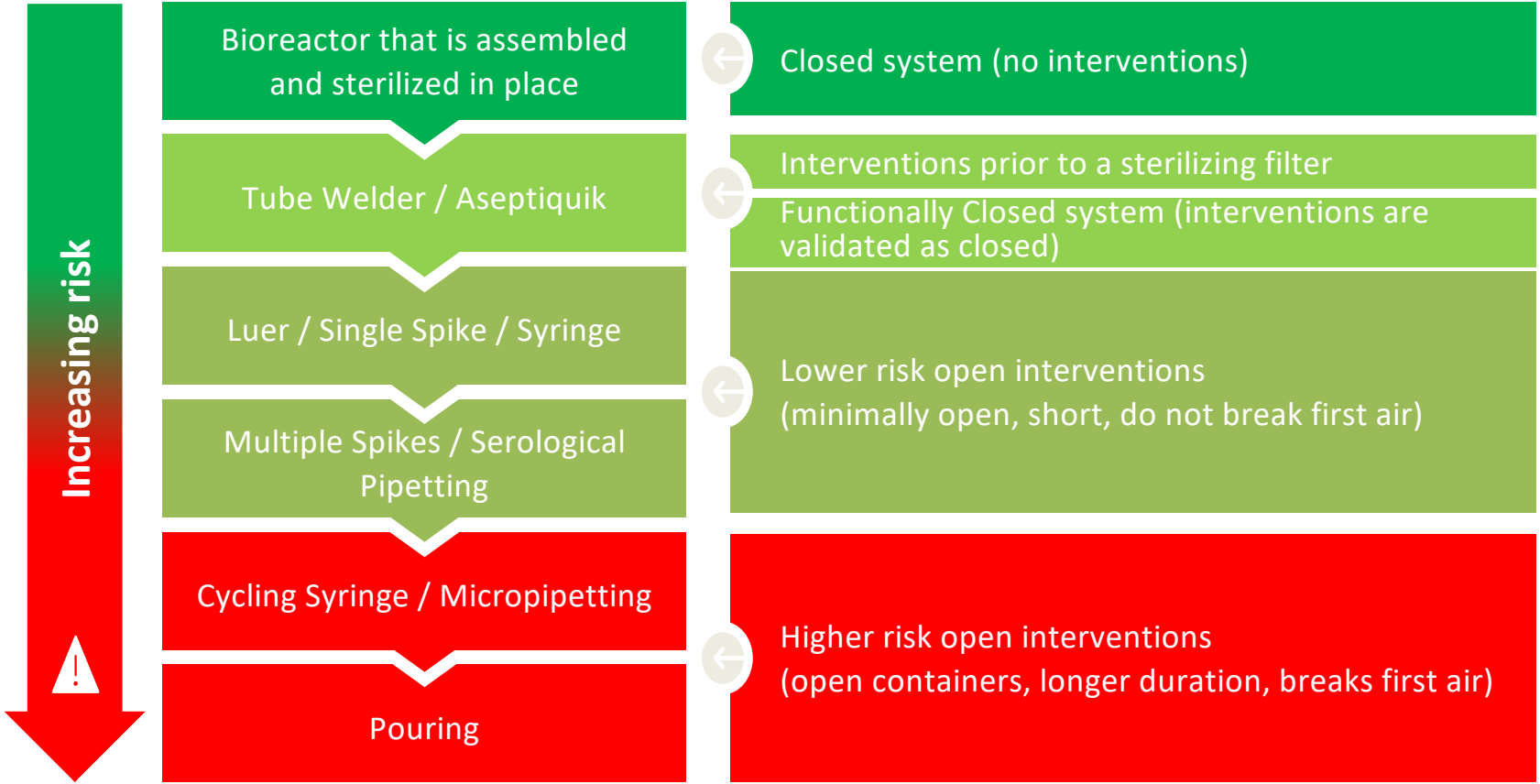
“ STATE THE PRINCIPLE AND THE RATIONALE AGAINST WHICH PART OF ANNEX 1 ARE GOING TO B
CONSIDERED, IN A VERY CLEAR AND DETAILED WAY”

WORST MISTAKE I HAVE SEEN IS “ We comply with Annex 1 principles”

Low Bioburden products

HOW CAN WE BASE THE RATIONALE AND THE JUSTIFICATION?

Sterility and Aseptic manipulations: Closure of process

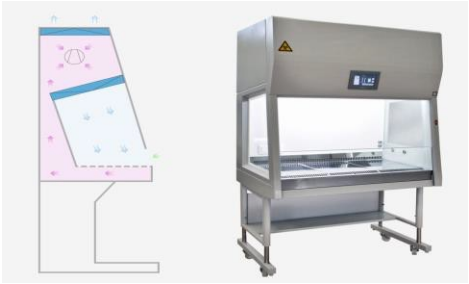


Once assessed the process:

1) **Think about what would be your worse case scenario in 5 years time**
2) **Use the outcome of the risk assessment to design/adjust the facility**
    1) Consider if the adjustment have any impact on the risk
3) **Identify and refer to the specific part of the Annex to justify and specify the cleanroom classifications**
4) **Design the qualification, monitoring and gowning on personnel to match or further mitigate the facility/process risk**
5) **CCS will be discussed together with the ATMPs**

What are the major driver for the new Annex 1

- CCS
- QRM
- Key operators out of critical aseptic operations
- Barrier Technologies



PIC/S

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

World Health Organization

Not all ATMPs are equal:

In general:

- If you can “sterilize” you should do it by whatever appropriate technology is compatible with the product
- If you can’t sterilize, there is an obligation to put in place all measures to “ not add” to the existing bioburden
- Do not add refers also to consideration on concentration or increasing of existing bioburden to level that can cause harm

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods (e.g. virus removal or inactivation). The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems and sterile disposable product-contact equipment can significantly reduce the risk of accidental contamination and cross-contamination.

Specific consideration related to interactions between PIC/S Annex 2A and Annex 1

3.11 provides one of the many links with Annex 1 and address some specificities of different ATMPs:

3.11 Where processes are not closed and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process, (e.g. during additions of supplements, media, buffers, gasses, manipulations) appropriate environmental conditions should be applied. For aseptic manipulations parameters in line with Annex 1 (i.e. Grade A with Grade B background) should be applied. The environmental monitoring program should include testing and monitoring of non-viable contamination, viable contamination and air pressure differentials. The monitoring locations should be determined

Specific consideration related to interactions between PIC/S Annex 2A and Annex 1

3.12 and 3.13 provide for some exceptions:

3.12 Only in exceptional circumstances when an appropriate environment is not available, a less stringent Section 3.11 above may be appropriate

3.13 For closed systems, a lower classified area than Grade A in background Grade B might be acceptable based on the outcome of a QRM assessment. The

(b) If the closed system can be shown to remain integral throughout the entire usage, a background of Grade D might be acceptable.

Requirements of Annex 1 regarding the provision of closed system should be considered.

Specific consideration related to interactions between PIC/S Annex 2A and Annex 1

Concurrent production provisions: Use of BSCs and Isolators

3.2 Concurrent production of two or more different ATMPs/batches in the same area might be permitted due to adequate operational and/or technical control where justified under QRM principles applied across the entire sequence of manufacturing steps. For example:

(a) The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials.

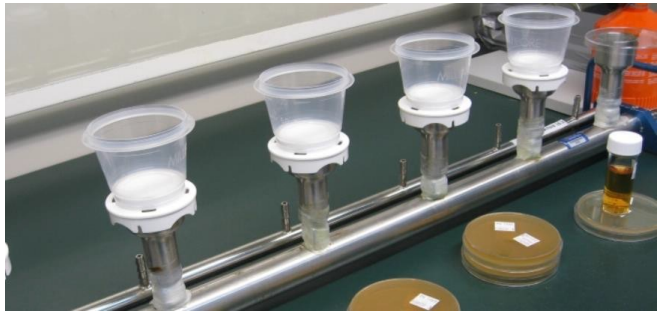
(b) When more than one isolator is used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility (i.e. no recirculation). In addition, in case of concurrent production of viral vectors, it is necessary to provide for closed, separate and unidirectional waste handling.

(c) The possibility of using more than one biosafety cabinet (BSC) in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities. The simultaneous use of more than one BSC entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid risks to the quality of the product and any mix-ups. The rationale should be justified based on QRM principles.

(d) The use of multiple closed systems in the same area is permitted, in the case that their close state can be demonstrated. (refer to point 3.13.)

Control Strategy can be used to address acceptable Bioburden

5.25 For products where final sterilization is not possible and the ability to remove microbial by-products is limited, the controls required for the quality of materials and on the aseptic manufacturing process assume greater importance. Where a C TA or MA provides for an allowable type and level of bioburden, for example at the ATMP active substance stage, the control strategy should address the means by which this is maintained within the specified limits.



Sterility and Aseptic manipulations

Aseptic Process Simulations

Frequency
Representative of the process

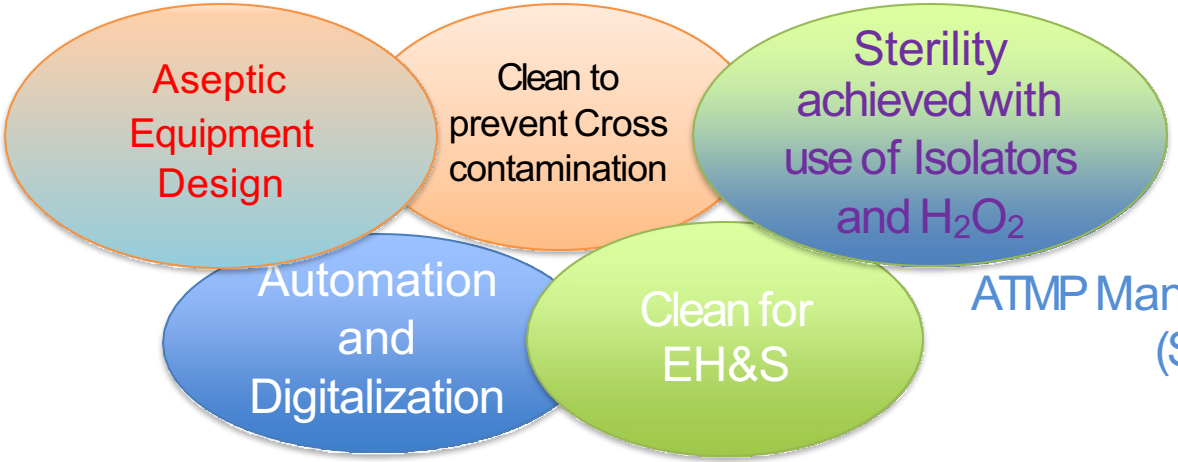
- **APS design can be challenging with multiple shifts per day and multiple processing days and large volumes of media. Combining process days into one APS design, modular APS, and Operator specific APS can help build a holistic program.**
- **The new Annex 1 includes more stringent APS requirements: Where manual operation (e.g., aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator.**
    - What do we do in general with Annex 1 , annex 2A was written at a time the A1 was in draft and despite all efforts some contradictions may arise (see above, the case may end up in a facility running APS and have no other time for actual product!)

Sterility and Aseptic manipulations

Sterility test methods

- Small volume products
- Sampling of tissues
- Different GMP status of labs in different jurisdictions
- Rapid Test ?

Example of a possible Contamination Control Strategy for ATMPs



ATMP Manufacturing control (Skan AG)

Some Exceptions for discussion

- Environmental conditions: Isolator for cell therapies? What to do when the same facility is used for different ATMPs?
- Process Simulation: What is needed for different ATMPs?
- Real-time release: How industries are planning to implement?
- Reference and Retention samples: Sometimes may not be available, how you are planning filing strategies?
- A/C Background: How to get clarity for QPs for a consistent approach?
- How can you use PIC/S 2A in jurisdictions where is not mandated?
- If a facility is making both ATMPs and other Biologics: how to implement both?