



DESIGN CONSIDERATIONS FOR ATMP PREMISES FROM THE EU POINT OF VIEW

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Guidelines on Good manufacturing Practice specific to Advanced Therapy Medicinal Products

EUdraLex, The Rules Governing Medicinal Products in The European Union, Volume 4

- These guidelines do not intend to place any restraint on the developments of new concepts of new technologies.
- Describes the standard expectations.
- Alternative approaches can be implemented if it is demonstrated that these are capable of meeting the same objective.



QUESTIONS TO BE ASKED

- Will it be a single or a multi-product facility?
- Assuming that the final product is supposed to be sterile
 1. Is it an aseptic process?
 2. Are open manipulations involved or is it a closed (automatic) process?

EXAMPLES OF MULTI- PRODUCT

- Starting material is different, eg stem cells and T-cells.
- Autologous treatments.
- Similar starting material, different process, different final product.
- Different vectors.

Slide 4

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Annie Rietveld, 5/4/2019



Multi-product facility

- Manufacture in a multi-product facility is acceptable
- Special precautions should be taken to avoid the mixing of autologous materials.
- The risk of cross-contamination should be assessed.



Measures to prevent cross-contamination (1)

- Segregated premises.
- Dedication the whole manufacturing facility or a self-contained production area on a campaign base.
- Handling of viral vectors should take place in a segregated area and in a biological safety cabinet or an isolator.
- Use of “closed systems” for processing and material/product transfer between equipment.



Measures to prevent cross-contamination (2)

- Use of air-locks and pressure cascade.
- Appropriate cleaning between each batch.
- Adequate measures to handling waste, contaminated rinsing water and soiled gowning.
- Imposing restrictions on the movement of personnel.



Measures to prevent cross-contamination (3)

- The totality of the measures applied should assure the absence of cross-contamination. Sole reliance should not be placed on any terminal process or finished product test.
- Periodic review of the effectiveness of the measures implemented.

Concurrent manufacturing of different batches/products (1)

- Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities as follows:
 - The use of more than one closed isolator in the same room is acceptable.
 - When two isolators are used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility. In addition, it is necessary to provide for closed, separate and unidirectional waste handling.

Concurrent manufacturing of different batches/products (2)

- Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities as follows:
- The possibility of using more than one biosafety cabinet in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities (e.g. strict material and personnel flow defined, no crossing lines in the use of equipment in the same room etc.) Demonstration required that the measures implemented are effective to avoid risks to the quality of the product and mix-ups.

Concurrent manufacturing of different batches/products (3)

- Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities as follows:
- A manufacturing activity in a clean room hosting an incubator which is used for a different product is acceptable, as long as there is separated expulsion of exhausted air from the incubator.

Concurrent manufacturing of different batches/products (4)

- Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities as follows:
- The simultaneous incubation/storage of different batches within the same incubator as long as.....
- However the simultaneous incubation/storage of replication competent vectors/products based on them with other materials/products is not acceptable.



Design and construction

- Separation of flows of non-sterile and used materials and equipment from those sterilized.
- Depending on specific risks of the product, the use of single pass air systems should be considered.
- Clean/contained areas should be accessed through an airlock with interlocked doors. The final stage of the air lock should, in the at-rest state, be the same grade as the area into which it leads.

Aseptic environment (1)

- Classifications of clean rooms should be done according to ISO 14644-1.
 - For qualification, the airborne particles equal to or greater than $0.5\ \mu\text{m}$ should be measured (at rest and in operation).
 - The microbial load of the clean room in operation should be measured as part of the qualifications.
- For grade A areas, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.



Aseptic environment (2)

- Monitoring of the $\geq 5.0 \mu\text{m}$ particle concentration is required for routine monitoring purposes.
- Continuous viable particle monitoring is required during critical operations where the product is exposed to the environment.
- With a view to identify potential changes the alert limits for grades B to D should be lower than those specified as action limits.



Aseptic environment (3)

- Detected microorganisms in a grade A area should be identified to species level.
- To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas.
- Pressure cascades should be clearly defined and continuously monitored.
- For containment reasons negative pressure in specific area may be required.



Aseptic manufacturing

Closed system (1)

- For production in an isolator or positive pressure isolators; a background clean area of grade D is acceptable.
- The transfer of materials into and out of the isolator is one of the greatest potential sources of contamination and appropriate control measures should put in place.
- When materials are added/withdrawn from the closed system without an aseptic connection (e.g. use of sterile connectors, filters), the system can no longer be considered closed.



Aseptic manufacturing

Closed system (2)

- In exceptional circumstances , closed systems may be placed in a controlled but not classified environment. This sometimes is necessary in case the material is obtained from a patient in the operating theatre and manufacturing also takes place in the operating theatre. This is only acceptable in exceptional cases and the product should not be exposed at any moment to the environment (e.g. supporting data from leak testing and pressure check of the equipment).



Aseptic manufacturing

Open system (1)

- A critical clean area of grade A with a background clean area of grade B is required for aseptic preparation and filling.
- Preparations of solutions which are to be sterile filtered during the process can be done in a clean area of grade C.
- The use of technologies such as *e.g.* processing inside disposable kits, incubation in closed flasks, bags or fermentors in a grade C environment may be acceptable.



Aseptic manufacturing

Open system (2)

For the manufacturing process of viral vectors, the following considerations apply:


- ❖ The expansion phase before the sterilising filtration can be performed in a critical clean area of grade A with a background clean area of grade C.
- ❖ The sterilising filtration and filling needs to be performed in a critical clean area of grade A with a background clean area of grade B.



Aseptic manufacturing

Open system (3)

- For introduction of articles in a clean area the use of double-ended sterilisers sealed into a wall or other effective procedures (e.g. H₂O₂ locks) should be used.
- Sterilisation of articles elsewhere is acceptable provided that there are multiple wrappings.
- When sterilisation of articles is not possible, a strictly controlled process should be implemented to minimise the risks.



Aseptic manufacturing

Open system (4)

- In-line sterilising filters should be used for routine addition of gases, media, acids or alkalis, anti-foaming agents, *etc.* to bioreactors should be used where possible.



Automated production of ATMPs

- Certified equipment for the intended use according to EU medical device legislation (CE mark) is not sufficient to demonstrate suitability as required for under the ATMP guidelines.
- All regular GMP requirements as qualification, maintenance, calibration etc. apply.
- The automated equipment should only be used under conditions that ensure aseptic processing.

Thank you for your attention.