10 good reasons to use an Isolator (closed system) rather than a Clean Room (open system) for the production of advanced therapy drugs (ATMPs)
Advanced Therapy Medicinal Products (ATMP) represent a new category of medicines with a wide therapeutic potential for treating different types of diseases such as cancer, neurodegenerative and cardiovascular diseases. ATMPs represent a continuous challenge not only for the improvement of the pathological conditions of millions of patients, but also for the development of innovative high-tech systems for the production of safe and effective drugs in “cell factories” in accordance with Good Manufacturing Practices.

The development of new generation technological solutions arises from the need to simplify the work-flow of even very complex processes in closed and automated systems.

**Why choose a closed system (Isolator) instead of an open system (Clean Room) in a cell factory?**
Isolators, closed systems, represent an advantageous alternative to use of Clean Rooms, open systems, for Advanced Therapies production.
Let's find out why.
1. Separation product/operator

The physical separation between product and operator allows a greater degree of safety for both the drug and the operator.

EUDRALEX Vol. 4, Annex 1 2020, states, on this specific topic, in paragraph 4.3, that: “[...] Isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of [...] Isolators should be justified.”¹ So if for a given system, the choice was to use a Clean Room instead of an Isolator, this alternative approach should be justified.

2. Installing a Grade A closed system in a class D

The possibility of installing a Grade A closed system in a class D (A in D) *simplify the operating procedures relating to personnel flow, gowning procedure, validations, infrastructure complexity*, compared to the use of Grade A Safety Cabinets (ISO 4.8) in a Grade B Clean Rooms (open system or A in B).

<table>
<thead>
<tr>
<th>Grade</th>
<th>At rest</th>
<th>In operation</th>
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<tbody>
<tr>
<td></td>
<td>0,5 µm</td>
<td>5 µm</td>
</tr>
<tr>
<td>A</td>
<td>3520</td>
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<td>B</td>
<td>3520</td>
<td>29</td>
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<tr>
<td>C</td>
<td>352000</td>
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<tr>
<td>D</td>
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Maximum permitted airborne particulate concentration during classification.
3. Economic saving of the facility’s operating costs

A closed system allows an economic saving of the facility’s operating costs of the order of 70% compared to an open system.

The savings were estimated by comparing two systems, respectively, a Grade B Clean Room with Biological Safety Cabinets (BSCs) for Class 4.8 (A in B) and a Grade D Clean Room in which an Isolator with a Grade A work area was installed (A in D), for the production of ATMPs.

The energy consumption, which in the case of the Clean Room A in B is onerous given the complexity of the HVAC systems to guarantee the zones in Grade D, C and B respectively, are greatly reduced when managing only the Grade D zone where an isolator is installed.

In addition to impacting on the operators, the gowning is a non-negligible running cost which in the case of the use of an Isolator is reduced by more than half, since the complete suit required for open systems is not necessary for A in D closed system solutions.

In terms of validation, the savings for the qualification of a smaller system is certainly a further not negligible aspect. The maintenance of a Clean Room over time remains of high economic impact which does not happen in the case of a closed system.
4. Easy control and monitoring

A closed system in a confined space is more easily controlled. A physically confined space is easily kept under control from all points of view. All system parameters are easily monitored through the system management software. Technical maintenance can often be carried out remotely without requiring to stop scheduled work activities.

- Smaller environment allowing easier monitoring and control;
- Increase of the stability of the environmental parameters in the working area;
- Possibility to install different units in a same room (independent alternative working area in case of problem).
5. Reduced space

With the same size of Grade A areas dedicated to production (in closed systems the work area of the Isolators, in open systems the work areas of the BSCs), reduced classified areas are required to install more Isolators in an A in D closed system, compared to an open system A in B solution.

It can be demonstrated that an Isolator allows approximately a 47% saving on the square meters needed for a Clean Room due to the passage from different Grades D, C, B required when using open systems.

INFRASTRUCTURAL REDUCTION

- Only Grade D surrounding environment required;
- Reduction of the central air conditioning system; No need for specific consumable;
- Reduction of used surface.
6. Quick and easy cleaning and decontamination

Cleaning and decontamination operations are simplified and faster by using \( \text{H}_2\text{O}_2 \) vapours and manual cleaning is streamlined. The same can be said of the validation and requalification operations.

Cleaning and decontamination operations in cell factories constitute a real process to be validated and applied in accordance with the regulations of Annex 1. These operations are entrusted to appropriately trained specialized personnel. A closed system is 100\% sterilisable with hydrogen peroxide in a completely automatic way. Manual cleaning of the isolator confined areas is also simplified given the possibility of reaching every point of the work area by the same operators who can thus sanitize the internal space of the Isolator at the end of the day.

Validation and qualification operations are more streamlined due to the limited space, the possibility of remote intervention and without the need to stop the systems for long periods as is the case in a Clean Room.

- Faster Qualification/Validation;
- Decrease in process time (no need for operator to progressively pass from a class D to a class A, no need for specific clothes);
- Decrease of decontamination time (\( \text{H}_2\text{O}_2 \) vapour).

TIME REDUCTION
7. Flexibility and process adaptability

The closed system is flexible and adaptable to different processes that can be implemented in different times and places.

Different processes can be implemented in an Isolator without problems. After sterilization with $\text{H}_2\text{O}_2$ vapours, the system is completely decontaminated and ready for the management of new production processes. The Isolator can be easily transferred from one place to another, a feature of flexibility that is practically impossible with a Clean Room.
8. Traceability of the production process

The SCADA software and the PLC specifically developed and designed for these applications make it possible to simplify all process traceability activities in accordance with GMPs in accordance with GAMP-21 CFR part 11 and Annex 11 of Eudralex Vol. 4.

The traceability of the production process is the foundation of GMP and its management requires an enormous effort by the operators who often find themselves having to manually note the various steps in the Clean Room. In an Isolator, the SCADA is a fully integrated system that can keep track of the entire process to be submitted to the authorities and for filing purposes in a single report.
9. Bioconfined transfer systems

It is possible to use bioconfined systems to move the preparations inside and outside the Isolator.

A weak point that is often indicated in the use of an Isolator compared to the Clean Room is related to the reduced space available that does not allow to manage large-scale productions. The concept of bioconfinement overcomes this limitation and further simplifies the workflow of handling finished and semi-finished products.

IsocellBIOBOX® is a new tool that allows the transfer of cultured cells in a sterile and bioconfined environment. The use of IsocellBIOBOX® allows the cells contained in flasks, which have been prepared in the Grade A work area of the Isolator, to be removed from the Isolator and incubated in standard external CO₂ incubators.

In addition to cell transfer, the IsocellBIOBOX® keeps the cells of different patients safe from cross-contamination, drastically reducing equipment costs, compared to other solutions that use specially designed CO₂ incubators.
The bioconfined systems used for the handling of the finished and semi-finished products in aseptic conditions, protects them from cross-contamination.
10. More productivity, less stress for the operator

Working in Grade D environments reduces stress: operators can work for more than 4 consecutive hours with a limited level of stress compared to what happen in open systems Grade B Clean Rooms and therefore greater attention can be applied to the production process.

IsocellPRO® Advanced Therapy Isolator

1. TRANSFER HATCH
   from D (ISO 8) to A (ISO 4.8).

2. WORKING AREA
   Grade A (ISO 4.8)
   Airflow and Positive Pressure
   Unidirectional airflow
   Sterilization with H2O2 vaporisation.

A. Microscope
   The working area with integrated microscope allow fast and easy observation without the need to leave the clean area.

B. CO2/O2 Incubator
   The incubator is a custom device design to fit into an isolator environment connected to the SCADA system.

C. Waste System
   The bin is placed below the isolator and has an opening RTP port inside the working area.

D. Control System
   Integrated SCADA managing system.
Conclusion

In a nutshell, the use of Isolators guarantees a very high level of protection against the risk of product contamination. At the same time, operators work comfortably in a safe environment.

The production of Advanced Therapy drugs in closed systems, thanks to their flexibility and limited management costs will be optimised and simplified, ensuring at the same time a strict GMP environment and providing a tool for easily reproducible work even for large-scale production at a running cost generally considerably lower than a classic cleanroom approach.
Thanks for your attention.