Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

A report /critical evaluation identifying barriers to fully enclosed production / common manufacturing standards for exemplar products

Funded by

UK Research and Innovation

Coordinated by

CATAPULT Cell and Gene Therapy

Advanced therapy medicinal products (ATMPs) are medicines for use in humans that are derived from cells, genes or tissues. The current portfolio of ATMPs are all aseptically manufactured sterile products. Due to the nature of the products it is highly unlikely that they can be subjected to a process of terminal sterilisation, therefore the closing systems used for manufacture are key to gaining appropriate sterility assurance for these products.

In addition to sterility assurance there are a limited number of manufacturers and an exponential growth in the field of advanced therapies. This combination has driven the desire to have multi-product manufacture within the same facility. This concept of multiproduct facilities is discussed within the European Commissions 'Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products'[1] (GMP for ATMPs). A key concern with multiproduct facilities is the robust segregation from one product to the next, it is accepted that closing the methods of manufacture is one important element in achieving this objective.

The concept of a closed system for manufacture can vary within the setting concerned. Conventional hospital pharmacies prepare medicines under the Section 10 exemption to the medicines act and one of the five conditions permitting this to occur includes the exclusive use of closed systems. In this context the standards consider that a single withdrawal from an ampoule is a closed system, despite the open nature of the broken ampoule top into which a needle is inserted for withdrawal and also allows for aseptic manipulations to be considered closed, despite the situation where the tips of syringes etc. will briefly be open to the surrounding environment.

With ATMPs the following factors increase the risk when compared to the above situation;

- The complexity of the manufacture
- The increased likelihood that the culture media and medium for final formulation will support microbial growth
- The length of time taken for manufacture
- The conditions for incubation would support the growth of common human pathogens

During the consultation period for the 'GMP for ATMPs' guide there was considerable demand that a definition of 'closed systems' with reference to ATMP manufacture was included with the guidance, particularly given that this term is used very frequently through the document.

The European Commission has addressed these requests and the final published version contains the following definition;

12. Closed system: A process system designed and operated so as to avoid exposure of the product or material to the room environment. Materials may be introduced to a closed system, but the addition must be done in such a way so as to avoid exposure of the product to the room environment (e.g. by means of sterile connectors or fusion systems).

A closed system may need to be opened (e.g. to install a filter or make a connection), but it is returned to a closed state through a sanitization or sterilization step prior to process use.

In response to the demand for closed systems for ATMP manufacture, multiple commercial companies have started to offer solutions to close the most common elements of manufacturing processes. Additionally established companies have broadened the portfolio of their offerings in response to this increased demand. The cost of these closed system solutions can be considerable, and the time to market can be significant due the validation required for these products and as many of these are sold as registered medical devices.

In contrast to the relatively slow process of developing closed manufacturing systems, the number of ATMP developers has exploded and the field is evolving faster than pharmaceutical legislation or device development.

It is uncommon for commercial solutions for closed systems to be available for atypical methods of manufacture, low volume products or, especially, for novel products.

Common reasons why non-enclosed systems are used based on exemplars are;

- Manual open systems for elements of manufacture where commercial solutions do not exist
- A combination of several discrete manufacturing steps using existing commercial systems. Often it is not possible to connect these using closed systems
- Use of conventional methods of manufacture to achieve the desired scale of manufacture.
- Scale provided by commercial systems are not adequate to achieve that intended
- Raw materials used have connections that are not compatible with the established commercial systems
- It was anticipated that existing large scale cell culture devices used in biopharma e.g. for production of viruses or antibodies would be applicable to cell-based therapeutics. However, biopharma products are harvested as bulk product supernatant which is subsequently purified, filtered and terminally sterilized. This is not applicable to cellular therapeutics, and the production methods do not port across readily to ATMPs.

Separate to these barriers, tissue engineered products by definition include some degree of scaffold or structure and are as yet not well catered for using enclosed manufacturing and are still extensively manufactured using historical techniques.

In summary, the field of advanced therapies is rapidly evolving and there are hugely varied methods of manufacture. There is however a recognition by the manufacturers of the importance of closing systems, and a continued focus by the device manufacturers to address unmet need. As a result when products become established and manufacturing volume increase and as such the patients concerned, systems will become available to fully enclose manufacture in a supply a demand scenario. In early phase clinical trials the number of novel solutions continues to increase but there remains a possibility that the manufacturing will remain partially open for the foreseeable future. This will continue to be managed by closing as many steps as possible and risk assessing the steps which must remain open.

References

[1]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 **(https://ec.europa.eu/health/system/files/2017-11/2017_11_22_guidelines_gmp_for_atmps_0.pdf)**