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Production Aspects of Advanced Therapy Medicinal Products

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Introduction

Background : Good Manufacturing Practice (GMP) guidelines established by the European Commission are essential to ensure quality, safety and efficacy of medicinal products. Guidelines are designed to address specific risks of medicinal products and as such, are continuously being adapted. Advanced Therapy Medicinal Products (ATMPs) are medicinal products that have been regulated in the European Union from 2007 to cover the emerging field of genes, tissues or cell-based therapies. Dedicated GMP guidelines for ATMPs are enforceable since 2017. Consequently, GMP guidelines covering manufacture of biological active substances and medicinal products for human use including biological active substances (hereafter "Biologicals") have been revised in June 2018 with the objective to prevent overlapping scope.

Research question and methods: Our hypothesis is that the biological nature that commonly characterize ATMPs and biologicals may sustain a large body of similarities in the manufacturing aspects as addressed by the respective guidelines. We aim to comparatively analyze the two following texts : *Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*, and *Manufacture of Biological active substances and Medicinal Products for human use* including biological active substances. Focus has been given on manufacturing, *i.e.* production recommendations including personnel, premises, equipment, documentation, starting and raw materials, seed lot and cell bank systems. In a systematic approach we highlighted similarities and specificities in the text outlines (paragraph and section titles). Then content has been comparatively investigated based on chosen relevant key words found in both texts (production, operation principles, production area, facilities, cross contamination in production, environmental monitoring and specifications, starting and raw materials).

Results

COMMON TOPICS

Premises & Equipments

- Constructed to avoid **cross-contamination**
- **Designed in logical order** to avoid risk
- **Campaigned manufacturing** (separation in place and/or in time)
- **Controlled** for particulate and microbiological contamination, maintained (air vent filters, positive pressure) and validated frequently by effective control strategy
- **Cleaned**
- Effective aseptic operations during the process for biological materials that cannot be sterilized

General Documentation

- Documentation for all manufacturing process & method
- Exhaustive **traceability** specially for batch, for starting and raw materials and for all products in contact with cells or tissues
- Traceability records to be for retained for **30 years**

Operations / Operating Principles

- Process design **robustness**, minimising variability, enhancing **reproducibility** to ensure quality and safety of the product
- Definition of **critical operational parameters, critical operations**
- **Product quality reviews** required
- Rules for process (entries, disinfected, wasted)

Starting and raw materials

Compliance with existing legislation on quality, safety, and traceability of human tissues and cells, especially on donation, procurement and testing

Seed lot and cell bank system

- Establishment of seed lots, and cell banks (master and working generation)
- Definition of appropriate specifications and qualification
- Management of a Controlled storage to avoid risk mix up

Risk-based approach/Quality risk management

- Prevent and anticipate hazards, control it and apply measures to minimise it
- Based on scientific knowledge and experience
- Quality and safety ensured since the first steps, even for investigational ATMPs.

Qualified person and Batch Release/Certification

- Functions of the Qualified Person:
- Verification and certification of the batches according to manufacturing/marketing/clinical trial authorization
 - Release/certification must be registered and notified if there is a deviation...

Personnel

- Qualified
- Trained and retrained

SPECIFIC TOPICS

Specific Guidelines for ATMPs

Aseptic Process & Environmental Monitoring

General principles

- Manufacturing to be conducted aseptically to limit introduction of contaminants and cross contamination
- Specific aseptic measures detailed for specific kind of manufacturing processes and open or closed operating systems

Aseptic processing validation

- Simulated by media fill test /media process test
- Documented as well as the cleaning process
- Environmental monitoring programme to be applied

Specific Guidelines for Biologicals

Animal sources

- The manufacturer must follow the Transmissible Spongiform Encephalopathy guidelines and have a recorded health program for other agents. Sick animals must be investigated, and everything has to be documented.
 - Housing must be separated from production and control areas.
- For each animal species, key criteria have to be defined and recorded. In the case of transgenic animals, traceability must be maintained in their creation.

Discussion and Conclusion

The ATMPs guidelines is a very detailed text covering the investigational and authorized stages from the raw materials to the final product. Technical measures are very extensively introduced for guidance of manufacturers. By contrast, guidelines on Biologicals is briefer and include more general requests and standards ensuring the quality of the product. A large part of manufacturing recommendations are commonly present in the two texts and in line with the manipulation of raw and starting materials of biological origin that raise common challenges in terms of quality reproducibility, traceability and risk of cross or exogenous contaminations. Main specificities associated to the manufacturing of these two categories of medicinal products, are related to specific aspects addressing the control of contamination risk. Regarding ATMPs guidelines, a section is dedicated to aseptic measures covering the entire process management. This specificity is justified by the usual lack of terminal sterilization of the product that requires to adopt preventive strategies to limit the introduction of contaminants. Regarding biologicals, specificities address the challenges of using animal sources in the manufacturing process and the associated risk of contamination. These specificities are relevant because a large proportion of biological medicinal products or active substances are issued from living or post-mortem animal sources, while ATMPs are mostly designed based on human materials. Raw materials of animal origin are poorly addressed in the ATMPs guidelines although this aspect could be of relevance.

References

- European Commission, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, 22 May 2018.
- European Commission, Manufacture of Biological active substances and Medicinal Products for Human Use, 26 June 2018.