Production of ATMPs: What are the specificities for quality aspects?

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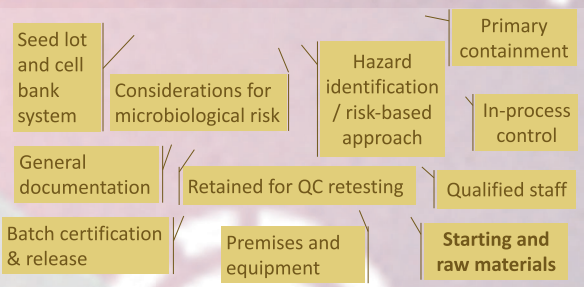
INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues that have been specifically regulated in the European Union (EU) from 2007. Their manufacturing (i.e. their production) raises specific challenges for ensuring quality and complying with regulatory requirements in order to obtain manufacturing and marketing authorizations. Hence, on top of its **guideline on the manufacturing of Biological active substances and Medicinal Products for Human Use** (26 June 2018, 25 pages revised to consider the new ATMP guidelines), the European Commission also issued **Good Manufacturing Practice specific to Advanced Therapy Medicinal Products** (22 November 2017, very detailed text of 90 pages).

Our hypothesis is that the biological nature that commonly characterizes ATMPs and biologicals may give rise to significant similarities in the manufacturing aspects as addressed by the respective guidelines. Through a comparative textual analysis of the GMP guidelines for biological medicinal products and ATMPs, this poster will highlight the key areas of similarities and differences. This analysis reveals why we have two different texts and whether they are based on substantial differences regarding production between ATMPs and other types of biological medicinal products.

COMMON TOPICS



Main similarities

Manipulation of raw and starting materials of biological origin raising common risks and challenges of quality reproducibility and sustainability, traceability and risk of cross or exogenous contaminations (compatibility of containments, importance of process controls, strategy for initial and final certification and batch release)

Similar spirit of the two texts

- Crucial role of manufacturing and control processes in determining the quality
- Biological origin and related inherent variability → requested standards of quality

SPECIFICITIES OF BIOLOGICALS VERSUS ATMPs

	ATMPS	BIOLOGICALS
Specific risks	as presented in the scopes and general principles of each text	
Specificities for manufacturing		
Stages to be considered	from raw material **to final production**	from raw material **to active substance**
Appropriate measures of quality control	**Complexity of products & processes, limited batch series, variability of starting materials** (especially in autologous setting) > Flexibility and "Risk-based approach"	**Procurement and quality of starting materials of animal origin, mitigation of a higher risk of low purity and microbiological contamination**, and **of greater variability of biological analytical techniques** > "risk quality management principles"
Especially control of contaminati on risk	Section dedicated to **aseptic measures** covering the entire process management. *Rationale:* Usual lack of terminal sterilization of the product requiring preventive strategies to limit the introduction of contaminants.	Provisions addressing the **use of animal sources** in the manufacturing process and associated contamination risk. *Rationale:* A large proportion of biologicals or active substances are issued from living or post-mortem animal sources versus ATMPs mostly designed based on human materials.

DISCUSSION & CONCLUSION

Explicitly stated that the text on biologicals does not apply to ATMPs which are covered by specific guidelines, but the two texts share common aspects related to the biological nature of the product:
Relevance of having two distinct and exclusive texts?

Some ATMPs specific requirements may be relevant to other biologicals

e.g., the validation of biological methods used for quality control and testing.

Variable levels of similarities and differences

As ATMPs are a specific category of biologicals, e.g., the "risk-based approach" for ATMPs seems matched to the "risk quality management principles" for biologicals, but the former is more prospective with the idea to anticipate and control current poorly known risks.

Some specific Biologicals requirements may be relevant to ATMPs

e.g., Raw materials of animal origin are poorly addressed in the ATMPs guidelines although ATMPs could also in the future be designed based on xenogeneic cells and are prone to necessitate the use of raw materials of animal origin (such as cell culture or extraction reagents etc..).

Unclear rationale for some style/form differences

Very different vocabulary used in the two texts while they have been adopted with a 7 months interval only, and often refer to the same ideas.

The two texts could benefit from being formulated in a more similar manner to facilitate full understanding and implementation by stakeholders, especially manufacturers.