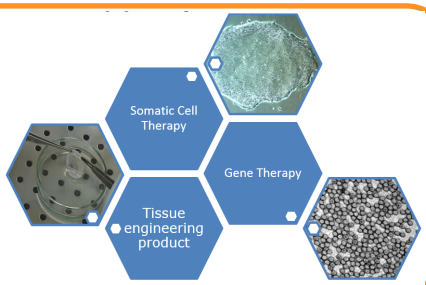
ATMP challenges in the EU - lessons for future applications

P. Maczuga, G. Corstens, A. Zwiers

Advanced Therapy Medicinal Products (ATMP) are new emerging types of medicinal products based on gene therapy, cell therapy or tissue engineering.

Marketing authorization applications (MAA) of ATMPs are challenging and complex.



Aims

Based on previous applications in EU, we identified issues and pitfalls that developers of ATMPs may encounter. We also highlighted incentives from European Medicine Agency (EMA) and Committee for Advanced Therapies (CAT) that foster successful development and commercialisation of ATMPs.

Methods

We analysed 14 products submitted since 2007 (adoption of regulation 1394/2007/EC on ATMPs) until December 2016 for which the review process was completed or the application was withdrawn. For each product, assessment history was analysed based on the EU public assessment report (EPAR) and communication with EMA and CAT.

Results

Out of fourteen products, eight applications successfully completed the procedure and have been granted a marketing authorization by European Commission. Three of these applications were for products that were on the market prior the ATMP regulation but according to the new regulation had to be re-registered. In contrast, five applications were withdrawn at different stages of the review process and for one product a negative opinion was adopted.

All applicants used the scientific/protocol advice (SA/PA) incentive from CAT/CHMP prior to MAA. Nevertheless, high numbers of major objections were raised during the review process. This may suggest that the applicants do not ask key questions during SA/PA or do not comply with CAT/CHMP recommendations. The major challenges and issues are described in Figure 1. Among the most common issues are problems related to manufacturing and consistency of ATMPs. For example: changes in manufacturing process during later stages of development may influence the final product and therefore may require comparability studies. Another common problem is proving efficacy in clinical trials. For ATMPs, randomized and large scale clinical trials are often not possible.

Conclusion

Upon evaluation of the data it looks like some of issues in MAA could have been already avoided by careful definition of product development and regulatory strategy.

Table 1: ATMP authorised in EU (* product registered nationally)

Name	MAH	License date	Type	Time from filing to MA	Comments
Chondro Celect®	TiGenix NV	05/10/2009	Tissue engineering	~29 months	Withdrawn 30 November 2016
Glybera	uniQure biopharma BV	25/10/2012	Gene therapy	~34 months	Exceptional circumstance, orphan drug
Holoclar	Chiesi Farmaceutici SpA	17/02/2015	Tissue engineering	~23 months	Conditional approval, orphan drug
Imlygic	Amgen Europe BV	16/12/2015	Gene therapy	~16,5 months	
Maci*	Vericel Denmark ApS	27/06/2013	Tissue engineering	~23 months	Suspended on 19 November 2014 (closure of EU manufacturing site)
Provenge*	Dendreon UK Ltd	06/09/2013	Somatic cell therapy	~24 months	Orphan drug, withdrawn due to bankruptcy 6 May 2015
Strimvelis	Glaxo-SmithKline	26/05/2016	Gene therapy	~13 months	Conditional approval, orphan drug
Zalmoxis	MolMed SpA	18/08/2016	Somatic cell therapy	~30 months	Conditional approval, orphan drug

Table 2: ATMP not authorised in EU (* product registered nationally)

Name	Applicant	Decision date	Type	Time from filing to decision	Comments
Advexin	Gendux Molecular Ltd	17/12/2018 Withdrawn	Gene therapy	~13 months (day 179)	Same product but different indication
Contusugene Ladenovec Gendux		12/06/2009 Withdrawn	Gene therapy	~12 months (day 120)	
Cerepro	Ark Therapeutics	13/07/2007 Withdrawn 08/03/2010 Withdrawn	Gene therapy	~22 months (re-examination) ~17 months(re-examination)	MAA < 1394/2007/EC reviewed by CHMP, 2nd review by CAT
OraNera	CellSeed Europe Ltd	14/03/2013 Withdrawn	Tissue engineering	~20 months (list of questions)	
Hyalograft C*	Anika Therapeutics Srl	14/01/2013 Withdrawn	Tissue engineering	~20 months (list of questions)	
Heparesc	Cytonet GmbH&Co KG	22/10/2015 Rejected	Somatic cell therapy	~22 months (re-examination)	

Figure 1: ATMP Challenges