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Challenges in development and market authorisation of Advanced Therapy Medicinal Products in Europe

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Introduction

Recent advances in biomedicine have brought about innovative therapies for diseases with high unmet medical need, such as gene therapy, cell-based therapies and tissue-engineered products. In the European Union these therapies are defined as advanced therapy medicinal products (ATMPs). While expectations are high and full pipelines are observed, eight ATMPs are currently on the EU market.

Aim

To identify challenges experienced by companies developing Advanced Therapy Medicinal Products in Europe and determine the association of these challenges with specific developers and product characteristics.

Methods

We conducted a cohort study among companies developing ATMPs.

COHORT: Clinical trial database searches, industry associations member lists and an open call via industry association websites and media, were used to identify all commercial ATMP developers in Europe with at least one product in clinical development stage.

DATA COLLECTION & SURVEY DESIGN: An online survey was used to collect developer and product characteristics and challenges experienced in development (pre- and post-authorisation). Information was collected on a product level and specified per development stage. Perceived individual challenges were grouped by domain (Clinical, Financial, Human Resource Management, Regulatory, Scientific, Technical and Other challenges) and scored by occurrence.

DATA ANALYSIS: A descriptive analysis was performed to determine associations between challenges and characteristics.

	Non-Respondents n (%)	Respondents n (%)
Number	203 (100)	68 (38)
ATMP type		
Gene Therapies	80 (40)	31 (46)
Cell-based products	121 (59)	36 (53)
Combined ATMPs	2 (1)	1 (1)
Company Size (total)		
SME	149 (73)	44 (65)
Large company	54 (27)	24 (35)
Geography (total)		
United Kingdom	36 (18)	16 (24)
Germany	33 (16)	11 (16)
United States	28 (14)	5 (7)
France	23 (11)	7 (10)
The Netherlands	16 (8)	8 (12)
Other (Europe)	64 (32)	19 (30)
Other (Rest of World)	3 (1)	2 (3)
ATMP Type (total)		
No. ATMPs in Development		
1	89 (44)	33 (49)
>1	114 (56)	35 (51)

Table 1: Respondent and Non-Respondent Characteristics. ***SME: Small Medium-Sized Enterprise (1-249 employees)***

Table 2: Developer Reported Challenges in European ATMP development ***Percentages are rounded off and displayed as fraction of total challenges (n=243). Challenge domains are bold. Only regulatory themes are split up in subthemes (italic).***

	n (%)
Regulatory Challenges	**82 (34)**
Regulatory Process	47 (19)
Country specific requirements	*40 (16)*
Submission Pathways	*4 (2)*
Pre-submission interaction	*2 (0)*
Product Logistics	*1 (0)*
Regulatory Dossier	33 (14)
Content Uncertainty	16 (7)
Meeting Information Demand	9 (4)
Information Relevance	5 (2)
Post Approval Commitment	3 (1)
Unspecified	2 (0)
Technical Challenges	**72 (30)**
Manufacturing	37 (15)
Quality Standards	13 (5)
Starting Materials	10 (4)
Supply Chain	5 (2)
Product Admission	4 (2)
Unspecified	3 (1)

	n (%)
Scientific Challenges	**34 (14)**
Trial Design	19 (8)
Preclinical Translation	8 (3)
Knowledge Gap	5 (2)
Unspecified	2 (0)
Financial Challenges	**24 (10)**
Reimbursement Perspective	12 (5)
Funding Development	12 (5)
Clinical Challenges	**23 (9)**
Trial Execution	9 (4)
Patient Recruitment	8 (3)
Efficacy and Safety	2 (9)
Unspecified	4 (17)
HRM Challenges	**5 (2)**
Human Resource	3 (1)
Skilled Resource	2 (0)
Other Challenges	**3 (1)**
Intellectual Property	1 (0)
Public Perception	1 (0)
Interdisciplinary Alignment	1 (0)

Results

We included 271 ATMP developers in our cohort. General characteristics did not differ between responders and non-responders (Table 1). We identified 243 challenges (Table 2), of which the top 3 domains are the regulatory (34%), technical (30%) and scientific (14%) domain.

Product characteristics: Gene therapy developers proportionally mentioned more regulatory hindrance, mainly driven by GMO legislation. Cell-based product specific challenges were encountered with customs and transporting of human tissue across member states.

*Developer characteristics: C*hallenges were found to be associated with company size. Large companies mentioned to be able to utilize their regulatory network and technical experience gained by non-ATMP development. Where SMEs mentioned to experience a lot of uncertainty across domains and proportionally requested more guidance. Developers mentioned more frequent authority interactions and Scientific Advice helped overcome challenges.

Non-ATMP specific, more general, challenges were encountered around product novelty, new and orphan indications.

Conclusions

- Of products in development, 65% is in early clinical development.
- A considerable number of challenges are non-ATMP specific, such as difficulty due to product novelty, new and orphan indications, and difficulties to meet regulatory requirements by SMEs.
- Most challenges were mentioned in the regulatory domain, specifically around regulatory requirements at the Member State level concerning Clinical Trial Authorization applications and Genetically Modified Organism legislation.
- This study identified and assessed challenges aiming to facilitate ATMP development and increasing patient access. Yet, after Marketing Authorization reimbursement and clinical adoption are needed to ensure patient access and learn about these therapies in clinical practice.

Acknowledgement

This research was performed within the Escher platform for regulatory innovation of Lygature. The project was supported by an unrestricted research grant from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and its specialized group European Biopharmaceutical Enterprises (EBE).

Publication

ten Ham, RMT, Hoekman, J et al. (2018). Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. Molecular Therapy - Methods and Clinical Development, 11, 121–130.

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