WHICH ACTORS TO INFLUENCE THE ADOPTION OF EU GUIDELINES FOR ADVANCED THERAPY MEDICINAL PRODUCTS?

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Background and Methodology

Genes, cells, and tissues based medicinal products are specifically regulated as Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU) from the adoption of Regulation (EC) n°1394/2007 on ATMPs. Beyond legislative requirements, the complexity and scientific technicity of these medicines, as well as the necessary flexibility to take into account the evolutions and the scientific and regulatory experience gained has led to the development of an important amount of guidelines in the field. These guidelines have mainly been adopted by the European Medicines Agency (EMA), the European regulatory agency especially in charge of the scientific assessment of medicines to be commercialised in the EU. Some of them have also been adopted by the European Commission (EC) which notably grants the final marketing authorization for ATMPs on the basis of EMA's assessment to enter the EU market. The adoption of EU guidelines involves a public consultation procedure to gather comments from stakeholders and interested parties.

These comments are then considered to establish the final version of the guidelines to be adopted to be used as reference documents in the field.

Who are these actors influencing the adoption of EU guidelines for Advanced Therapy Medicinal Products?

Our research team searched both the EMA and EC websites in order to identify all guidance documents specific to ATMPs. This led to the establishment of a list of 57 documents, among which 27 guidelines. This poster is dedicated to guidelines only.

Out of all 27 applicable guidelines identified, we considered only those for which a consultation process report was available. For older guidelines, sometimes no consultation was organized, and sometimes the subsequent report was not available on the EMA website.

Once all guidelines and associated reports on public consultation were collected, we identified all the actors involved in the consultation process: this led to the establishment of a database with 195 contributions from 147 organisations corresponding to thirteen guidelines for which dates of production range from 2006 to 2022.

For every guideline, we collected its title, date of publication, as well as the type of therapy to which it referred (either Advanced Therapy Medicinal Products (ATMPs) generally, Medicinal products based on Genetically Modified Organisms (GMO MP), Cell Therapy and Tissue Engineering Products (CT and TEP), or Gene Therapy Medicinal Products (GTMP)).

For each guideline, all organisations participating in the public consultation process were indexed and sorted in a table. Additional information was collected on the organisations' websites, regarding their typology, country of registration and specific activity.

The typology of organisations was constructed using all information available to sort out organisations to clearly identify the main polarizations between them.

Main figures

Table 1: Numbers of organisations involved in different types of guidelines

Guideline	Author	Theme	Date	Number of orgs
Non-clinical testing for inadvertent germline transmission of gene transfer vectors	EMA	GTMP	16/11/2006	4
Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs)	EMA	GMO MP	11/12/2006	4
Human cell-based medicinal products	EMA	CT and TEP	21/05/2008	20
Non-clinical studies required before first clinical use of gene therapy medicinal products	EMA	GTMP	30/05/2008	4
Scientific requirements for the environmental risk assessment of gene-therapy medicinal products	EMA	GTMP	30/05/2008	7
Follow-up of patients administered with gene therapy medicinal products	EMA	GTMP	22/10/2009	1
Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products	EMA	ATMPs	15/10/2010	6
Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer	EMA	GTMP	21/07/2016	4
Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products	EC	ATMPs	22/11/2017	53
Quality, preclinical and clinical aspects of gene therapy medicinal products	EMA	GTMP	22/03/2018	29
Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products	EC	ATMPs	10/10/2019	34
Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	EMA	GMO MP	12/11/2020	20
Guideline on core SmPC, Labelling and Package Leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells	EMA	ATMPs	10/05/2022	9

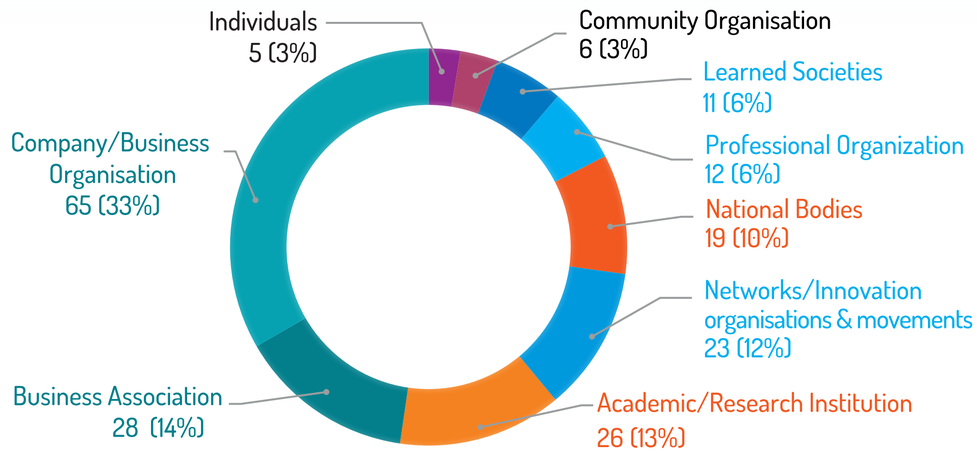
Results

- 11/13 guidelines have been adopted from 2008.
- 11/13 guidelines have been established by EMA while 2/13 guidelines have been established by EC.
- 4/13 guidelines relate to ATMPs in general.
- 6/13 guidelines relate to GTMP.
- 2/13 guidelines relate to GMO MP.
- 1/13 guideline relate to CT & TEP

Discussion

- There is a wide scale of involvement in public consultation processes, ranging from only 1 to 53 organisations having been involved. The number of organisations involved in public consultations processes is linked to the guidelines' topics and not to a potential increase due to better awareness of the process with time.
- Almost half of the guidelines for which a report on public consultation is available, have been adopted in the field of GTMP which highlights the rise of this type of ATMPs as well as the particular need for regulatory guidance for their development and commercialisation in the EU. On the opposite, only one guideline covers CT & TEP together.
- The guidelines which involved the highest number of organisations during the public consultation processes are the ones adopted by the EC. This can be explained by both their highest legal value and the wider scope of their topic on particularly challenging aspects of ATMPs development: Good Manufacturing Practice and Good Clinical Practice specific to ATMPs.
- The other guidelines involving a high number of organisations during the public consultation processes relates to wide scientific aspects of the main types of ATMPs: Quality, preclinical and clinical aspects of gene therapy medicinal products for GTMP (29), Human cell-based medicinal products for CT & TEP (20), and Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells for GMO MP (20). Here also, the guideline on GTMP has involved more participation than for other types of products. Guidelines on CT & TEP and on GMO MP have involved the same number of organisations, even though only the first one covers two sub-categories of ATMPs explicitly defined at the legislative level (Regulation (EC) n°1394/2007 and Directive 2009/120/EC).
- The other guidelines involving less organisations (9 maximum) relate to various types of ATMPs, or ATMPs generally and they cover very particular scientific (e.g., potency testing) or regulatory (e.g., packaging & labelling) aspects of their development, or specific procedure (e.g., certification).

Organisations' profile

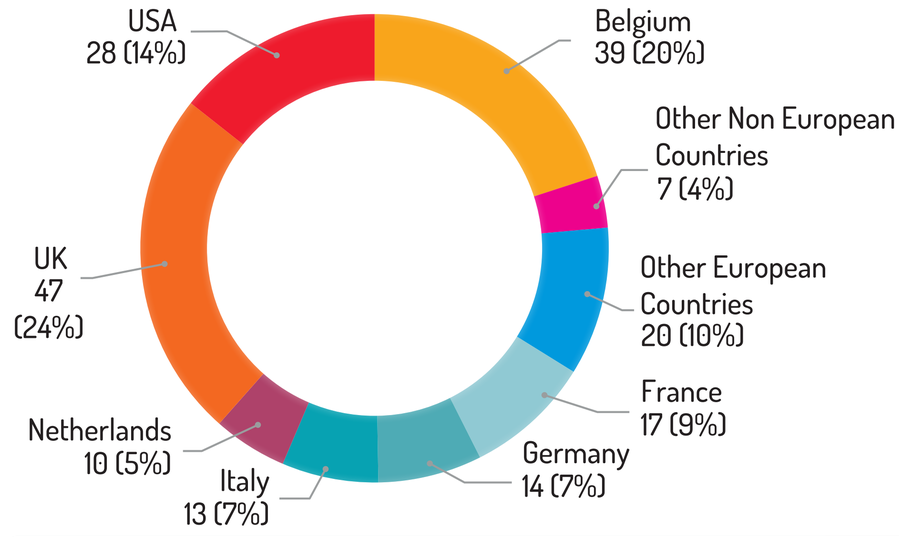


Graph 1: Typology of organisations involved in the consultation processes of ATMPs guidelines.

Discussion: Companies and business associations account for almost half of all contributions (47%). Community organisations (3%) and individuals (2%), on the contrary, seldom contribute. As for public sector organisations, such as national bodies and academic institutions, they hold the middle ground (24%). These results can be explained by the availability of means (human and financial ones in particular regarding necessary time and knowledge) to contribute to the process of public consultation.

Discussion: The countries most represented are the most active in the development of ATMPs: UK, Belgium, USA, France, Germany, Italy and the Netherlands. Nevertheless, the important involvement of Belgium (20%) should be put in perspective with the European institutions being mainly established in Brussels, which leads to an important amount of organisations having their headquarters there.

The important involvement of the UK (24%) can be explained by the UK being one of the leading countries in the field, although almost all public consultations processes considered (12/13) occurred before Brexit. Thus, such main position of the UK may change in the future. The important involvement of the USA (14%) can be astonishing given that the public consultations relate to European regulation. However, it reveals how much the field is International and how much the European Market is targeted by external countries, especially the USA.



Graph 2: Organisations involved in the consultation processes of ATMPs guidelines by country.

Most contributing organisations

Table 2a: Organisations by number of contributions

Number of contributions	Organisations
Three or more	9
Two	23
One	115

Out of the 9 organisations which have contributed to 3 or more guidelines:

- 4/9 are located in Belgium.
- 4/9 are Business Associations
- 5/9 are from the private sector (Company or Business Association).
- 2/9 are Networks/Innovation Organisations.

Table 2b: Name, type and country of organisations answering to 3 or more guidelines

Organisation	Type	Country	Number of contributions
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Business Association	Belgium	6
European Association for Bioindustries (EuropaBio)	Business Association	Belgium	5
Alliance for Regenerative Medicine (ARM)	Networks/Innovation Organisation	USA	4
Cell and Gene Therapy Catapult	Networks/Innovation Organisation	UK	4
European Association of Hospital Pharmacists (EAHP)	Professional Organisation	Belgium	4
European Biopharmaceutical Enterprises (EBE)	Business Association	Belgium	4
International Society for Cell & Gene Therapy (ISCT)	Learned Society	Canada	4
German Pharmaceutical Industry Association (BPI eV)	Business Association	Germany	3
Voisin Consulting Life Sciences (VCLS)	Company/Business Organisation	France	3

Discussion

- As long as only few organisations have contributed to 2 and to 3 or more consultations, and 78,2% of organisations contribute only once to a consultation process on ATMPs guidelines, it appears the contribution are based on the topics of the guidelines rather than on an habit to be involved in this process.
- Among organisations contributing most often, the private sector is leader given the means it can dedicate to this activity; and Belgium is the most represented country given the strategical position of being in Brussels to know and influence EU policy and regulation. Surprisingly, the public sector, mainly represented by National bodies and academic/ research institution, does not appear among the organisations contributing the most often to public consultation regarding ATMPs guidelines. It implies a participation based on the topics of the guidelines rather than an habit. Although this can be understood for academic/ research institution which generally focus on specific area of research even in the delimited field of ATMP, it is more questionable for national bodies, and especially national authorities, such as national medicines agencies, which could have been considered as the main contact point for ATMP developers, despite main EMA competence, given national languages and their potential interface's role between the EMA and ATMPs developers located in National EU Member States.

General conclusion

- Most guidelines have been adopted after the adoption of Regulation (EC) n°1394/2007 on 13 November 2007 and have contributed to its practical implementation.
- Most guidelines applicable to ATMPs have been established by the EMA. It highlights both the main role of the agency in this field and the technical specificity of ATMPs. Guidelines on Good Manufacturing Practice and on Good Clinical Practice specific to ATMPs have been adopted by the EC in accordance with the provisions of Regulation (EC) n°1394/2007.
- **More EMA guidelines but more contributions on EC guidelines** due to highest legal value and wider scope of their topic on particularly challenging aspects of ATMPs development
- **A wide scale of involvement in the public consultation processes**: from 1 to 53 organisations
- **The more general a guideline is, the more contributions it obtains**
- **Involvement in the public consultations processes is linked to the guidelines' topics**, and neither to a potential increase due to better awareness of the process on time nor to an habit to contribute even for national regulators.
- **GTMP is the category of ATMPs raising the most of interest**
- **The private sector is leader in answering public consultation on ATMPs guidelines,** both regarding the overall amount of contributions and the organisations that contributed the most often.
- **The countries most represented are the UK, Belgium, USA, France, Germany, Italy and the Netherlands**
- The major involvement of the UK may change in the future following Brexit.
- The important involvement of the USA reveals how much the field is International and how much the European Market is targeted by external countries, especially the USA.
- The important involvement of Belgium should be put in perspective with the European institutions being mainly established in Brussels which leads to an important amount of organisations having their headquarters there and to organisations that may be more used to EU policy and regulation (Belgium is the most represented country among the organisations contributing most often).

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