Development of Advanced Therapy Medicinal Products in Europe

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Introduction

During the 1990s, new types of innovative medicinal products emerged i.e. tissue-engineered medicinal products and cell therapies. At this time, these innovative products were regulated under national law in each European Member State with different regulatory statuses (i.e. medicinal product, medical device, medical practice, etc.) until 2003 when the European Commission started to focus more attention on these products.

In order to initiate a harmonisation taskforce in 2003, the first definition of tissue-engineered medicinal products and cell therapies was established by the European Commission, according to Annex IV of the Directive 2003/63/EC, modifying the Directive 2001/83/EC. According to the definition, these products fall within the framework of medicinal products and a new class of medicinal products was defined: the 'Advanced Therapy Medicinal Products' (ATMPs), which included at this time the tissue-engineered medicinal products and the cell therapies. Due to the emergence of new products, including combined products or tissue-engineered products, the legislation was reinforced to harmonise the European position on the regulatory status and the scientific criteria to be considered for the authorisation of such products and to define the responsibilities of the competent authorities. This resulted in the adoption by the European Commission of Regulation (EC) No 1394/2007, the regulation applicable to ATMPs.

The Regulation was implemented in order to ensure consistency between the existing regulatory frameworks, to harmonise and ease the market access of such products, while ensuring a high level of public health. Approximately 9 years after the implementation of the Regulation, an evaluation of the efficiencies and limitations of the implemented measures can be made. A review of the regulatory requirements specific to ATMPs is provided together with a review of specific experiences with these products and, finally, a quantitative and qualitative evaluation of the incentives in place – the evaluation is based on the report that was prepared by the European Commission five years after the implementation of the Regulation.

I. Regulatory requirements applicable to the advanced therapy medicinal products

The Regulation (EC) N°1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N° 726/2004, is based on the procedures, concepts and requirements applicable to standard medicinal products in addition to certain specificities.
Three types of medicinal products are considered ATMPs (Figure 1):

- Gene therapies,
- Somatic cell therapies,
- Tissue engineering products.

The classification of a product as an ATMP can involve complex scientific considerations. For example, to differentiate a cell therapy (ATMP) from a cell or tissue based product (not ATMP), reference is made to substantial manipulation of the material or to the exercise of a function similar or different between the donor and the recipient.

The ATMPs are distinct from hospital preparations, which are prepared in a unique setting under specific quality conditions and which are used in a single Member State, in a hospital under the exclusive responsibility of a physician, to execute a medical prescription for a product made for a specific patient. The hospital preparations are not further covered in this document.

Figure 1. Definition of advanced therapy medicinal products

GENE THERAPY MEDICINES

- These contain genes that lead to a therapeutic, prophylactic or diagnostic effect.
- They work by inserting recombinant genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.
- A recombinant gene is a length of DNA that is created in the laboratory, bringing together DNA from different sources.

SOMATIC-CELL THERAPY MEDICINES

- These contain cells or tissues that have been manipulated substantially to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body.
- They can be used to cure, diagnose or prevent diseases.

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Source: www.ema.europa.eu

A. Marketing Autorisation for ATMPs

Centralised European Procedure

The scientific evaluation of the Marketing Authorisation Application (MAA) dossier is performed by a specialised Committee, the Committee for Advanced Therapies (CAT) that provides an opinion transmitted to the Committee for Human use of Medicinal Product (CHMP). As for any evaluation of MAA dossiers through the centralised procedure, other Committees can be involved in the review of the dossier, i.e. the Pharmacovigilance Risk Assessment Committee, the Paediatric Committee (PDCO) or the Committee for Orphan Medicinal Products (COMP).

Evaluation by a specialised Committee, the CAT

The creation of the CAT has been a key milestone in the implementation of the Regulation on ATMPs. This Committee is composed of European experts in charge of the evaluation of the quality, safety and efficacy of ATMPs.
The CAT also makes recommendations on the classifications of ATMPs, evaluates the certification requests for quality and non-clinical data, contributes to scientific advice procedures for ATMPs, participates to the procedures related to the evaluation of the pharmacovigilance or the risk management systems for ATMPs and is also involved in European projects for the development of ATMPs, contributing a scientific expertise.

Regulatory texts applicable to ATMPs

The regulatory framework applicable to ATMPs is organised around the Regulation (EC) N°1394/2007 on ATMPs and several European directives applicable to medicinal products or to products containing genes, cells or tissues. The main texts applicable are presented in Table 1.

Table 1 Regulatory texts applicable to ATMPs

REFERENCE	TITLE	IMPORTANT INFORMATION FOR ATMPS
Regulation (EC) N° 1394/2007	Of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004	Definition of ATMPs, regulatory framework and incentives
Directive 2001/83/EC	Of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use	Regulatory framework of medicinal product for human use
Commission Directive 2003/63/EC	Of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use	Amendment of the Directive 2001/83/EC – addendum to Part IV of Annex I. Definition of somatic cell therapy and gene therapy and information contained in MAA dossier for ATMP.
Commission Directive 2009/120/EC	Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products	Modification of Part IV to Annex I of Directive 2001/83/EC. Defines combined products and products issued from tissue engineering.
Regulation (EC) N° 726 /2004	Of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	Registration of ATMPs through the centralised procedure.
Directive 2004/23/EC	Of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	Dispositions applicable to the manipulation of tissue and cell donation and distribution of human tissue and cell
Directive 2006/17/EC	Of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells	Dispositions applicable to the manipulation of tissues and cells donation and distribution of human tissues and cells

B. Incentives to foster development of ATMPs

In order to encourage the development of ATMPs in Europe, the Regulation (EC) N°1394/2007 includes measures to promote early interactions with European Medicines Agency (EMA), to guide developers on the applicable regulatory framework and to reduce the development cost by introducing reduced fees for certain regulatory procedures.

A review of the planned measures is presented hereafter:
- Classification procedure for ATMP,
- Data certification,
- Financial incentives.

Classification procedure for ATMP

Many innovative products potentially fall into the regulatory framework of ATMPs. In order to address uncertainties related to the classification of borderline products (eg. medical device) and to guide developers on the choice of the regulatory framework applicable to their specific product, a classification request can be addressed to EMA. Through this procedure, confirmation from the CAT is received on whether the product containing genes, cells or tissues fulfils the criteria for an ATMP. This procedure is free of charge.

Data certification by EMA

In order to attract investors and to obtain grants for the development of ATMPs, the certification of quality and non-clinical data can be performed by the CAT. The certification is then granted by the EMA. This incentive is restricted to the small and medium size enterprises (SMEs). The dossier submitted for the certification is an abridged version of the future MAA dossier containing only the pharmaceutical and non-clinical parts.

Financial incentives

Early interactions between developers and regulatory agencies are important to increase the success rate during the development of an ATMP with the objective of obtaining a MAA. As ATMPs are mainly developed by SMEs or academics, an early comprehension of regulatory requirements during scientific advice with EMA is required to guide the developers in the development strategy and in the choice of regulatory procedure. Thus, as per the Regulation (EC) N°1394/2007, a 65% reduction in the fees for scientific advices of ATMPs and a 90% reduction in the case of SME applicants is applicable.

II. Specificities for the development of ATMPs

ATMPs are complex products by nature, being derived from biological material (cells, viral vectors or tissues) and their unique characteristics (small batches, specific mode of action, complex structure and product defined by the process and implying several steps key for the quality of the final product) require tailored approaches throughout their development. Certain requirements for the manufacturing of medicinal products are not applicable to ATMPs. In particular, difficulties are encountered with the change of manufacturing process during the pharmaceutical development, in order to establish a manufacturing process adapted to the production of commercial batches, for the validation of processes but also for the characterisation of the finished product due to short expiration periods.

The non-clinical and clinical development of medicinal products classified as ATMPs must also be adapted. For example, suitable animal models must be identified and, for the design of clinical studies, it must be taken into consideration that the patient populations will often be very small, resulting in strong inter-subjects variability and complex administration methods.

In addition to any specificities applicable to these products, the regulatory framework in place for all medicinal products also needs to be considered (e.g. clinical study design to consider endpoints relevant for the proposed indication).

Presented below are the specificities applicable to ATMPs only, including the risk-based approach, interactions with regulatory authorities throughout the development, followed by a review of the ATMPs for which a MAA has been granted in the EU.

Risk based approach

Taking into account the pharmaceutical, non-clinical and clinical constraints, the development of ATMPs will vary on a case-by-case basis and a risk-based approach must be undertaken to evaluate the data (quality, non-clinical and clinical) included in the MAA dossier, as per the Directive 2009/120/EC modifying the Part IV of Annex I of the Directive 2001/83/EC.

In order to establish the risk profile of an ATMP under development, the risks associated with the administration, the quality or the activity of the ATMP are evaluated. The following criteria should be taken into account:

- Origin of the product (autologous or allogenic);
- Proliferative and differentiation properties;
- Ability to initiate an immune response;
- Extent of cell modification (in vitro/in vivo expansion, activation, genetic modification);
- Mode of administration (local or systemic);
- Duration of exposure;
- Combination ATMP product;
- Clinical data available, or experience with similar products.

Once the risk profile of the product is established, the developer can justify the data included in the MAA dossier through a presentation of the development strategy, risk analysis and the data contained in the dossier in order to address those risks.

ATMP development in collaboration with regulatory authorities

The development of ATMPs cannot be conducted in a straightforward manner when compared to standard chemical medicinal products. The development of such products must be tailored and interactions with regulatory authorities throughout the development, and at key milestones, are highly recommended. Regulatory procedures are in place for such interactions through the consultation of ATMP expert workgroups:

- at the national level (e.g. MHRA Innovation Office, ANSM Innovation Cell)
- at the EU level ;
  - The innovation task force (ITF) at EMA,
  - The scientific advice procedure,
  - The PRIME programme which provides early and proactive support by the EMA for the development of medicinal products with a high potential.

Flexibility during the MAA evaluation of ATMPs

Up to date, 15 requests for MAA of ATMPs have been received by the EMA leading the authorisation of 8 products, including one MA under exceptional circumstances and one conditional MA. Among these 8 MAA, 3 have subsequently been suspended or withdrawn (Table 1).

A review of the assessment reports published by the EMA presented hereafter shows a flexibility of the regulators to grant the MA in presence of major objections but under the condition of performing the CHMP recommendations as laid down in the Article 14 (2) of the Regulation (EC) N° 1394/2007.

The medicinal products of Glybera, Maci, Provenge, Imlygic or Strimvelis have been authorised under the conditions of pursuing the pharmaceutical development under CHMP recommendations (e.g. Potency assay validation, addition of a step for viral inactivation etc.). The MAAs have been granted in view of the clinical data that did not suggest any safety issues deriving from these pharmaceutical parameters. Similarly, the requirements pertaining to the non-clinical data have been adapted notably for Chondrocelect, where the MA was granted based on nonclinical data obtained under non-GLP conditions in contrary with pharmaceutical standards. The CHMP deemed this approach acceptable in view of the specificity of the development programme of this product and of the clinical data where no safety issue was raised. Finally, flexibility in the evaluation of this type of products was also observed at the clinical level. For example, Chondrocelect was authorised while the primary efficacy criteria of a pivotal clinical study was not compliant with Good clinical practice (GCP). Indeed, the primary efficacy criteria was defined during the clinical study after invalidation of the primary criteria defined a priori. Another example, Glybera was approved in absence of conventional PK/PD studies that was deemed acceptable by the CAT for a gene therapy developed in an orphan condition. In another example, Provenge was authorised based on clinical data from studies performed outside of Europe and using a product similar but not identical to the product planned for the commercialisation in Europe.

However, the experience of medicinal products for which marketing authorisation was granted, subsequent withdrawal or suspension for 3 products, illustrates that beyond the marketing authorisation, other constraints pertaining to the market access or reimbursement should be anticipated to avoid MA withdrawal or suspension.

Table 1 ATMP medicinal products with MAA in Europe (July 2017)

TRADENAME	DESCRIPTION	ATMP TYPE	INDICATION	MA	DATE CHMP OPINION	MA STATUS
Chondrocelect	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	TEP	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present.	Full	June 2009	MA withdrawn in July 2016 for commercial reasons. Withdrawal effective as of 30 Novembre 2016.
Maci	Characterised viable autologous chondrocytes expanded ex vivo expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine derived Type I/III collagen membrane.	Combined ATMP	MACI is indicated for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm2 in skeletally mature adult patients.	Full	April 2013	MA suspended in Septembre 2014 follwoing closure of European manufacturing site
Provenge	Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (Sipuleucel-T)	Somatic cell therapy	Treatment of asymptomatic or minimally symptomatic metastatic (nonvisceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.	Full	June 2013	MA withdrawn in May 2015 for commercial reasons
Glybera	Alipogene tiparvovec contains the human lipoprotein lipase (LPL) gene variant LPLS447X in a vector. The vector comprises a protein shell derived from adeno-associated virus serotype 1 (AAV1), the Cytomegalovirus promoter, a woodchuck hepatitis virus posttranscriptional regulatory element and AAV2 derived inverted terminal repeats. Alipogene tiparvovec is produced using insect cells and recombinant baculovirus technology.	Gene therapy	Indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein.	Under exceptional circumstances	Negative CHMP opinion in June 2011 (in accordance with CAT) Negative CHMP opinion following re-examination in Octobre 2011 (against CAT positive opinion) Positive CHMP opinion in July 2012 following re-evaluation requested by EC	Valid MA

TRADENAME	DESCRIPTION	ATMP TYPE	INDICATION	MA	DATE CHMP OPINION	MA STATUS
Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells.	TEP	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 mm2 of undamaged limbus is required for biopsy.	Conditionnal	December 2014	Valid MA
Imlygic	Talimogene laherparepvec is an attenuated herpes simplex virus type-1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF) (see section 5.1). Talimogene laherparepvec is produced in Vero cells by recombinant DNA technology.	Gene therapy	Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease	Full	October 2015	Valid MA
Strimvelis	An autologous CD34+ enriched cell fraction that contains CD34+cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells.	Gene therapy	Treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available	Full	March 2016	Valid MA
Spherox	Autologous cultured chondrocytes integrated in a scaffold	TEP - combined	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults."	Full	May 2017	Valid MA

EC=European Commission ; CHMP= Committee for medicinal products for human use ; ATMP=Advanced therapy medicinal product ; TEP= Tissue engineering product

Source : http://www.ema.europa.eu/ema/

III. Assessment of the effectiveness and limitations of incentives

Five years after the implementation of the Regulation (EC) N°1394/2007, the European Commission has published a report which provides good signals on the extent and limitations of the measures laid down in the Regulation[1]. In addition, to evaluate the possibilities to foster the development of ATMPs and to increase the access to the patients, the EMA organised in May 2016 a workshop with the stakeholders including researchers, academics, SMEs, big pharma, patients' organisations, national competent authorities and representatives of the European Commission[2]. Based on these 2 sources of information a first quantitative and qualitative assessment can be drawn and is presented hereafter.

Quantitative assessment

Classification requests

On 20 June 2013, the CAT had received 87 requests for classification and issued recommendations in 81 cases. About half of the requests were made by SMEs and 15% by non-profit organisations. The requests from big pharma represented only 5% of the submissions. The classification procedure is recognised as a progress as it provides a harmonised opinion amongst Member States of the UE. Furthermore, the procedure is free of charge and is adapted to the stakeholders, in particular to the SMEs, by helping them to develop the products from the early stages of development upon the applicable regulatory framework and optimising the success rates of obtaining a MA. However, the classification procedure extent is limited, as it is not binding on the future development of the product and because Member States cannot consult the CAT in case the question is raised directly during national procedures.

In May 2016, 211 classification procedures had been reported by the CAT, showing a clear increase over the last years.

Scientific advice procedures

At the cut-off date of 30 June 2013, the EMA had given scientific advice for ATMPs during 93 procedures for 65 different products. The high number of scientific advice requests is a positive signal of the transition of research into pharmaceutical development projects. The majority of the requests were made by SMEs, the fee reduction being considered as an appropriate measure. However, the exclusion of non-profit organisations without the SME status is identified as a limitation of this incentive limiting academic researchers to request scientific advice to the EMA.

In May 2016, the CAT had been involved in a total of 197 scientific advice procedures related to ATMPs, showing an important increase of requests for these procedures over the last few years in concordance with the increase observed for classification procedures.

Certification procedures

As off 30 June 2013, only 3 requests for certification had been performed, two concerning quality data and the third one concerning quality and nonclinical data. In the 3 cases, the certification was granted by the CAT. In May 2016, a total of 7 procedures was identified, showing an increase over the last few years. The low number of certification procedures is a disappointing result of the incentives laid down by the Regulation. This might be explained by the exclusion of non-profit organisations in addition to a lack of visibility by the stakeholders. Thus, a need for clarification between the certification procedure and the MA procedure or the extension of the certification procedure to other parts of the dossier (e.g. Clinical data) seem necessary. In addition, the preparation of the certification dossier represents a financial burden and requires human resources in small companies which might not always be used to preparing dossiers under the regulatory format.

1 European Commission. 2014. REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

2 European Medicines Agency. 2016. Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Friday 27 May 2016

MA procedure

Between 2009 and June 2013, 10 MAA have been submitted to the EMA. Five of these products were commercialised in the European market before the implementation of the ATMP Regulation and 7 out of 10 procedures had received a scientific advice. Of these 10 products, a MA was granted for 4 products, however, the procedure failed in 4 cases including one product that was commercialised before the implementation of the Regulation. In May 2016, MA was granted for 7 products. Before the implementation of the ATMP Regulation, certain innovative products with medical device or medicinal product status were already commercialised at the national level. A total of 31 products was identified by the Member States. Following the implementation of the regulation, about 60 exemptions to the MA in favour of the hospital exemption status have been granted up to April 2012. Because of differences in the interpretation of "non-routine" use of the product, differences have been raised for the use of this procedure. In particular, the development costs and MA maintenance for ATMP being higher than for hospital exemptions, the developers seeking for MAA face a competitive disadvantage with regards to the products available under the hospital exemption. A systematic use of the hospital exemption regulatory pathway can be deleterious to the public health in absence of the conduct of robust clinical studies and in absence of information transmission to the competent authorities of other Member States after the administration of a product to small groups of patients and by unequal access to patients of the Member State within the European Union.

Finally, the regulatory pathway such as a MAA via the centralised procedure can be perceived constraining by the stakeholders of the ATMP market which are essentially SMEs and non-lucrative organisations.

Qualitative assessment

The implementation of the ATMP Regulation represented an important step for the protection of patients to potentially dangerous treatments. At this stage, we are still at the start of the ATMPs with only 7 products for which a MA was granted.

Research on advanced therapies is essentially conducted by small companies with notably 70% of clinical trials conducted by non-profit organisations and big pharma representing only 2% of sponsors.

During public consultation by the stakeholders, a lack of flexibility was raised with regards to the pharmaceutical development in order to take into consideration the scientific progresses and the characteristics of the ATMPs. Suggestion was also made to consider other alternatives to reduce the costs, such as granting MA based on limited data for use of the product under restricted conditions that should be envisaged in case of unmet medical needs. For autologous products, the medicinal product status can, in certain cases, be associated with exaggerated and non-appropriate requirements. Indeed, in case of products manufactured at the hospital, the quality controls and fabrication requirements (e.g. Drug release per treatment, pharmaceutical establishment status) limit the development of this type of products.

Furthermore, the need for a better uniformity of the regulatory requirements applicable to the Member States was highlighted. The Regulation on ATMPs being only a piece of the ATMP regulatory framework, other pieces such as the directive 2001/83/EC on medicinal products for Human use, the directive on GMP, the directive on GMOs, the directives on tissues, cells and products derived from blood or also the directive on clinical trials present notable differences during their implementation in the MS. Similarly, the border between ATMPs and hospital exemption being subject to differences in interpretation by the Member States, an harmonisation would be appreciated. An example would be for a better collection of data in view of a MAA or a restrictive use to the situations corresponding to an unmet medical need. Additionally, research on ATMPs also concerns academics, therefore the incentives should be broadened to these types of developers.

Finally, an inconsistency is perceived between the flexibility agreed by the competent authorities on the level of requirements to obtain MAs and the difficulties encountered to access the market of expensive products. Thus, a better coordination with the health technology bodies from the early stages of development would be needed so that the likelihood to allow access to patients is increased.

IV. Conclusion

The implementation of the European Regulation on ATMPs promoted the the increase in development of ATMP products and to increase the access to the European market. About 8 years after the implementation of the Regulation, several incentives demonstrated their efficiency bust some adjustments should be made to reach the main objective to improve access to European patients for safe and efficacious innovative products. It is important to remind that the development of innovative therapies is at its early stages only and that a better harmonisation of the requirements within the EU and an evolving regulatory framework will align the scientific advantages to the regulatory requirements. Finally, a better adjustment of the incentives to the stakeholders concerned by the development of ATMPs (i.e. academics/SMEs) is required to increase the chances of success.

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