MOLECULAR AND EXPERIMENTAL BIOLOGY IN MEDICINE

ADVANCED THERAPY MEDICINAL PRODUCTS – AN OVERVIEW

Mirna Golemovic[1, 2]

Abstract: Advanced therapy medicinal products (ATMPs) represent an innovative group of medicines comprising gene therapies, somatic cell therapies and tissue engineered products. These therapies offer opportunities for new therapeutic approaches in numerous diseases. However, there are many issues related to the development of such complex therapies that greatly differ from traditional developments of new chemical entities or biologics. The regulatory framework, high cost of development, translation from research to clinical trials and finally into clinical practice are still issues that make marketing authorization (MA) of ATMPs in the European Union (EU) a very challenging task. Nine years after the implementation of a common regulatory framework for ATMPs in the EU, only 9 ATMPs have been granted MA. Three of them are not available on the EU market anymore. This overview aims to give a short insight into the challenges this innovative field of medicines is facing today.

[1] *Clinical Department of Transfusion Medicine and Transplantation Biology, University Hospital Centre Zagreb, Zagreb, Croatia*

[2] *University of Applied Health Sciences, Zagreb, Croatia*

Corresponding author:
Mirna Golemovic
Clinical Department of Transfusion Medicine and Transplantation Biology, University Hospital Centre Zagreb
Kispaticeva 12, 10000 Zagreb, Croatia
e-mail: mgolemov@kbc-zagreb.hr

Submitted: November, 2017
Accepted: December, 2017

Key words: advanced therapy medicinal products, ATMP; European medicines agency, EMA; Committee for Advanced Therapies, CAT; marketing authorization, MA

REGULATORY FRAMEWORK

Advanced therapy medicinal products (ATMPs) represent a group of innovative products derived from a variety of biological materials offering new opportunities for treatment of a number of diseases and injuries. This complex group of medicinal products includes gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (sCTMP) and tissue-engineered products (TEP).[1] Unlike cell and tissue transplants, cell-based medicinal products (sCTMP and TEP) undergo substantial manipulation during production that can result in substantial changes of their biological properties or they could be used for a different essential function in the recipient (non-homologous use).[1]

The regulatory pathways to authorize medicines in the European Union (EU) have been harmonized and they are based on the principles laid out in the Directives and Regulations of the European Parliament and Commission. The European medicines agency (EMA) was founded in 1995, and since then it has been involved in ensuring efficacy and safety of human and veterinary medicines across the EU. In order to provide a common legal and regulatory framework for ATMPs in the EU, a Regulation (EC) 1394/2007 of the European Parliament and the Council of the EU (hereinafter, ñATMP Regulationò) was adopted in 2007, and it came into force in 2008. Since then a series of accompanying ATMP guidelines have been issued by EMA.

EMA's scientific committees provide independent scientific opinions on medicines, based on a comprehensive scientific evaluation of data. The Committee for Advanced Therapies (CAT) was established in accordance with ATMP Regulation as a multidisciplinary committee responsible for assessing the quality, safety and efficacy of ATMPs. The majority of new, innovative medicines, such as

ATMPs, pass through the centralized authorization procedure in order to obtain a single marketing authorization (MA) throughout all EU member states and in Iceland, Lichtenstein and Norway (EEA states). Therefore, a marketing authorization application (MAA) for a new ATMP is a prerequisite for its use on the EU market. The CATôs main responsibility is to prepare a draft opinion on each ATMP application submitted to EMA, before the Committee for Medicinal Product for Human Use (CHMP) adopts a final opinion on the MA of the medicine in question.[2]

The vast majority of stakeholders developing ATMPs are small- or medium-sized enterprises (SMEs) and non-commercial organizations (academic institutions, hospitals, charities).[3, 4, 5] These stakeholders usually tend to have limited financial resources and need support to cope with demanding regulatory procedures. The fee for the MAA is substantial, so in addition to funds invested in research and development, a refusal of the MA for the proposed ATMP can lead to a large resource loss. Therefore, an early contact with EMA/CAT in order to get scientific and regulatory advice at early stages of a new product development is highly encouraged.

There are tools that EMA/CAT can provide for the early assessment of new ATMPs in order to improve outcomes of future MAAs. For example, ATMP classification (free of charge) and Scientific advice (fee charged) are procedures open to all applicants.[5] ATMP certification is a procedure restricted only to SME developers (fee charged).[5] The latter procedure can provide scientific evaluation and certification of all relevant quality and non-clinical data related to specific ATMP independently of MAA.

The EU pharmaceutical legislation includes several provisions to foster patientsô early access to new medicines that address public health and are eligible for the centralized procedure.[6] Such provisions include accelerated assessment, conditional marketing authorization and compassionate use. Recently, a new scheme, PRIME ï Priority medicines, has been introduced in order to additionally enhance support to the development of medicines that target unmet medical needs.

In some cases, the use of ATMP within the member state (MS) where it is produced might fall in the category of products without the need for an MA, the so-called ñhospital exemptionò. This situation is described in Article 28(2) of the ATMP Regulation.[1] Such custom-made products are usually produced on a non-routine basis according to specific quality standards and used in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient.[1] However, it should be noted that national traceability and pharmacovigilance requirements, as well as specific quality standards, are equivalent to those provided for ATMPs for which an MA is required. One of the most important issues related to the ñhospital exemptionò clause use is its non-harmonized implementation across different MS. Very often systemic follow-up or information about clinical efficacy and safety data from hospital exemption ATMPs are not available. Still, clinical trials are the safest route for obtaining clinical data on certain ATMPs. Clinical trials are under the responsibility of the National Competent Authorities (NCA).

ATMP CLASSIFICATION

All ATMP developers, regardless of whether they plan to produce ATMP under the hospital exemption rule or with the intention of placing it on the EU market, have access to an optional procedure provided by CAT in order to address, as early as possible, questions of borderline cases where classification of a product based on genes, cells or tissues is not clear.[7] This activity enables the EMA, in close collaboration with the European Commission, to determine whether or not a given product meets the scientific criteria which define ATMPs. This Scientific recommendation on classification of ATMPs is free of charge and a legally non-binding procedure that helps developers to clarify the applicable regulatory framework and facilitates further communication with the regulators at the national level.

The ATMP classification is based on the provisions set down in the ATMP Regulation and the definitions of a medicinal product and gene and somatic cell therapy product in Annex I to Directive 2001/83/EC.[1, 7, 8]

The classification procedure is only applicable when a product is based on genes, cells or tissues.

The cells or tissues are considered ñengineeredò if they have been subject to substantial manipulation, so that their biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved and/or the cells or tissues are not intended to be used for the same essential function in the recipient as in the donor (non-homologous use).[7]

According to Article 2(1)(a) of ATMP Regulation, an ATMP means any of the following medicinal products for human use:

- a gene therapy medicinal product (GTMP) - defined in Part IV of Annex I to Directive 2001/83/EC as amended[8, 9]
- a somatic cell therapy medicinal product (sCTMP) - defined in Part IV of Annex I to Directive 2001/83/EC, as amended[8, 9]
- a tissue engineered product (TEP) - defined in Article 2(1)(b) of ATMP Regulation[1]

The claimed mode of action (MoA) of the product is particularly important for ascertaining whether the product is for treatment, prevention or diagnosis of a disease, and exerts its activity via pharmacological, immunological or metabolic action, or whether the product is intended for regeneration, repair or

replacement of cells/tissues.[1, 7] In this regard, GTMP is a product containing an active substance which contains a recombinant nucleic acid and has a therapeutic, prophylactic or diagnostic effect that is directly related to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.[8, 9] That means that the recombinant nucleic acid should be directly involved in the MoA and therapeutic action of the product. sCTMP is a product containing cells or tissues that have been subject of substantial manipulation, and that is intended for treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.[8, 9] If no substantial manipulation of the cells or tissues takes place, the classification is based on the essential function of the cells or tissues (homologous or non-homologous use).[8, 9] TEP is a product containing engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.[1]

In addition to mentioned classes of products, in Article (2)(1)(d) of the ATMP Regulation there is also definition of ñcombined ATMPò as a product that incorporates an active substance (cellular or tissue part) and one or more medical devices as an integral part of the product.

In order to facilitate the access to the ATMP classification procedure and to give guidance for the steps to be followed by the applicant, the CAT has published procedural advice for the ATMP classification.[10] The outcomes of the ATMP classifications assessed so far by the CAT are available on the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac058007f4bc).

CURRENT SITUATION – AUTHORIZED ATMPs

In October 2009, the first MA was granted to an ATMP in the EU. ChondroCelect was an autologous cell culture product consisting of chondrocytes expanded in vitro intended for the treatment of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults. The product was withdrawn from the market in 2016 because of reimbursement issues.

Three years later, in 2012, another MA was granted to Glybera. Glybera is a gene therapy medicinal product indicated for the long term correction of lipoprotein lipase deficiency aiming to control or abolish symptoms and prevent complications in adult patients clinically diagnosed with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis despite dietary fat restrictions. The marketing authorization of this product will not be renewed, and therefore by the end of 2017 this product will no longer be authorized in the EU.

In 2013, two ATMPs were authorized for the EU market; MACI and Provenge.

Provenge was a somatic cell therapy product consisting of autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor. Provenge was an immunotherapy designed to induce an immune response targeted against prostatic acid phosphatase (PAP) expressed in most prostate cancers. The product was indicated for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated. The product was withdrawn from the EU market in 2015 because of poor commercial performance.

MACI was a product consisting of matrix applied characterized autologous cultured chondrocytes. It was 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 cm^2 in skeletally mature adult patients. In 2014, the EU manufacturing site for MACI in Denmark was closed. Consequently, the license of the manufacturing site was withdrawn and MA suspended. Therefore, MACI has become unavailable in the EU unless a new manufacturing site is approved and manufacture resumed.

In 2015 additional two ATMPs were granted MA, Holoclar and Imlygic.

Holoclar is a product consisting of *ex vivo* expanded autologous human corneal epithelial cells containing stem cells, and it is intended for the 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.

Imlygic is a first-in-class oncolytic immunotherapy derived from the wild-type herpes simplex virus 1 (HSV-1) genome that is designed to selectively replicate in tumour tissues. It is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease.

In 2016 two ATMPs were authorized; Strimvelis and Zalmoxis.

Strimvelis is a product consisting of autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence. It is indicated for the treatment of patients with severe combined immunodeficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Zalmoxis is a product based on T-cells genetically modified to express the Herpes Simplex Thymidine Kinase (HSV-TK) suicide gene and a truncated form of the human Low Affinity Nerve Growth Factor Receptor (qLNGFR) genes (for identification of transduced cells). The therapy is conceived as an

adjunctive treatment in haploidentical haematopoietic stem cell transplantation of adult patients with high-risk haematological malignancies.

In 2017, one more ATMP was authorized: Spherox, a tissue engineered product for the 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 of up to 10 cm^2 in adults.

All listed authorized products are/were the subjects of additional monitoring, making the products monitored even more intensively than other medicines.

Glybera, Holoclar, Strimvelis and Zalmoxis are products designated as orphan drugs. The "orphan designation" means that these medicines are used to treat life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the EU, or are medicines which, for economic reasons, would be unlikely to be developed without incentives.

Glybera was authorized under exceptional circumstances, meaning that applicant showed that at the moment of issuing MA they were unable to provide comprehensive data on efficacy and safety of the medicine due to the rarity of the condition it was intended for.

Holoclar and Zalmoxis were granted conditional approval. In such cases an approval of a medicine is made on the basis of less comprehensive data than normally required. The positive opinion is based on data that indicate that the medicine's benefits outweigh its risks. However, the applicant is expected to provide comprehensive data generated after authorization within an agreed timeframe. The conditional approval is renewed on a yearly basis until all obligations have been fulfilled, and then it can be converted from a conditional approval into a normal approval.

CONCLUSION

In 2016, Hanna et al. published an analysis of all ATMPs clinical trials conducted between 1999 and June 2015 using three clinical trials databases; ClinicalTrials.gov, The International Clinical Trials Registry Platform of the World Health Organization and EudraCT.[11] In that study, 939 ATMP trials were identified, 34 registered in 1999-2003, 333 in 2004-2010 and 572 in 2011-2015.[11] Oncology remained the dominant therapeutic area accounting 24.8% of the ATMP trials identified. Three analyzed periods were selected for the following reasons; 1999-2003 represented the period before the initiation of EudraCT; 2004-2010 was a period after EudraCT initiation and the first term of CAT and adoption of the CAT work program (2010-2015) that aimed to foster the development of ATMPs.[11] Based on the presented numbers of ATMP clinical trials, it is possible to make a conclusion about the impact of the ATMP Regulation on the expanding development of these innovative medicinal products.[11, 12] Still, nine years after the implementation of ATMP Regulation only 9 ATMPs have been approved in the EU. Two of them were withdrawn from the market because of poor commercial performance, for one, the MA will not be renewed, and one product is suspended because of manufacturing site closure. One of the major problems is that produced ATMPs usually target orphan diseases and therefore have very limited use and a limited market. In addition to that, the development of ATMPs is usually more expensive and can be a big challenge in relation to reimbursement than conventional products. For example, Glybera has a million euro price tag. It represents one of the most expensive treatments in the world today, thus facing the challenges of poor commercial performance as well. The ATMPs need to be sustainable in order to stay on the market and this presents one of the major issues to address in the further development of the ATMP field.

In August 2017, the US FDA approved Novartisô chimeric antigen receptor (CAR) T-cell therapy, Kymriah, for the treatment of relapsed acute lymphoblastic leukemia. Novartis plans to submit an application for market authorization with the EMA as well. This was a big step forward because Kymriah was the first GTMP approved in the US, and at the same time the first CAR-T therapy that was internationally approved.

Product development in the ATMP field faces a number of unique challenges due to the complex nature of ATMPs that differs greatly from traditional developments of new chemical entities or biologics. Despite that, there is no doubt that recent and future advances in the fields of biomedical research and biotechnology will provide possibilities for even broader development and production of ATMPs. The issues related to sustainability of ATMPs on the market and effective translation of such expensive therapies to reach patients still persist. Although only few ATMPs have been authorized so far on the EU market, there are many products in the pipeline and regulators might play a major role in guiding and supporting development of the field. One of the CATôs major tasks is to help to bridge this translational gap in the ATMP development in the EU.

REFERENCES

1. The European Parliament and the Council of the European Union; Regulation (EC) No. 1394/2007 of the European Parliament and the Council of 13 November 2007 on Advanced Therapy Medicinial Products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union 10.12.2007(L324);50:121-137.
2. European Medicines Agency: Committee For Advanced Therapies (CAT). http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&mid=WC0b01ac05800292a4
3. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of Advanced therapy medicinal products in Europe: evidence that regulators

must be proactive. Molecular Therapy 2012;20(2):479-482.

4. 3 June 2016 EMA/345874/2016 Advanced therapy medicines: exploring solutions to forster 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. (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf)
5. Celis P, Ferry N, Hystad M, Schüßler-Lenz M, Doevendans PA, Flory E, Beuneu C, Reischl I, Salmikangas P. Advanced Therapy Medicinal Products: How to bring Cell-Based Medicinal Products Successfully to the Market - Report from the CAT-DGTI-GSCN Workshop at the DGTI Annual Meeting 2014. Transfus Med Hemother 2015;42:1974-199.
6. European Medicines Agency: Support for early access. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000856.jsp&mid=WC0b01ac0580b18c78
7. 21 May 2015 EMA/CAT/600280/2010 rev.1 Committee for Advanced Therapies (CAT). Reflection paper on classification of advanced therapy medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf)
8. 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. Official Journal of the European Union 28.11.2001(L311);44:67-128.
9. The Commission of the European Communities: Commission Directive 2009/120/EC of 14 September 2009 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. Official Journal of the European Union 15.9.2009(L242);52:3-12.
10. 13 December 2013 EMA/CAT/99623/2009 Rev.1 Committee for Advanced Therapies (CAT). Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No 394/2007. (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf)
11. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. J Mark Access Health Policy. 2016; 4: 10.3402/jmahp.v4.31036
12. Farkas AM, Mariz Segundo, Stoyanova-Beninska V, Celis P, Vamvakas S, Larsson K, Sepodes B. Advanced Therapy Medicinal Products for Rare Diseases: State of Play of Incentives Supporting Development in Europe. Front Med (Lausanne). 2017 May 16;4:53. doi: 10.3389/fmed.2017.00053.