The Regulatory Landscape for ATMPs in the EU and US: a Comparison

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Abstract

Every year, a small number medicinal products receive marketing authorisation or a product licence. However, in their wake several thousand drug candidates fall by the wayside. The discovery and development journey through to the approval and marketing stages of these successful candidates as we know it can take over 12 years and often much longer and costs approximately $2.6 billion (Sullivan, 2019).

Prior to the regulatory authorities granting a marketing authorisation or product licence, the sponsor is required to provide a dossier that includes relevant administrative, quality, nonclinical and clinical data. In addition, both the EU and US regulatory bodies require preclinical testing of the drug to be marketed and three clinical trial phases among the drug development process. These are lengthy, complex processes and in most cases patient access to medicines in a timely manner is very challenging.

With this in mind, both the EU and US regulatory authorities have adopted new initiatives which aim to make the availability of certain therapies accessible to patients in an expedited manner. Many of these initiatives focus on therapies that address unmet clinical needs. These initiatives are also available for many Advanced Therapy Medicinal Products (ATMPs).

However, as of October 2020, only 15 ATMPs have been approved in the EU in the last decade with five of them withdrawn from the market. In addition, only 14 such therapies have been approved in the US.

There have been some improvements since the commercialisation of the first ATMP yet many hurdles remain which have limited and will continue to limit the availability of safe, efficacious high quality products in a timely manner to patients in much need of these promising therapies.

1. Introduction

Every year, several medicinal products receive marketing authorisation or a product licence. For example in 2018, 103 novel therapies were approved in the EU (44 therapies) and US (59 therapies) (Leitgeb, 2019, *BioPharm International*, 2020). Meanwhile, 48 therapies were approved in the US in 2019 compared to 66 therapies receiving a positive opinion in the EU (Kashoki *et al.*, 2020,)

However, in their wake several thousand drug candidates fall by the wayside. The discovery and development journey through to the approval and marketing stages of these successful candidates as we know it can take over 12 years and often much longer and costs approximately $2.6 billion (Sullivan, 2019).

Prior to the regulatory authorities granting a marketing authorisation or product licence, the sponsor is required to provide a dossier that includes relevant administrative, quality, nonclinical and clinical data. In addition, both the EU and US regulatory bodies require preclinical testing of the drug to be marketed and three clinical trial phases among the drug development process. These are lengthy, complex processes and in most cases patient access to medicines in a timely manner is very challenging. With this in mind, both the EU and US regulatory authorities have adopted new initiatives which aim to make the availability of certain therapies accessible to patients in an expedited manner, Many of these initiatives focus on therapies that address unmet clinical needs. These initiatives are also available for many Advanced Therapy Medicinal Products (ATMPs).

This paper will review and compare the EMA (European Medicines Agency) and FDA (Food and Drug Administration) approval pathways for ATMPs. It will also access whether these initiates are fit for purpose for such therapies

ATMPs are a fast-growing field of novel therapies which have shifted the traditional strategy of “one-size fits all” to a more personalised medicinal approach. Cell therapies (discussed below), for example, can be allogeneic (universal) therapies where the therapy is dependent on a single source of cells (donor) to treat several patients. To date many of the approved cell therapies have been autologous, where the cells are derived from the patient, modified, expanded and used to treat the same patient. (Farid and Jenkins, 2018, De Riva, 2020).

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ATMPs offer revolutionary new prospects for the treatment of diseases and injuries such as Alzheimer's disease, cancer and muscular dystrophy and have huge potential for the future of medicines. ATMPs fall under the regulatory framework of biological medicines. In the EU, these therapies encompass gene therapy medicinal products (GTMPs), tissue-engineered products (TEPs) and cell-based therapy medicinal products (CTMPs).

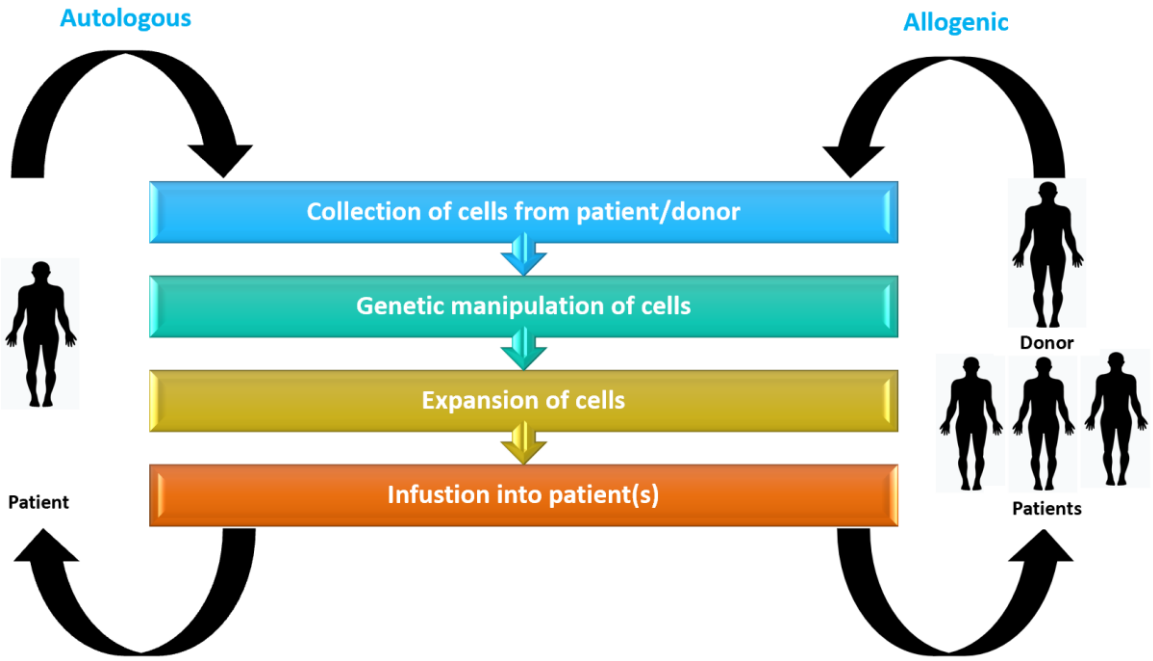

Figure 1. Cell Therapy Generation Process ((modified from) De Riva, 2020)

It is worth noting that the subclassification of ATMPs in the EU differ from those in the US. In the EU, the ATMP subclassification consists of four groups (somatic cell therapies, genre therapies, tissue engineered therapies and combination therapies) while that in the US consists of two subclassification which are cell therapies and gene therapies. (US FDA, 2019). In the US, these therapies are generally referred to as cell and gene therapies (CGT) while in the EU they are referred to as ATMPs. However, in both territories, these therapies fall under the regulations of biologics (Iglesias-Lopez *et al.*, 2019). An ATMP that integrates a medical device, is referred to as a combination therapy (cATMP) (Regulation (EC) No 1394/2007, Iglesias-Lopez *et al.*, 2019).

ATMPs are defined in "*section 506(g)(8) of the FD&C Act as including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271)"* (FDA and CBER, 2019).

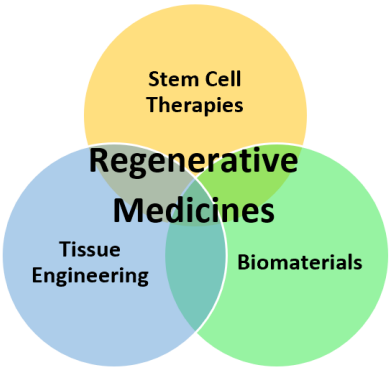

Figure 2. Regenerative medicines (modified from Gross, 2017).

2. Regulatory Framework

Advanced therapies were introduced into EU legislation as a new classification of biological medicinal products in 2003 through Directive 2003/63/EC, amending Directive 2001/83/EC. Meanwhile, the first EU wide regulatory framework relating to ATMPs Regulation 1394/2007 amending both Directive 2001/83/EC and Regulation (EC) No 726/2004 entered into force on 30 December 2007 and applied from 30 December 2008. Other Directives/Regulations relating to ATMPs include Directive 2009/120/EC of December 2009 relating to medicinal products for human use as regards advanced therapy medicinal products (and amending Directive 2001/83/EC), Regulation 726/2004/EC community procedures for the authorisation and supervision of medicinal products for human and veterinary use) (Eder and Wild, 2019).In the US the legal framework for biological products relating to ATMPs includes the regulation for biologics under section 351 of the Public Health Services Act (PHSA) and the Federal Food, Drug, and Cosmetic Act (FD&C Act) as well as Title 21 of the US Code of Federal regulation (CFR) 600 – 680 and also 21 CFR 1271. In addition, in December of 2016, section 506 of the of the FD&C Act of the 21st Century Cures Act was amended by adding a new section (section 30330) which explicitly addresses the expedited development and review of some

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regenerative medicine therapies designated as Regenerative Medicine Advanced Therapy (RMATs) (US Congress.Gov - 21st Century Cures Act, 2016).

In some cases, the approval process of a novel medicinal product is expedited. In the US this occurs through one of FDA's expedited programmes, such as the Fast Track Designation scheme and in the EU through pathways such as the Priority Medicine Designation Scheme (Smith, 2017, FDA, 2017). This expedited development pathway only applies to certain therapies which treat severe or life-threatening illnesses and are considered to offer therapeutic benefit over current approved medicines. Advanced therapies typically meet these criteria. The approval pathway depends on the medicine's characteristics and the target patient population (Detela and Lodge, 2019a).

In the US, the FDA launched the Fast Track Designation (FTD) and Breakthrough Therapy Designation (BTD) while in the EU, the Priority Medicines (PRIME) Designation scheme was launched and prior to that, the adaptive pathway which was formerly known as 'Adaptive Licensing' (FDA, 2014, EMA, 2016, Article 14(8) of Regulation (EC) No 726/2004, EMEA, 2005, (Gannedahl, Udechuku and Bending, 2018). In addition to this, in the EU, other options are available for ATMPs which includes Orphan Designation, Compassionate Use and Hospital Exemption. A hospital exemption (HE) is granted on a non-routine basis. It permits the use of an ATMP in the EU member state's territory without the need for a marketing authorisation. This exception only applies to custom made therapies in hospital settings and only in certain circumstances where a patient is in much need of a treatment and where no medicines are currently available particularly in areas of high unmet medical need. If such therapies are granted a HE, they still need to comply with the same requirements that apply to authorised medicinal products in regard to quality, traceability as well as pharmacovigilance (Medicines Agency, 2016, Yano and Yamato, 2018).

- **Fast Track Designation (FTD)**

This program was developed to expedite the development and review process of medicines intended for serious or life-threatening conditions, where clinical or non-clinical data indicate these medicines fill an unmet medical need (FDA, 2014).

Fast track drugs are potentially eligible for the Accelerated Approval and Priority Review schemes. Accelerated Approval is a scheme established for therapies that are intended for

serious conditions and that cater for an unmet medical need. They must also demonstrate their effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit or on a clinical endpoint (*Accelerated Approval | FDA*, 2018).

In addition, it is designed for illnesses where the disease course is long, and an extended period would be required to measure the intended clinical benefit of the drug. Developers of such therapies are permitted to market their product while continuing to conduct confirmatory studies to obtain full marketing approval (Gault, 2015). On the other hand, Priority Review expedites the therapy's approval process from the standard ten months to six months (Gault, 2015).

- **Breakthrough Therapy Designation (BTD)**

This program was developed to expedite the development and review process of medicines for serious or life-threatening conditions with primary evidence of considerably enhancing at least one clinically significant endpoint over current available medicines (FDA, 2014).

Breakthrough therapies are entitled to fast track benefits as well as priority review and accelerated approval.

- **Regenerative Medicine Advanced Therapy (RMAT)**

According to se*ction 3033 of the 21st Century Cures Act, a drug is eligible for RMAT designation if:*

a. *The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;*
b. *The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and*
c. *Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.*

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These therapies are eligible for the expedited programs, comprising Breakthrough Therapy Designation, Fast Track Designation, RMAT Designation, Priority Review Designation and Accelerated Approval (FDA, 2019). A medicine that obtains RMAT designation may be eligible for priority review if it meets the criteria at the time of marketing application submission. Furthermore, therapies that receive RMAT designation may be offered accelerated approval (FDA, 2019).

- **PRIority Medicines (PRIME) Designation**

This program was developed in 2016 and was intended to enhance the support given for the development of medicines that target an unmet medical need. It uses processes that were already part of the regulatory framework such as accelerated assessment, conditional approval, and scientific advice. It was also designed to initiate early dialogue between the EMA and the therapy developer (FDA, 2014). Medicines under this scheme are usually granted Accelerated Assessment. This assessment is a process that reduces the time required for an application to be reviewed (150 from the standard 210 days).

- **Conditional Marketing Authorisation (CMA)**

This scheme was developed for medicinal products with promising, yet incomplete efficacy data are granted market authorisation on the condition that they are further evaluated while on the market (Gulfo, 2016, Bonnano, *et al.*, 2017). In addition, specific obligations are mandatory with regard to collection of pharmacovigilance data (EMEA, 2005, Troncoso and Diogene, 2014, Godman *et al*., 2015). However, the authorisation is not intended to remain conditional indeterminately. The CMA is only effective for one year. Upon review of information collected during the conditional approval period, these medicinal products may be withdrawn from the market, granted traditional standard approval or continue to be marketed conditionally, depending on the data collected during that period (Gulfo, 2016). The CMA scheme was launched in 2006, however it was later integrated within PRIME (Antoñanzas, Juárez-Castelló and Rodríguez-Ibeas, 2018).

- **Authorisation Under Exceptional Circumstances (ECMA)**

A marketing authorisation under exceptional circumstances is only applicable to therapies that cannot obtain a standard marketing authorisation as the required safety and efficacy data cannot be provided due to the disease being so rare or because a clinical endpoint is challenging to measure due to ethical or scientific reasons (EMA, 2005, Nicotera *et al.*, 2019). Since it is not possible for these therapies to obtain a standard MA, an ECMA is granted on the basis that the applicant agrees to continuously monitor product safety and reports any product incidents to the competent authorities. After an ECMA is granted it is valid for five years with annual re-assessment procedures performed. Generally, therapies licenced through this scheme would have an orphan drug designation. However, orphan drugs are only eligible for the ECMA designation if they meet the criteria of same (Detela and Lodge, 2019b).

Table 1. Overview of US Expedited Pathways (FDA, 2014, EFPIA, 2016)

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review	Regenerative Medicine Advanced Therapy
Nature of Program	Designation	Designation	Approval Pathway	Designation	Designation
Year Introduced	1997	2012	1992	1992	2016
Qualifying Criteria	A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR • A drug that has been designated as a qualified infectious disease product	• A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labelling change pursuant to a report on a paediatric study under 505Ab OR • An application	A drug is a regenerative medicine therapy, AND the drug is intended to treat, modify, reverse, or cure a serious condition, AND preliminary clinical evidence indicates that the drug has the potential to address

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			mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	for a drug that has been designated as a qualified infectious disease products OR • Any application or supplement for a drug submitted with a priority review voucher	unmet medical needs for such disease or condition
Timeline for response	• Within 60 calendar days of receipt of the request	Within 60 calendar days of receipt of the request	Not specified	Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement	• Within 60 calendar days of receipt of the request
Features	• Actions to expedite development and review • Rolling review	All fast track designation features, including: ♣ Actions to expedite development and review ♣ Rolling review • Intensive guidance on efficient drug development, beginning as early as Phase 1 • Organisational commitment involving senior managers	Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements

Table 2. Overview of EU Expedited Pathways (EMA, 2016, Early access, Valid Insight, 2016, EFPIA, 2016)

	Conditional Marketing Application	Authorisation Under Exceptional Circumstances	PRIME	Accelerated Assessment
Nature of Program	Expedited Development	Expedited Development	Early dialogue with product developer	Expedited Review
Year Introduced	2005	1993	2016	2005
Qualifying Criteria	Intended for serious life-threatening or debilitating diseases OR For use in emergency conditions OR for Orphan medicines Intended for medicines where benefit of their availability outweighs the risks of less comprehensive data than usually required	Intended for when data on safety and efficacy is not possible due to information not being available or due to a rare condition or unethical reasons	Intended for therapies that may have the potential to address an unmet medical need OR a therapy that offers significant advantages through a significant enhancement of efficacy	Intended for therapies that are of interest to the public in so that they offer innovative public benefit
Timeline for Response	210	210	210	150 days instead of 210
Features	• Similar to FDA Accelerated Approval • May be eligible for expedited assessment	Full safety and efficacy data not required	• Enables Accelerated Assessment • Similar to FDA's Breakthrough Therapy Designation	Equivalent to FDA Priority Review

3. ATMP Approvals in the EU and US

In 2009, ChondroCelect® was the first ATMP approved in the EU and is a TEP for the treatment of cartilage defects (Kassim and Somerville, 2013). About a year later, the US approved its first ATMP,PROVENGE®, a somatic cell therapy indicated for the treatment of certain prostate cancers (*European Medicines Agency, 2013).* Meanwhile, Glybera® was the first gene therapy approved in the EU in 2012 (*European Medicines Agency, 2013).* It should be noted that several of the earliest approved ATMP therapies were later withdrawn from the market for

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various reasons. For example, after the expiry of Glybera's marketing authorisation (MA) its marketing authorisation holder did not apply for an MA renewal. The CEO of uniQure Matt Kapusta, stated that *"Glybera's usage has been extremely limited, and we do not envision patient demand increasing materially in the years ahead"*(WARNER, 2017). ChondroCelect was also withdrawn from the market in July 2016, at the request of the marketing authorisation holder citing commercial reasons (EMA, 2019). Zalmoxis was also withdrawn from the market with the MA holder stating that is has decided to permanently discontinue the marketing of the therapy for commercial reasons(EMA, 2019).

Table 3. Current approved ATMPs in the EU as of October 2020 (*KEGG DRUG: New Drug Approvals in Europe*, 2020) (*European public assessment reports: background and context | European Medicines Agency*, no date).

Therapy Name	Licence Holder	Approval Date
ChondroCelect	TiGenix	Oct 2009 – Jul 2016
Glybera	UniQure	Oct 2012 – Oct 2017
MACI	Vericel	Jun 2013 – Sep 2014
Provenge	Dendreon	Sep 2013 – May 2015
Zalmoxis	MolMed	Aug 2016 – Oct 2019
Holoclar	Chiesi	Feb 2015
Imlygic	Amgen	Dec 2015
Strimvelis	GSK/Orchard Therapeutics	May 2016
Kymriah	Novartis Europharm Ltd.	Aug 2018
Luxturna	Spark Therapeutics Ireland Ltd.	Nov 2018
Spherox	CO.DON	Jul 2017
Yescarta	Kite Pharma EU	May 2018
Zolgensma	AveXis EU Limited,	May 2020
Zynteglo	Bluebird Bio	May 2019
Alofisel	Takeda/ TiGenix	Mar 2018

Table 4. Current approved ATMPs in the US as of October 2020 (FDA, 2020).

Therapy Name	Licence Holder	Approval Date
Allocord	SSM Cardinal Glennon Children's Medical Center	May 2013
Clevecord	Cleveland Cord Blood Center	Sep 2016
Ducord	Duke University School of Medicine	Oct 2012
Gintuit	Organogenesis Incorporated	Mar 2012
Hemacord	New York Blood Center, Inc	Nov 2011
Imlygic	Amgen Inc.	Oct 2015
Kymriah	Novartis Pharmaceuticals Corporation	Aug 2017
Laviv	Azficel-T	Jun 2011
Luxturna	Spark Therapeutics, Inc.	Dec 2017
MACI	Vericel Corporation	May 2019
Provenge	Dendreon Corporation	Apr 2010
Tecartus	Kite Pharma, Inc.	Jul 2020
Yescarta	Kite Pharma, Inc.	Oct 2018
Zolgensma	AveXis, Inc	May 2019

Looking at the above tables (Table 3 and Table 4), only 15 ATMPs have been approved in the EU in the last decade with five of them withdrawn from the market. Meanwhile, only 14 such therapies have been approved in the US. In addition, the approvals in the two regions somewhat differ from each other. One would ask, why is there only a limited amount of approvals so far and also some withdrawals?

Generally, market withdrawal is due to product safety or for commercial reasons. For example, Glybera (the first gene therapy to receive an MA in the EU) was withdrawn from the market as its developers decided not to apply for MA approval due to Glybera's commercial failure in the EU. The developers also encountered difficulties getting the Glybera to the US and hence it is not listed in table 4. Glybera had a market price of €1million and a very limited target population. This added to its failure on the market as the governments were not interested in paying for it (Cynober, 2020).

Moreover, the main challenges that have been shown to impede the approval process are specifically safety and efficacy issues as well as hurdles related to product quality and/or product scale-up.

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product scale-up. One of the EMA's Committee for Advanced Therapies (CAT) initiatives it to provide developers with quality data certification. This involves the scientific evaluation of a product's quality data and is set to identify any potential issues early in the development process so that they can be addressed ahead of the submission of a MAA. However, this quality certification is only available to developers who have a micro-, small-, or medium-sized enterprise (SME) status. Hospitals, academia and other non-profit organisations do not hold SME status and therefore, would not benefit from CAT's certification process. This is a big obstacle as these non-profit organisations generally tend to be the main ATMP sponsors (Carvalho, Martins and Sepodes, 2019).

Even though the EU and US expedited pathways applicable to ATMPs offer additional flexibility and the prospect for accelerated market authorisation they are still criticised as being too complex and lengthy. They are also considered too ambiguous by non-profit organisations and SMEs due to restricted regulatory oversight (Elsanhoury *et al.*, 2017).

Furthermore, as mentioned earlier, a hospital exemption is a dedicated pathway available in the EU that permits the use of unlicenced ATMPs in a member state's territory without the need for an MA. However, this pathway has its own limitations for example this pathway is only available for custom-made products developed for individual patients (Cynober, 2020). This option is only available for ATMPs prepare and administered in a hospital setting. Moreover, under the HE these therapies can be administered to a patient even if there is an alternative therapy available on the market (Houses of Parliament, 2017).

These HEs may encourage product developers not to apply for centralised marketing approval and an HE might be seen to offer a more pragmatic option. However, not opting for the central licencing route limits the availability of ATMPs to patients throughout the EU which means less patients have access to them.

Currently, there is a push from organisations such as European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) to control the use of such exemptions and to standardise/harmonise their use throughout the EU member states.(EUCOPE, 2020).

It is evident that more needs to be done to expedite the drug development, approval and support processes so as to ensure more ATMPs are approved in a timely manner for patient

access. In January of this year, the Alliance for Regenerative Medicine (ARM) published a positioning paper outlining its recommendations on how the above raised question can be addressed. These recommendations are:

- *"Establish a 'one-stop shop' ATMP coordination body at EU/EEA level to act as a broker between the different stakeholders and facilitate cross-border patient treatment and funding.*

- *Create 'one-stop shop' ATMP coordination bodies in countries with regional funding or with multiple payers/insurers to ensure authorities in the regions of treatment are compensated for the costs of treating patients from other regions.*

- *Encourage more effective coordination of HTA activities to ensure greater alignment within Europe on product value assessment measures."*(The Alliance for Regenerative Medicine, 2020).

In conclusion, ATMPs are complex and are costly to develop and manufacture. A high level of expertise is required for their development. Having said they, these therapies present the potential cures and not just treatment for diseases. Even though there have been some improvements since the launch of the first ATMP, many regulatory hurdles remain which have limited and will continue to limit the availability of safe, efficacious, high quality products in a timely manner to patients in much need of these promising therapies. It is evident that the regulatory framework is not best fit for purpose for ATMPs and that changes are needed to streamline the availability of such therapies to patients. Some recommendations include the following:

1. Harmonisation between the EU and the EU member states national competent authorities.

2. Regional harmonisation between the EU and US regulatory bodies.

3. Establishment of a streamlined approval process

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4. The development of regulations with a focus on developing a practical risk-based approach.

5. Streamlining and unifying the approval processes of ATMPs

6. Early support and communication between the regulatory authorities and all ATMP developers and not just SMEs.

7. Harmonisation of the re-imbursements strategies available to ATMP developers on an EU level as well as on a global level

8. Permitting the free movement of ATMPs within the EU.

9. Developing a "mutual recognition" approval pathway between the EU and other regions that is applicable to ATMPs

10. Identifying the skills and expertise needed to develop and regulate ATMP and fostering specialist centres and programmes to nourish and sustain these requirements

The road to success is long, but vital to address the unmet needs of the patient.

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