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ARM Response to the Roadmap on the Pharmaceutical Strategy – Timely patient access to affordable medicines.

About the Alliance for Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organisation dedicated to realizing the promise of advanced therapy medicinal products (ATMPs). ARM promotes legislative, regulatory and reimbursement initiatives in Europe and internationally to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing ATMPs. In its 11-year history, ARM has become the voice of the sector, representing the interests of 350+ members worldwide and 70+ members across 15 European countries, including small and large companies, academic research institutions, major medical centres and patient groups. To learn more about ARM, visit http://www.alliancerm.org.

Advanced Therapy Medicinal Products are life-changing therapies

Advanced Therapy Medicinal Products (ATMPs) including cell therapies, gene therapies and tissue engineered products, constitute a new category of innovative products whose full potential is beginning to emerge. The advanced therapies sector is creating transformative, durable treatments and potential cures for some of humankind's most devastating diseases – many currently untreatable via conventional treatments – through the use of ground-breaking scientific discoveries and technologies.

The Covid-19 crisis revealed the importance of investing in healthcare, particularly in areas of unmet needs. ATMPs can play an important role to meet these needs and represent an opportunity for Europe to take a leading role in embracing this new field of innovation.

Appropriate regulation for ATMPs is critical to ensuring patients are safe and therapies are effective

With the adoption of EU Regulation (EC) 1394/2007 in 2007, the European regulatory authorities paved the way to set sound standards for the review of, and marketing authorisations for ATMPs. The European Medicines Agency (EMA) was the first regulatory agency globally to evaluate and approve ATMPs and continues to provide invaluable support for the translation of ATMPs into patient treatments. During the first decade after the adoption of the EU Regulation, the number of ATMPs gaining marketing authorisations and their market adoption have remained limited. However, the development of ATMPs has accelerated, with a dramatic increase in the number of clinical trials, scientific advices and Priority Medicines (PRIME) designations over the last few years. According to its Executive Director in April 2019, the EMA expects "between 10 and 20 approvals or submissions for ATMPs each year within the next 5 years".

The applicable regulatory standards obligate product developers to satisfy a number of requirements before they may bring an ATMP on the market. These include: regulatory

oversight of pre-clinical and clinical evaluation of the investigational product, adherence to pre- and post-market approval requirements, and demonstration that the product is being manufactured according to current good manufacturing practices (cGMP) to assure quality, efficacy and safety of a product before it reaches a patient.

Such requirements are of paramount importance to ensure that cell- and gene-based treatments are safe and effective. Patients using unproven or unregulated ATMPs - such as those promoted by stem-cell clinics and by some physicians or hospitals - have reportedly suffered serious, sometimes fatal, side effects. Recently, the European Medicines Agency issued a warning against unproven cell-based therapies, re-affirming that circumventing the marketing and clinical trial authorisation procedures deprives future patients of access to potentially curative medicines.

The need for robust, transparent, evidence-based and harmonised procedures for ATMPs as well as recommendations for increased transparency and harmonisation in hospital exemption procedures was also recently stressed by academic and industry stakeholders. ARM believes that a good practices guide and specific recommendations regarding a common interpretation and implementation of the hospital exemption across the different Member States is urgently needed. To this effect, ARM is planning to release a series of updated, more specific recommendations based on a recent analysis of the legal implementation and actual use of the hospital exemption across Europe.

While the ATMP sector in Europe is dynamic, the region lags others in attracting clinical trials which can impact innovation and manufacturing

The predictability and clarity of the regulatory framework, adequate innovation incentives, and highly skilled workforce, combined with an excellent network of academic and healthcare infrastructure have contributed to establish a strong innovation-base and important R&D investments in Europe in the ATMP sector. In 2019, the total global financing in the ATMP sector was 9.8 Billion $, of which 3.0 Billion $ (2.7 Billion €) was raised by companies headquartered in Europe. This shows how vibrant and attractive this sector is, including in Europe, creating many jobs and contributing to economic growth. At the end of 2019, there were approximately 237 ATMP companies headquartered in Europe, representing approximately 25% of all ATMP developers.

An active and sustainable ATMP industry in Europe is key to maintaining innovation and manufacturing capabilities in the region. However, there are indications that Europe is losing its competitiveness in the sector to the benefit of other regions, in particular North America and Asia. A study conducted by ARM last year indicated that:

- Though the number of ATMP therapeutic developers based in Europe is approximately half of that based in North America, the number of clinical trials that have been initiated in Europe during the 2014-2018 period is only about a third of that in North America.
- During the same time period, the number of new clinical trials during the 2014-2018 period increased by 32% globally, 36% in North America, 28% in Asia, and less than 2% in Europe.
- There are proportionally more new gene therapy clinical trials (utilizing gene delivery, gene editing, and gene modified cell therapy technologies) in North America (71% of all ATMP trials) than in Europe (55% of all ATMP trials).

(see on https://alliancerm.org/indication-data/clinical-trials-in-europe/)

The fragmentation of regulatory bodies and ethical committees and the lack of harmonization on various aspects (e.g. donor testing requirements, patient information consent forms, contracting agreements) across the different countries may explain the complexity in starting new ATMP clinical trials in Europe.ain
In particular, the complexity of European Genetically Modified Organisms (GMO) requirements and the approval process is an important factor contributing to the fewer number of gene therapy trials in Europe. The GMO legislation was not originally designed for medicinal products and is not fit-for-purpose, it was designed mainly to cover plant and animal genetic modification with a goal to protect food consumers and crops from contamination, not so much to protect patients or caregivers.

ARM believes that the GMO legislation does not add value to protect citizens from the unwanted effects of the majority of medicinal products consisting of, or containing GMOs: the environmental and biosafety risk does not exist for non-replicating viral vectors and genetically modified human cells as these do not replicate and cannot survive long in the environment. Additionally, human individuals treated with in vivo therapies should not be considered as GMO.

ARM believes that the temporary exemption for Covid-19 vaccines and treatment to comply with GMO legislation is an excellent opportunity to test whether there is added value for imposing these GMO requirements to medicinal products consisting of, or containing GMO, and for the European Commission to reconsider the scope of the GMO legislation.

The implementation of the Clinical Trial Regulation (EU) N° 536/2014 is a unique opportunity to increase Europe's attractiveness for the conduct of clinical trials, including for ATMPs. Delays in the initiation of clinical trials have serious implications for ATMP developers, are particularly detrimental for small and medium enterprises and lead to delays in access to treatments for patients with high unmet medical needs. Therefore, it is important to ensure that ATMP clinical trials are approved in the shortest possible timeframe. In order to make the clinical trial approval process faster, national competent authorities need to allocate sufficient resources and ensure an adequate level of expertise for the review of applications for ATMPs. The interplay between the Clinical Trial Regulation with other applicable legislations such as the GMO Directives 2001/18/EC and 2009/41/EC, as well as the new Regulation (EU) 2017/745 for Medical Devices and Regulation (EU) 2017/746 for In Vitro Diagnostics will be of paramount importance to ensure that these do not act as disincentives to conduct clinical trials with ATMPs in Europe. As GMO and medical device approvals lie outside the Clinical Trial Regulation, ensuring timely and streamlined approvals will be necessary.

The consideration of the above aspects in the EC strategy could contribute to increase Europe's attractiveness for the conduct of clinical trials, to retain investment and production capacity in Europe and to favor earlier access to these ground-breaking, life-saving treatments.

New approaches are needed to ensure patient access to ATMPs

The pipeline of ATMPs in development and prices of some ATMPs have stimulated stakeholder dialogue on affordability and financial sustainability challenges. The Covid-19 crisis has pointed out the devastating effects of the lack of investment in health system. Investment in healthcare and specifically in areas of unmet needs, where ATMPs can play an important role are critical for patients. Because of their durable and potentially curative effect, ATMPs can provide savings in health systems in the long term as recently shown in a report (see on: https://alliancerm.org/?smd_process_download=1&download_id=5862). Concerns around financial sustainability impact both payers and developers and are of major importance

for a broader set of stakeholders including patients, governments and healthcare providers. If the stakeholder community fails to identify viable solutions to the structural challenges that have been identified, there is a risk that a number of potentially transformative treatments will never reach European patients, with the resulting negative individual, healthcare, societal and economic effects.

ARM is committed to facilitate an inclusive and solution-driven dialogue with all interested stakeholders and in July 2019 published the report 'Getting Ready for Advanced Therapy Medicinal Products in Europe' with a series of recommendations that will hopefully lead to timely and sustainable access to a large number of transformative treatments (see report on https://alliancerm.org/sector-report/market-access-report/).

The recommendations can be summarized as follows:

- Better adapt Health Technology Assessment (HTA) frameworks to ATMPs
- Support wider application of conditional reimbursement schemes
- Develop pan-European initiatives to build Real-World-Evidence (RWE) infrastructure
- Develop pan-European initiatives to create new early dialogue opportunities with regulators, HTA bodies and payers
- Build on the European legislation and guidelines to facilitate cross-border treatment and ensure timely and effective access to ATMP treatment for all EU patients
- Favor wider application of innovative access and funding arrangements such as pay-for-performance, annuity payments, and special funds for transformative treatments. Lift barriers preventing the adoption of such payment models, such as the ones stemming from ESA 2010 accountancy framework.

ARM recommendations provide balanced, fair, and effective solutions to ensure EU countries' readiness for the adoption of ATMPs. If implemented, these recommendations can improve the potential for:

- Timely patient access to ATMPs that may treat chronic, severe disabling or fatal conditions with high medical unmet needs,
- Reducing patient, societal, health care system and health insurance burden associated with a number of health conditions,
- Having a positive macroeconomic impact on the European Union and on individual European countries,
- Addressing some of the financial sustainability challenges of health systems and developers.

While HTAs and the pricing and reimbursement of medicinal products are national competencies, the role of the EC is particularly instrumental in the implementation of several of the above recommendations, in particular:

- in launching a new initiative for a high-level, multistakeholder forum to define a common set of principles for RWE and disease registries that could meet the needs of all: regulators, HTA bodies, payers, industry, healthcare professionals and patients.
- in coordinating HTA activities at the EU-level. In order to ensure greater alignment on ATMPs' clinical value assessment, it is proposed that HTA activities are coordinated in a more effective and efficient manner across the EU. ARM believes that the adoption of a EU joint clinical assessment, with no repetition of assessment at national, regional or local levels, will build a common understanding of ATMPs' clinical value across the EU that will accelerate patients' access and ultimately benefit all stakeholders.
- in facilitating cross-border treatment with ATMPs. ARM has identified a number of initiatives that should be taken at the European level to ensure that all European patients

can get access to ATMPs irrespective of the country or region they live in (see more on https://alliancerm.org/press-release/the-alliance-for-regenerative-medicine-outlines-recommendations-on-enabling-cross-border-and-regional-access-to-advanced-therapy-medicinal-products-atmps-in-europe/)

- In supporting the adoption of innovative pricing and payment models for ATMPs to ensure continued patient access to innovative therapies while preserving the sustainability of health systems in the EU.

In summary, ATMPs promise great clinical value for patients, society, and healthcare systems.

To ensure patients across Europe have access to safe and effective ATMPs, the following priorities should be addressed in the EC pharma strategy:

- **Ensuring that regulatory procedures are robust, transparent, evidence-based and harmonized in Europe**
  - **limiting hospital exemption and other regulatory carve outs that threaten patient safety**
- **Streamlining regulatory requirements for clinical trials with ATMPs across the different Member States,**
  - **ensuring smooth implementation of the upcoming clinical trial regulation**
  - **reconsidering the scope and implementation of the GMO legislation to medicinal products.**
- **Ensuring patients' timely access to ATMPs by**
  - **launching new initiative to build RWE infrastructure and disease registries at pan-European level.**
  - **coordinating ATMP clinical assessment at EU level, while adapting the HTA evaluation, pricing and reimbursement processes to capture and value the long-term benefits and risks of ATMPs,**
  - **facilitating cross-border treatment with ATMPs, and**
  - **supporting the adoption of innovative pricing and payment models for ATMPs to ensure continued patient access to innovative therapies while preserving the sustainability of health systems in the EU.**

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