ALLIANCE for Regenerative Medicine

Position on possible solutions to foster development and expand patient access for Advanced Therapy Medicinal Products in Europe

14 March 2018

Foreword

On 27 May 2016, the European Medicines Agency (EMA) convened a multi-stakeholder meeting to explore ways to foster ATMP development and expand patient access. The meeting was attended by leading academics and researchers, incubators and consortium organisations, including the Alliance for Regenerative Medicines (ARM), and representatives from patients and healthcare professionals' organisations, small and large pharmaceutical companies, the investment community, health technology assessment (HTA) bodies, national competent authorities (NCAs) and the European Commission (EC).
Further to this meeting, the EMA published a report summarising the main ideas and solutions proposed during the meeting as well as responses sent ahead of the meeting via a questionnaire[1].
More recently, an action plan on ATMPs was published by the European Commission (DG Health and Food Safety) and the EMA, listing proposed actions to improve the regulatory framework for ATMPs[2].
The present paper outlines and elaborates ARM position on the ideas and solutions proposed, with emphasis on aspects that should be dealt with high priority. The topics and proposals discussed in this paper follow the structure and main proposals as reported in the document issued by the EMA in June 2016[1].

1. Research and Development:

1.1. Pragmatic approach with the licensing requirements for ATMPs:

Specific requirements have already been adapted in different ways to facilitate the development and the licensing requirements for ATMPs. The existence and activities of the Committee for Advanced Therapies at the EMA and the several guidelines issued by CAT/EMA testifies for the acknowledgement of the specific expertise and different approach to be taken for ATMPs.

Risk-based approach:
The concept of the risk-based approach introduced to the legislation (with the revision of Annex 1, part IV of Directive 2001/83/EC as amended by Directive)[3] is a good illustration of the flexible approach taken by regulatory authorities to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application (MAA).
Such flexible and specific approach is particularly welcome and is strongly supported by ARM. The fact that it has not been widely used to date, due to uncertainty on expectations could be addressed by having workshops organised by the EMA to specifically illustrate how this approach could be used to support MAA content for different kinds of products.

Innovative manufacturing models:
ARM believes that the current regulatory system should address how the centralised marketing authorisation can accommodate situations where manufacturing, testing and product release solutions for the production of patient-specific ATMP products are not carried out in traditional manufacturing facilities and QC laboratories but in multi-site controlled but not classified areas using automated closed manufacturing and testing systems. This includes production of autologous products using the same automated closed manufacturing system at multiple sites with appropriate validation of the equipment and process should be allowed under a single manufacturing authorisation.

Use of Master Files:
ARM would welcome a Master File system for excipients and raw materials used in the production of ATMPs.
In addition, ARM encourages the implementation of a Cell History/Master File system such as the Drug Master File applicable in the US or the Plasma/Vaccine Master File in the EU. The adoption of a Cell History File as a non-mandatory document which acts as a 'passport' for the history and provenance of cells has been endorsed in the UK. Such concept could be expanded to all Member States in the European Union. This file will remove some of the administrative burden for applicants for requesting information from suppliers, which they often do not share due to the confidential nature of some data.
It will help both support regulatory submissions (Clinical Trial Applications as well as Marketing Authorisation Applications) but also in due diligence exercises.

1.2. GMO requirements:

Gene therapy products and some somatic cell therapy medicinal products fall under the definition of Gene Modified Organisms (GMO) and must comply with requirements of the GMO Directives and Regulations[4] when clinical trials for gene therapy investigational medicinal products are conducted in Europe. The 2 main directives applying to GMOs (Directive 2001/18/EC and Directive 2009/41/EC) are not specifically designed for medicinal products, raising a number of specific issues when gene therapy medicinal products need to gain approval from GMO authorities at national or regional levels. In addition, there are wide divergences in their implementation in Member States, and competent authorities for GMO differ from competent authorities for medicinal products. Since requirements differ among Member States, the integration of GMO assessment in clinical trials authorization poses a challenge, particularly in the context of multicentre clinical trials.

ARM, along with EFPIA, EBE and EuropaBio believe that, in order to maintain EU competitiveness for the development of innovative ATMPs and allow patient access to these important medicines in a timely fashion, a series of proposals to address these issues, detailed in a position paper published in September 2017, should be considered by the European Commission and Member States. The near- and medium-term solutions could be implemented quickly to allow streamlining of the assessment for clinical trials that continue to be reviewed under the Clinical Trials Directive, while long-term solutions need to be considered for the transition to the Clinical Trials Regulation.

More information with a detailed description of the proposals can be found in the joint position paper (see here).

1.3. Convergence of cell, tissue and blood requirements across the European Union

Cells, tissues and blood are key starting materials for the products but cannot be treated as conventional starting materials because of their human origin, the voluntary nature of the donation and the safety requirements for donors and patients to be treated with ATMPs.

ARM warmly welcomed the initiative of the European Commission to make available a database of accredited tissue establishments in Europe mentioning the authorised operations (procurement, importation, etc.) and the types of human tissues and cells available to ATMP manufacturers.
Similarly, the implementation of the Single European Code (SEC) for Tissues and Cells greatly facilitates enforcement by ATMP manufacturers of traceability requirements of tissues and cells in the EU of ATMP manufacturers[5]. However, it is less understood how this will be implemented in manufacturing processes.

Tests for donors vary greatly country by country. Wherever possible, duplication of donor testing requirements by country should be avoided and convergence of requirements on testing for cells and

tissue should be reached at international level. An ICH guidance to reach convergence on the minimal requirements would be helpful. It is suggested that a standard set of requirements for donor testing for tissues and cells used as starting materials for ATMP is established across all European Member States.

In addition, greater transparency on whether the Cells and Tissue Directive or the Blood Directive should be used as the basis for some starting materials is desirable and a pragmatic approach is encouraged as already done by some Competent Authorities.

Streamlining requirements for operations on human tissue and cells that fall under the scope of Directive 2004/23/EC (donation, procurement and testing of human tissues and cells) or Directive 2002/98/EC ("Blood directive") and requirements for ATMP manufacturing within the same entity/facility is recommended. For instance, inspections and documentation for obtaining Tissue Establishment (TE) and Pharmaceutical establishments/GMP certifications could be aligned and to the extent possible, granted by the same authority & inspected by the same inspectorate. This would result in increased efficiency in time, documentation and manpower, both for the authorities and ATMP manufacturers. The joint and/or delegated inspection introduced in the UK is viewed as a best practice and could be implemented in other, ideally all, Member States.

1.4. Need to develop standards for the field

The lack of standards can be an obstacle to product development, manufacturing, evaluation and testing of advanced therapies. Even though this topic has not been raised during the workshop in May 2016 and is not mentioned in the EMA report of June 2016 or the action plan in October 2017, ARM believes this is an area of priority action. This gap has been acknowledged in the U.S. and the US Senate Committee on Health Education Labor and Pensions passed legislation that directs the FDA to facilitate the establishment of a Standards Coordinating Body (SCB). The mission of the SCB is to work with standards developing organizations to support the development of national and international standards, to establish a Public-Private Partnership to support the development, dissemination, education and implementation of standards and to serve as a source of knowledge and experience to enable more efficient and successful clinical and commercial therapies. This initiative involves several stakeholders comprising US federal agencies (NIST, NIH, DoD, NSF,…), international bodies (CCRM, NIBSC, FIRM), standards developing organisations (ISO, ASTMi), industrial organisations (large pharma/biotech and SMEs) and additional stakeholders (professional societies, CMOs, CROs, tools providers, academia). The SCB has been officially launched early 2017 along with information on the work plan for the four working groups: gene therapy, cell therapy, tissue engineering and biomaterials and cell-based drug discovery[6].

ARM sees the need for greater engagement and coordination in Europe for the development of standards to ensure that standards are harmonised in the different regions, to improve product quality, enhance health and safety, and to strengthen market access and trade internationally. ARM would therefore encourage the participation of the EMA/CAT as well as EDQM or other EU agencies to the SCB. Better representation of Europe in this initiative will help to meet the objective to ensure progress and greater convergence on material and process standards essential to the timely advancement, approval and access of advanced therapies.

2. Regulatory processes:

2.1. ATMP Certification and GMP certification

The certification procedure is currently only open to SMEs. ARM proposes that the certification should also be made available to non-SMEs, including academia and spin-off incubators as well as to larger companies.

It is also proposed that GMP certification should not be required before applying for a clinical trial authorisation but that the GMP inspection and certification could take place in parallel to the clinical trial evaluation by regulatory agencies.

2.2. Interactions with regulatory agencies during development

Gaining scientific advice from regulatory authorities is the best way to guide and validate development plans. In order to further stimulate SMEs and academics to request advice at an earlier stage, it is proposed that their first scientific advice procedure is made free of charge by EMA and national Competent Authorities.

Nevertheless, scientific advice procedures typically last several months and are not adapted to meet the needs of ATMP developers, particularly SMEs with limited resources who cannot afford to wait for an opinion to pursue development. Procedures that allow a more frequent, informal and real-time dialogue between ATMP developers and regulatory agencies would therefore be very helpful and be made possible for all ATMP developers.

In addition, EMA could consider rapid-access schemes for scientific advice with pre-defined criteria. For example, it could limit the number of questions and the size of the document and/or limit the rapid-access schemes for products addressing situations of high unmet medical need. This would enable urgent issues to be tackled speedily. Furthermore, an option to request/have face-to-face discussion with Scientific Advice Working Party as a regular part of the procedure could further add value. It is currently up to SAWP to make that decision but a routine discussion as part of scientific advice would add significant value to the procedure and would particularly benefit SMEs.

An innovation office such as has been established in some Member States such as the UK and Germany and serve as a vehicle for facilitating such dialogue.

At the EU level, the Innovation Task Force already exists at the EMA and performs an important function for developers at an early stage in product or process development. Initiatives such as Adaptive Pathways and PRIME also provide sustained for developers of these innovative products. However, for companies developing products not eligible for schemes such as Adaptive Pathway and PRIME or not willing to use such schemes, there is a gap between discussions with the Innovation TF and SA procedures, including the EMA/HTA parallel scientific advice procedures. More flexibility and opportunities for dialogue could be envisaged, such as for questions regarding manufacturing process which often have to be resolved in a timeframe not compatible with a SA procedure. This could be achieved by a broadening of the scope of the Innovation TF and by making it open to all as there are many partnerships and collaborations between entities.

Regulatory agencies should ensure they have sufficient expertise and know-how in ATMPs to provide the requested advice to ATMP developments. Such innovation office should be open to all those engaged in ATMP development, including academia, research centres or non-for-profit organisations.

2.3. Guidance on IMPD and MAA structure

The format of the Common Technical Document has been initially designed for small molecules or biotechnology products but is often difficult to apply for ATMPs. As an example, it is often difficult to make a clear distinction between the drug substance and the drug product for an ATMP.
ARM recommends a pragmatic approach to the use of the eCTD format for these non-standard pharmaceutical products.

As an example, it is often difficult to make a clear distinction between the drug substance and the drug product for an ATMP. Similarly, the notion of assay for testing the drug product is often challenging for expanded cell products.

A template for IMPD and MAA, adapted to take account of the nature of the product, cell-based therapies or gene therapies, allogeneic or autologous, could be suggested. The current structure should be kept but there should be additional guidance, e.g. to get additional clarity on what constitute a drug product and a drug substance. This could be part of global effort as similar issue exists in the US and other countries; it could be considered whether ICH can take a role to streamline the format/structure of such application.

2.4. GMO requirements:

Regulatory processes for products that also fall under the definition of GMO could be facilitated as explained above (see above under 1.2.).

3. Hospital exemption:

Hospital exemption (HE) has been introduced in the European legislation[7] in order to make products available to individual patients on a non-routine basis and at the request of the treating physician.

HE is a useful pathway to enable patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available for an indication with a high unmet medical need. However, it is important to ensure that patients are protected from unnecessary risks and that hospital exemption is not misused to circumvent the applicable legal instruments for the marketing of safe and effective medicinal products in Europe.

ARM believes that the vastly different interpretations and enforcements of Article 3(7) of Directive 2001/83/EC across the European Union warrant priority action and formulates the following series of proposals:

- The European Commission should consider issuing guidelines defining more specifically the scope and requirements for HE for ATMPs, stating clearly that when patients have access to an ATMP with a Marketing Authorization, Member States should not authorize HE for the same medical indication. The guidelines should also address the possible interference of HE with recruitment of patients in clinical trials for the same indication.
- In order to increase transparency and exchange of information, it is proposed to have a publicly available registry of all sites using ATMP under hospital exemption and their therapeutic indications in all EU Member States.
- The Member States could consider making HE subject to the approval of an ethical committee review on a case-by-case basis. The submission to the ethics committee would include the patient consent form and a statement about the lack of alternative treatments.
- Initiatives such as tutorials to educate the medical community and research institutions on requirements for ATMPs, clinical studies and marketing authorization could be supported by the European Commission and/or EMA.
- Additional incentives to stimulate academic/industry collaborations could be envisaged at the EU and/or Member States level.

More information and details on the recommendations can be found in the ARM position paper published in February 2017 (see here).

4. Funding, investment and market access:

4.1. Funding and investment

Risk capital is limited and fragmented in Europe compared to the US. This is a significant issue for EU based SMEs, particularly when confirmatory trials should be carried out (typically at the start of phase II/III studies), which may prevent them from competing effectively. Any initiative that would increase the critical mass of risk capital available in Europe and remove national boundaries for access to capital in Europe would be highly valuable.

In general, convergence of regulatory and market access requirements, including on hospital exemption or on GMO requirements during clinical studies, across all Member States will improve the predictability and outlook for ATMP in development and will increase the attractiveness for investments in the sector.

4.2. Market access

Advanced therapies offer the potential of curing or dramatically improving serious and costly diseases. Today, most payers and reimbursement agencies focus on the cost for ATMPs and their more expensive nature than traditional medicines. However, it is important to acknowledge the potential value of these treatments to patients, and to recognize that uptake and appropriate reimbursement of these medicines based on the value they bring is needed if innovation in the area of advanced therapies is to continue.

At the same time, we also need to recognize that these treatments pose some distinct challenges to traditional healthcare systems in Europe, which may introduce undesirable barriers to their adoption to the detriment of patients in need.

ARM has identified four categories of potential barriers to their adoption:

- *Uncertainty:*
  Only 9 advanced therapies have been approved in Europe to date, only about half of them are commercialised and real-world experience is very limited. For some diseases, it may be decades before we know if the clinical impact has been as profound and as durable as anticipated on the basis of the available evidence at the time of regulatory approval. Health Technology Assessment (HTA) bodies in Europe limit the value assessment of ATMPs to their contribution to healthcare as demonstrated in the limited clinical data available at time of regulatory approval. As a result, policy makers may significantly undervalue new ATMPs and adopt a 'wait and see' approach to the adoption of these therapies, to the detriment of patients.
- *Economic disincentives:*
  In most cases, payers limit their analysis to the impact on their annual budget over a limited period of typically 1-3 years, which is inadequate to capture the savings in the long term. The other societal benefits that such products may deliver such as an increase of work productivity, reduction of the impact on caregivers, etc. are also typically not considered by HTA agencies in Europe.
- *Product complexity:*
  Some ATMPs are very complex and involve different procedures separated over time, care settings and even national territories, which may challenge healthcare systems that are set up around more conventional therapies. Specific delivery processes such as requiring the use of special devices or specific physician training, raise some additional difficulties as payment codes for these may be lacking or at the least require additional substantial investments to be implemented in routine practice (e.g. mandatory 15-year long-term follow-up patient monitoring).
- *Reimbursement and funding paradigm:*
  Healthcare systems are generally not configured to pay for new products in a manner other than a

price per unit (vial, treatment, procedure), exacerbating the divergence in timing of product cost and benefits generated by the product for one-time therapies. There may be statutory or legal barriers for reimbursement bodies at national or regional levels that pose reimbursement and/or funding challenges for ATMPs.

ARM believes that potential solutions to address some of the above-mentioned barriers need to be explored and discussed with the various stakeholders in Europe. Alternative reimbursement and/or financing models such as pay-for-performance and annuity models may need to be developed to address the potential uncertainty and economic disincentives that may be associated with ATMPs. The various healthcare systems in Europe may need to be prepared to adopt one or multiple solutions that are tailored to the specific attributes of the disease and the advanced therapy involved and the local healthcare system. To this end, ARM encourages HTA agencies and/or reimbursement authorities in the various Member States to carry out a mock appraisal based on one or different hypothetical product profiles that would be representative of some ATMPs under development to consider both the methodological challenges involved in the assessment of ATMPs and the potential impact on availability, patient access and development incentives for ATMPs. Such an exercise would be useful to better understand the specific difficulties that an ATMP could face and the possible remedies that are available considering the constraints and characteristics of the local healthcare system.

In order to facilitate the market access of advanced therapies, ARM proposes to foster a debate with HTA agencies, pricing and reimbursement competent authorities and policy makers in Europe to encourage pragmatic approaches when addressing issues such as:

- how to ensure the acceptability of data generated for marketing authorisation by HTA organisations and payers, for instance when data from double-blind randomised clinical trials cannot be made available;
- how the potential long-term value of ATMPs can be fully captured in pricing and reimbursement assessments despite the likelihood of high uncertainty and the limited data at launch;
- how post-commitments and real-world evidence data collection could be streamlined in integrated registries at pan-European level to meet the requirements of both the regulatory and national reimbursement authorities;
- how timely reimbursement of ATMPs could be granted when a marketing authorisation has been granted on the basis of short to medium-term data or limited data such as when conditional approval is granted, including mechanisms for price adaptation (up- and downwards) and/or review of conditions for reimbursement when more mature data become available;
- how reimbursement of new diagnostic tools, devices or medical procedures could be granted in a coordinated way when these are required for ATMP administration;,
- how mechanisms and methods such as risk-sharing frameworks could be adapted or designed, and innovative approaches be developed to assess and reimburse ATMPs such as curative treatments (e.g. annuity based payments could be adopted to spread the budget impact over time, pay-for-performance contractual agreements, etc);
- Whether and how HTA agencies and payers could be encouraged to reward the degree of innovation and avoid to unduly penalise highly innovative therapeutic approaches (such as breakthrough technologies using new mechanism of action) compared to more traditional medicines with known mechanisms of action. Taking the patient and societal perspectives in the value assessment, rather than exclusively focusing on relative efficacy/effectiveness of the product, may help to capture the other elements of value and some elements of innovation.

ARM would welcome a pragmatic approach by HTA agencies on these aspects.

Greater and more active involvement of HTA agencies during parallel regulatory-HTA scientific advice procedure or early consultation/dialogues procedures would also help companies to better understand

the expectations and constraints for market access and agencies to understand the limitations to the data that can be generated at launch to support assessment of ATMPs. Such procedures exist for several years and are now extensively used by companies, particularly SMEs, but the participation of HTA agencies remains too limited, thereby limiting their usefulness to applicants. The new parallel consultation procedure between EMA and EUnetHTA, as detailed in the guidance document ref. EMA/410962/2017 published in July 2017 is very welcome and it is hoped that this new procedure will facilitate the active participation and dialogue with HTA agencies.

ARM also calls on national health authorities to engage stakeholders (patients, physicians, payers, industry) to investigate barriers to patient access in their country and create a plan to facilitate patient access to ATMPs.

5. Conclusion

ARM is in broad agreement with all the proposals and recommendations defined in the report from the EMA summarizing the outcome of the multi-stakeholder meeting held on 27 May 2016. It also supports the EMA/EC plan of actions and encourages the EMA, the EC and national authorities to consider some of the proposals, including on aspects not currently addressed in its plan, in defining and implementing the actions that can be taken to improve the regulatory framework for ATMPs in Europe.
The above-mentioned recommendations represent the consensus view from the ARM broad membership base on the priority actions and provide more details on how these could be implemented. New ideas and proposals such as to support the development of international standards are included too. The recommendations regarding hospital exemption and GMO requirements have been explained more in details in separate position papers that have been released earlier in 2017. ARM is very grateful to the EMA and the European Commission for their efforts to support ATMP development and market access in Europe and stands available for further contribution and collaboration with all stakeholders to make ATMP more rapidly developed and available to patients in Europe.

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About the Alliance for Regenerative Medicine:

The Alliance for Regenerative Medicine (ARM) is a global, multi-stakeholder organization that promotes innovation, growth, and delivery of transformative treatments or cures for patients suffering from chronic, debilitating, and often life-threatening diseases, many of which are rare diseases. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 280+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patient advocacy organizations, and other members of the global advanced therapies community. The organization's aim is to connect all parts of the innovation lifecycle to address current unmet medical needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org.

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References:

[1] Advanced therapy medicines: exploring solutions to foster development and expand market access in Europe. EMA/345874/2016 – 3 June 2016.
[2] European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/10/WC500237029.pdf

[3] Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products. 11 February 2013 - EMA/CAT/CPWP/686637/2011.

[4] GMO legislation include Directive 2001/18/EC on the deliberate release of GMOs into the environment (as amended), Directive 2009/41/EC on contained use of genetically modified micro-organisms, as well as Regulation (EC) 1946/2003 on transboundary movements of GMO's and Regulation (EC) 1830/2009 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced by genetically modified organisms.

[5] Coding of tissues and cells set out in Directive 2006/86/EC as amended by Directive (EU) 2015/565.

[6] Standards Coordinating Body: https://www.standardscoordinatingbody.org/

[7] Regulation (EC) N) 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products, amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use by the addition of article 3(7).