

Innovative Medicines Initiative consultation

‘Facilitating the translation of advanced therapies to patients in Europe’

ARM response to the Consultation Document

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 240+ 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>.

General comments:

ARM welcomes the IMI initiative to consult on challenges for Advanced Therapy Medicinal Products (ATMP) research, development, and market access aiming to identify collaborative projects that could benefit the ATMP sector.

ARM considers that many of the challenges faced by the sector have been properly identified in the consultation document and the preliminary proposed recommendations have generally adequately been described.

ARM believes that some important aspects are missing and should be addressed to enhance R&D of advanced therapies, as well as to maintain and increase the competitiveness of Europe in this sector. These mostly relate to training and education for multiple stakeholders.

In addition, ARM believes that collaborative initiatives should be taken in order to prevent ‘stem cell tourism’ (whereby people travel to another country for a purported unregulated stem cell treatment, clinically unproven, that is not available in their home country); to address some ethical aspects such as those associated to gene editing to avoid misunderstanding and to clarify the exact issues and various ethical, legal and safety recommendations; to explain the ATMP classification (differences between cells for infusion/transplantation and ATMPs) and the requirements for ATMPs to healthcare professionals; to understand the adequate use and requirements for hospital exemption, etc. ARM suggests the initiative could investigate the effect of the enactment of the hospital exemption clause in the various member states.

These aspects are described more in details in response to question 3 below. The more specific aspects relating to preclinical development, clinical development, manufacturing, pricing, reimbursement and access that are missing or have been insufficiently described have been addressed in response to question 1.

ARM understands that a workshop on ATMPs will be held during the IMI stakeholders' forum on September 28 and 29. We would like to volunteer to take part and contribute to this forum and will contact you subsequently to discuss the role we could potentially fulfil.

Responses to questions:

1. Have the key challenges that can be addressed through collaborative, public private initiatives been properly identified?

ARM acknowledges that the IMI concept paper identifies the challenges that exist in the field of ATMP and generally agrees with the description of the challenges and the potential collaborative proposals to stimulate the development and facilitate market access of advanced therapies but would like to add a few issues that could be addressed as well.

- **Preclinical development:**

Model systems: The issues caused by immunosuppression in xenotransplantation are a strong limitation for animal studies using human cells. Research on specific animal models, more tolerant to human cells and which may include large animals or alternatives to animal models, would therefore be highly beneficial and should be strongly encouraged. Whilst a large animal model may be desirable in many instances, they are not available nor easy to use due to challenges arising e.g. the requirements for immunosuppression. Large animals may also include primates as they are relevant for liver transfection and for research in ophthalmology (they have a retina closer to humans than any other species).

Vector systems: ARM agrees that there are limited suppliers of viral vector development, manufacture and testing and would encourage investment in this area.

Regulatory considerations: Many regulatory agencies do not like the term GLP-Like as there is no definition of what this means. ARM believes the studies should be performed to the best research laboratory practice available (which may constitute GLP), they should be protocol controlled, monitored and it is strongly recommended that tissues for histology/pathology assessment are reviewed by an independent pathologist. ARM supports the encouragement for early and 'fast track' regulatory interaction.

- **Clinical development:**

We fully agree with the statements relating to clinical studies in the concept paper and would like to stress that a better characterisation of the natural history of diseases is an important element that could help to define treatment effect, even at early, preclinical, development stage. The mapping and collection of data is therefore important but would need to be available at an early stage for product development.

We also agree that communication to the general public is important, not only to understand the complexities of ATMPs and how these therapies can offer potentially life-saving or life-changing treatment options for patients, but also to understand the dangers of unregulated use of stem cells and avoid the so-called 'stem cell tourism' as well as to understand the exact nature and the ethical, legal and safety considerations that should prevail on therapeutic human gene editing.

- **Manufacturing:**

We agree on the proposals made such as the development of a common technology for the specific vectors for gene therapies, and to create an international consortium of academics to bring ideas to address some of the specific issues for cell therapies.

The following issues could also be addressed in addition to those described in the document:

- The logistics management of fresh cell therapy products is a major difficulty that many ATMP companies face that could be addressed in a collaborative way, for instance by advancing the assessment of potency and clinical efficacy of fresh cell therapy products compared to the same products formulated and stored as frozen materials.

- The creation of centers of excellence for final formulation and delivery of ATMPs that would take some responsibility for the handling and final release of the products (such as the final formulation of frozen materials or after the final washing and formulation steps at the site where cells are administered to patients) is also a concept that could be explored through IMI pilot projects. Clarification on requirements for the final manufacturing steps would be helpful, for instance in the case of frozen materials and a few steps such as washing or formulation needs to be carried just prior to patient administration.

- Standardization and harmonization of international requirement regarding the quality of starting, raw or ancillary materials for ATMP processing. Despite several existing initiatives around standardization and harmonization of international requirements, this topic continues to be a major issue for ATMP manufacturers and proposals that would further stimulate harmonization of requirements within the different EU member states or internationally would be welcome. In particular, it would be highly beneficial to avoid unnecessary duplication of donor testing requirements by country and reaching convergence of requirements on testing for cells and tissues internationally.

- Regarding genetic therapies, it would be of interest to carry out work around immunity and exclusion criteria for systemic AAV injection so as to define the need for future vectors with lower immune response or natural neutralising antibody.

- Regarding requirements for QC release testing, it would be helpful to define the minimum data required to release the product for patient administration and the additional data that could be analyzed later on (in analogy with bone marrow transplantation and CFU test released 14 days after treatment).

- **Pricing, reimbursement and access:**

IMI should enhance the commercialization environment to better stimulate and incentivize innovation. We highly value EMA initiatives aiming to facilitate early market access of innovative products but unfortunately, these will be vain if the HTA and pricing and reimbursement authorities do not view these therapies as a unique set of therapies which requires an adaptation of the decision-making processes used for traditional medicines.

IMI should support initiatives and pilot testing that would encourage HTA and payers to allow early reimbursement of ATMPs based on limited data such as when conditional approval is granted, including the establishment of a mechanism for price adaptation (whether up or down) and/or the review of conditions for reimbursement when more mature data become available.

Similarly, IMI should also support the development of models that would encourage HTA and payers to take account of the level of innovation and risk undertaking for the development of new therapeutic approaches, as well as taking a societal perspective for the value assessment (rather than exclusively focusing on relative efficacy/effectiveness of the product).

In order to ensure successful market entry for ATMPs and encourage investment in the field, the IMI should make it a priority to support the development of new health systems provisions for innovative reimbursement and payment models to facilitate market access and adoption.

ARM feels like EUnetHTA could be instrumental in this regard and could take a leading role in the context of an IMI initiative to address these aspects and foster changes at national and regional levels.

ARM also agrees that the inconsistent implementation of the hospital exemption should be examined, and specifically the effect on innovation should be examined with the aim to produce recommendations on its appropriate or inappropriate use, including using data deriving from hospital exemption use in HTA evaluations. Additional clarification regarding the conditions when hospital exemption could be used should be addressed in a general way and not necessarily only in the context of pricing, reimbursement or access. Indeed, the use of products made under hospital exemption in some indications, particularly rare indications, could be a strong deterrent for companies to initiate the proper development of a product in such indications.

- **Regulatory aspects:**

It is ARM's opinion that some of the regulatory aspects have not been addressed in the concept paper and could be added as they often constitute a major difficulty for ATMP development and could be addressed in a collaborative way.

The varying GMO requirements by country and the fact that these are not specifically adapted to medicinal products constitute a major difficulty for the developers of gene therapy products. Projects aiming to simplify and harmonise GMO requirements among the different member states such as making recommendations for the classification for contained or deliberate release or for the standardisation of application forms would be highly valued.

We believe that additional clarification regarding the conditions when hospital exemption could be used should be addressed, guidelines defined and broadly publicised in partnership with scientific and other professional organisations (see comment above).

In addition, the lack of standards in regenerative medicine and advanced therapies is a key obstacle to product development, evaluation and review. This gap has been acknowledged in the U.S. and the US Senate Committee on Health Education Labor and Pensions (HELP) recently passed legislation that directs the FDA to facilitate the establishment of a Standards Coordinating Body (SCB) to develop standards for regenerative medicine. The establishment of a SBC or similar to develop and implement material and process standards essential to the timely advancement and approval of new regenerative therapies to treat major unmet medical needs could be set up in Europe and could work in partnership with similar initiatives internationally.

2. Which of the proposed initiatives should be prioritised?

ARM believes that collaborative initiatives on:

- hospital exemption,
- pricing/reimbursement and market access,
- GMO requirements,
- standards setting (manufacturing and analysis),
- training and education (see response to question 3),

should be prioritised as they affect a very large proportion of ATMP companies and stakeholders.

3. Are any areas missing?

ARM believes that the aspects of training and education have been insufficiently addressed in the document.

As the production and development of ATMPs is a new science, there is a lack of technical expertise and other appropriate competent personnel both in companies and regulatory authorities, including pricing, reimbursement and HTA agencies. Initiatives to foster the interest, knowledge and competences in cell- and gene therapies in partnership with universities and academic centres would be highly beneficial to multiple stakeholders.

In addition, regenerative medicine and advanced therapies raise a number of new ethical challenges such as:

- The unregulated use of stem cells for unsubstantiated therapeutic claims, leading patients to travel to receive such treatments, at high risk and substantial cost, with the danger that severe adverse events could lead to casualties, cast doubt on the technology and field overall and hamper the development of useful regulated applications and deployment for the benefit of patients and community;

- Gene editing technology. The UK government agency has recently approved the use of gene editing technology to alter the genomes of human embryos for research purposes, opening a new front in genetics research. A broad understanding of the technology, its applications and the consequences thereof by multiple stakeholders, including patient communities, the general public and policy makers is of paramount importance to reach consensus of what is ethically acceptable and to avoid a disparity of opinions and regulations across the different member states that would complicate and possibly hinder research and development, thus limiting market access and the competitiveness of Europe in this field;

- Divergent applications of hospital exemption requirements, leading to unequal and limited access but also preventing investments in the sector and hampering the execution of validated development process. In this respect, ARM believes that physicians and scientific communities need to be better informed and educated on requirements for advanced therapies as substantial manipulations and/or non-homologous use of cells is not uncommon in hospital setting with no knowledge and no oversight by regulatory authorities, potentially putting patient safety at risk in some cases. A potential solution could be to develop and post a series of web-based tutorials to foster education of the medical community, academics and research institutions on ATMPs, their requirements and the regulatory process (including the classification procedures possible at EMA or national levels). Such tutorials or

any other initiative to raise the level of awareness on the qualification of ATMPs and their requirements could be developed in a collaborative way.

In the U.S.A., the National Academy of Sciences and the National Academy of Medicine have recently launched a multi-stakeholder 'Regenerative Medicine Forum' to guide decision-making regarding key issues in this sector, including stem cell tourism, commercialisation issues, standards development, bioethics and human gene editing, etc. ARM believes that a similar multi-stakeholder initiative could be launched in Europe to look at all or a selected number of these issues. ARM has been instrumental in supporting this initiative and could engage in a similar one in Europe.

4. What the key European and national initiatives that IMI shall synergise with?

- EUnetHTA for all initiatives relating to pricing, reimbursement and market access.
- ARM and the International Society for Cellular Therapy (ISCT) have signed a memorandum of understanding earlier this year to establish an ISCT-ARM joint committee to advance potential projects, such as the formation of and participation in the international Standards Coordinating Body; working group activities related to ISO standards for cell therapy and other regenerative medicines; participation in each organization's conference programs; support for international communication and education initiatives related to cell therapy; and more.
- ICH, the International Alliance for Biological Standardisation (IABS), the European pharmacopeia/EDQM and the Alliance for Regenerative Medicine (ARM) for all initiatives relating to standardisation and quality aspects.
