

Innovative Medicines Initiative consultation

Facilitating the translation of advanced therapies to patients in Europe

1. Introduction

Recent advances in biomedicine are now opening the door to new treatment approaches for diseases with high-unmet medical need. These approaches include medicinal products based on genetic engineering, innovative cell-based therapies and tissue-engineered products. In the EU, these new therapies are commonly known as advanced therapy medicinal products (ATMPs). As per Regulation EC 1394/2007, they are classified into four main groups: gene-therapy medicines (transgene, type of vector, genetically modified cells); somatic-cell therapy medicines; tissue-engineered medicines; combined ATMPs; using either autologous cells or allogeneic cells.

Research into ATMPs is growing, as demonstrated by the 511 clinical trials have been conducted from 2011 to 2014 for 303 different ATMPs products. However, numerous factors complicate the translation from research into patient access.

- Product development in this field faces a number of unique challenges inherent to the complexity of ATMPs that differ from traditional developments of new chemical entities, or biologics such as antibodies and vaccines, and involve substantial scientific and technical uncertainties, limited experience with clinical and commercial use and challenges of SMEs to access funds for product development and commercialisation.
- One specific challenge for the ATMP sector is a difficulty to meet all the requirements to obtain a marketing authorisation from regulatory authorities. A comprehensive framework for the regulation of ATMPs in the EU was established in 2007 consisting of Regulation (EC) 1394/2007 and a series of accompanying guidelines issued by the European Medicines Agency. This framework aims to harmonise the European market for ATMPs by mandating authorisation of ATMPs via the centralised procedure, taking into account the unique characteristics of ATMPs and the rapidly evolving knowledge base. Approval of clinical trials for ATMPs remains a national competency.
- It is also possible within the EU regulatory framework to treat patients with ATMPs in the absence of a marketing authorisation under a so-called Hospital Exemption (HE), for a limited number of patients, to facilitate early access of new treatments in case of unmet medical needs. A HE can be granted when the product is prepared on a non-routine basis according to specific quality standards and used in a hospital under the exclusive professional responsibility of a medical practitioner. Nevertheless the growing number of unregulated application of HE (which does not require long and costly safety, quality and efficacy demonstrations) acts as a disincentive to small and big companies, which aim at putting standardised and safe products on the market. Once marketing authorisation is granted, decisions about price and reimbursement take place at the level of each Member State in the context of the national health systems. The value proposition for these treatments is complex and challenging to justify for healthcare systems as the pharmaco-economic evaluation of such products are setting new standards and require a paradigm shift in the manner in which such evaluations are performed.

2. Time for action in Europe

Until now, only five ATMPs have been granted a marketing authorisation in the EU. Two of these products have been taken off the market due to limited uptake in clinical practice. At this time, only one product,

ChondroCelect, is reimbursed in Belgium, Netherlands and Spain, while for the others reimbursement assessments are in progress.

At the same time, many players believe that the conditions exist today to lift barriers and exploit opportunities for enhancing R&D of advanced therapies in Europe as a full-fledged industrial activity to make EU more competitive and making advanced therapy products available to all patients in need. This is driven by the scientific state of the art which has made significant progress over recent years.

On 23 October 2015, the Innovative Medicines Initiative (IMI) hosted a workshop with industrial players and a group of key opinion leaders to discuss how Europe could play a leadership role in this new generation of therapeutics and whether the IMI platform can facilitate the collaboration to put Europe at the forefront of ATMPs development.

3. Discussion and preliminary recommendations

3.1. Preclinical development

The key challenges in the area of preclinical development with regards to bringing ATMPs to the patients as effective new therapies can largely be grouped in 4 different sections: Model systems for proof of concept (PoC) and safety, vector systems, targeted gene editing, and regulatory considerations.

Model systems

The need for demonstrating PoC in relevant animal models is crucial for successful translation into clinical development. Therefore, large animals that are comparable in both scale and physiology to human patients (e.g. pigs and dogs) should be evaluated. The interaction with the field of veterinary sciences would be beneficial. It is important that safety is investigated in disease/mechanistic animal models where survival can be monitored.

Models such as human organoids (e.g. human induced pluripotent stem cells: hiPSC-based) should be considered for safety evaluations, and might be able to replace animal experimentation in the long run.

Vector systems

Assessment of established vector systems and development of new enhanced vectors will be very beneficial to the field. The risks of insertional mutagenesis linked to the vector characteristics need to be further addressed.

Targeted gene editing

Genome editing based therapy includes correction or inactivation of deleterious mutations, introduction of protective mutations, and addition of therapeutic transgenes and disruption of viral DNA. Genome editing represents an important boost to the field and must be considered.

Regulatory considerations

Academic preclinical work should be conducted under good laboratory practice ('GLP-like') standards according to regulatory requirements. A close interaction with the regulatory authorities at very early stages of development is important. There is a need to adjust regulatory framework where possible, speed-up EMA

scientific advice service and develop a 'fast track' process to accelerate development in the field so that Europe remains competitive with other regions of the globe.

Many of these challenges could be addressed in a pre-competitive platform (or platforms), which could be established under the IMI umbrella, as public private partnerships.

3.2. Clinical development

Different questions have been raised around exploratory studies to demonstrate safety and proof of concept / initial efficacy of ATMPs. In this context, primary endpoints including safety, dose finding, and secondary endpoints including biodistribution, PD/PK and efficacy need to be taken into account. Interpretation of preclinical to clinical translatability could also be based on potential biomarkers and surrogate markers linked to pathophysiology and to evidence of clinical effectiveness.

One priority would be to consider the clinical condition and patient populations with the perspective of a case-by-case basis and/or specific categories. Access to early regulatory consultation is important as regulatory authorities may be more comfortable and knowledgeable with regards to one class of ATMPs over another (e.g. a cell therapy versus a gene therapy product).

Single confirmatory studies for safety and efficacy demonstration will be required including available comparator or control group for specific disease conditions and clinical populations studied. Overall benefit-risk, pharmacovigilance monitoring need to be addressed.

It is evident that not all specific criteria would be applicable to all ATMPs and each case may be different (in monogenic versus complex diseases for example).

It will be important to assess the value of data from clinical data bases (registries, hospital exemptions, compassionate use) to compensate for the uncertainties (i.e. efficacy or safety) including aspects such as quality, pharmacovigilance and follow-up. How these data can be incorporated in the overall interpretation of evidence (or substantial evidence), effectiveness and in the context of clinical meaningfulness will require further elucidation.

A mapping and inventory of the clinical use programmes (registries, HE, compassionate use) in Europe as well as the type of data available in those programmes would be of great value in order to make choices on which disease types to target. In addition, a meta-analysis of published and reported information in this area would be beneficial. The integration of these sources of information would provide a basis to address many of the issues under discussion today and could lead to a more targeted strategy in the first instance.

Communication to the general public, production of an education package to explain the complexity of ATMPs and how these therapies can be potentially life changing for patients will be critical.

3.3. Manufacturing

The manufacturing of the ATMPs can be really challenging from a scale and consistency point of view. There is a lack in common best practices and 'automated' production platforms. This hinders the translation of therapies to real, cost-effective commercial products that can treat patients.

From a manufacturing perspective there are two major groups: gene therapy and cell therapy (not to forget tissue engineered products, combined ATMPs and organoids).

For both groups the quality and supply of the raw materials is challenging because there are variable levels of purification following production (depending on the type of product under consideration). The variability of the raw materials influences the functionality and stability. Raw materials like cell culture media, with or without serum or other supplements are decisive for the critical quality attributes of the ATMP, and as a consequence

its usage as a therapy. The ATMP industry suffers from the fact that their demand for raw materials is insignificant compared to the demand of other industries with less qualitative requirements.

The establishment of a 'Biophorum-like' initiative, where the ATMP industry as a group approaches these kinds of issues, was suggested.

In general there is a lack of manufacturing knowhow, regulatory sciences and Current Good Manufacturing Practice (CGMP) related to ATMP usage. More education specific for the ATMP business is needed. Besides that, there is a shortage of well-trained engineers that understand the manufacturing processes and are capable to develop automated/robotic methods and common platforms. Due to this deficiency new developments, which would lead to a more consistent and reproducible manufacturing of ATMPs, are in need of investment.

For the genetic therapies the purification of the viruses is problematic and cumbersome. During an infection of the host cell not only infectious virus particles are produced, but also empty virus particles without genomes. More characterisation of the process of virus production at the cellular level to deliver high quality infectious particles and limit the empty particles is required. Large-scale purification technologies to enrich the infectious virus particles in the final gene therapy product are not available. Qualified small-scale models are lacking and the knowledge on formulation of the final product of a genetic therapy is restricted. This results in high production costs combined with considerable regulatory challenges and quality concerns.

The use of a generic virus/vector system would increase significantly the basic process knowledge and kinetics of the virus production as this would (i) enable the development of innovative purification and analytical tools leading to a simpler and consistent manufacturing technology; (ii) reduce concerns around intellectual property; and (iii) make it possible to have a cross industry solution. This system could also be used to develop new validated, analytical tools to facilitate proper quality control (QC) release testing.

In summary, a common technology platform for the production of specific vectors based on innovative production and analytical tools, and equipment are required. In-depth knowledge of cell biology combined with culture technology up to innovative solutions in bioprocessing technology and bioreactor engineering, with respect of all aspects of the current regulatory standards on safety, stability, robustness and validation, will accelerate progress in this field immensely.

The world of the cell therapies is rapidly evolving and new types of cellular therapies are advancing rapidly (embryonic and adult stem cells, iPS cells, Car T-cells...). Overall control of consistency of the production of these cells should be achievable (Targeted Product Profile, Critical Quality Attribute). Autologous cell therapy approaches struggle with patient derived cell variability and complicate manufacturing of the high doses currently needed. The 'universal' allogeneic cell therapies, where many patients could be treated with cells from the same source could provide a solution, however, immunogenicity creates an enormous problem in this scenario. Genetic re-engineering of the cells to lower the immunogenicity is only beginning to emerge and a lot of additional research is necessary. A consortium with the academic specialists would be very beneficial to move this field forward.

A lot of the current manufacturing methods are developed at universities, hospitals or in SMEs and are difficult to transfer/scale up to commercial processes that are needed for the market. Automated & closed processes/platforms would accelerate the field. This could be established by the combination of automotive principles (robots...) with disposable bio-processing technology, which at the same time reduce the requirements for duplicating facilities, labour and QC costs and increase robustness.

Newly developed highly sensitive analytical tools are not only beneficial for QC control, but also for manufacturing itself because sampling volumes are currently a major concern, because the needed sample volumes for testing often take up a considerable part of the final product. There is a requirement for miniaturisation of analytical methods and scaled down/micro assays development. Synergy with lab-on-a-chip technologies should be envisioned.

All the above-described aspects comprise a space of knowledge that can only be covered by an international consortium of academics and industry bringing ideas to a commercially attractive reality for patients and society.

3.4. Pricing, reimbursement and access

ATMP space in EU has grown substantially, but still has much room to grow. There are close to 350 ATMPs in development (EUDRA CT data), however 60% of development is executed by research centre and hospitals – none of them with any commercial capability. However, the research centre maintains them as transplantation and transfusion products – there is some resistance to industry commercialisation to ATMPs.

EU has clear regulatory pathway (Committee for Advanced Therapies: CAT&EMA) for ATMPs, but there are divergent regulatory perspectives within EU states; there is close interactions between FDA, EMA and health Canada. Classification of ATMP vs transfusion is not very clear. ATMPs are classified as medicine, thereby all orphan drug and SME incentives apply; but comes with all GMP/GLP/GCP (Good Clinical Practices) obligations as well. HE process is in place in EU as a way to experiment and care for patients with no other options and is meant to cease when options become available to patients. However HE if misused could be a threat for innovation and protection of intellectual property. Currently there are institutions already providing gene therapy through the HE clause.

Compared to traditional medicines, there are specific considerations related to ATMPs that can have an implication on pricing and reimbursement that need to be deliberated. These are listed in table below.

Dimension	Traditional therapies	Uniqueness of ATMPs	Pricing and reimbursement implications
Treatment Regimen & Effect	Certain treatment duration, with cycles, or chronic	One-time/short term treatment with Long-term benefits	No recurring use or payment after one treatment
Funding & Pricing Decisions/Policy	Well-established pathway and decision making process	No specific policy/process in place yet	Uncertainty in process but opportunity to shape the environment
Manufacturing & Logistics	Mass production Simpler logistics	Individualised production Complicated logistics	Substantial cost of goods to be covered by price to avoid financial loss; ability to track patients by indication, minimise waste & uncertainty of future treatments
Available Data for filing	Mostly Ph III with comparator and survival data	Ph II single arm, short-term results	Challenge to meet payers' survival and comparative data requirements
Experience	Strong track record and experience	Only few ATMPs in market with varied commercial successes	Leverage existing knowledge and explore innovative partnership approach
Treatment Process	Individual physicians and single touchpoint	Treatment pathway with multiple touchpoints	Institution-level decision; ability to track individual patient outcomes

In the context of market access, several topics are currently under debate among which the following should be prioritised for future research investments:

1. Health Technology Assessment (HTA) implications for ATMP including:
 - demand for head to head comparator and protracted HTA process versus what is ethically possible
 - costs and consequences of long term follow-up requirements (e.g. 15 year safety follow up?)
 - early access pathways from regulatory not in line with reimbursement pathways at EU states
 - potential cure but with uncertainty of long term benefits
2. Hospital exemption including:
 - Appropriate or inappropriate use

- Report on existing use or maintenance of registry
3. Develop health systems provisions for innovative reimbursement and payment mechanism including:
- Long-term managed-entry agreements
 - Annuity or multi-year payment mechanisms with payers
 - Provision of incentives to attract development incentives for ATMPs and patient access.
 - Potential special designation for one-off short term treatments with long term future benefits
4. Delivery through select Centres of Excellence:
- Define opportunities for cross-border health care delivery
 - Optimisation of care delivery for ATMPs.

4. Next steps - consultation and identification of project(s)

IMI, as a public private partnership, involving large number of companies from pharma (and increasingly, from non-pharma) sectors on the one hand, and with the ability to involve all stakeholders from the healthcare value chain on the other hand, represents an ideal platform for addressing a range of translation challenges in the pathway from science to healthcare systems and patients.

IMI and EFPIA are looking for input from scientific, regulatory, patient and healthcare systems communities on the following questions:

1. Have the key challenges that can be addressed through collaborative, public private initiatives been properly identified?
2. Which of the proposed potential initiatives should be prioritised?
3. Are any areas missing?
4. What are the key European or national initiatives that IMI shall synergise with?

On the basis of input, a second workshop will be organised by IMI in 2016 that will draw conclusions from and conclude the consultation. These conclusions will inform the development of an IMI ATMP portfolio of projects that could be launched from 2017 onwards.

The present draft is now available for consultation.

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