

German Federal Ministry of Health/Paul-Ehrlich-Institut (reports to the German Federal Ministry of Health)

Please find detailed comments on the concept paper in the following document. In addition, there are some general comments which you find below as well as a response to the questions raised at the end of the concept paper.

Generally, the wording of the document often appears somewhat vague leaving room for interpretation or misunderstanding. Elaborating the issues to be addressed in more detail may improve the clarity and reasoning of the document (cf. attached document for specific points).

ATMPs are described as complex products posing many challenging questions and difficult issues to be addressed. On the other hand, it is advocated to develop regulatory fast track processes including speeding up scientific advice procedures. Providing adequate data to address the crucial issues may automatically speed up the whole regulatory process; however, speeding up the process alone with the aim to be competitive at an international level is not regarded as a sound and valid approach to resolve crucial safety and efficacy issues for ATMPs.

With respect to the preclinical development, suitable animal models are not available for many cell-based medicinal products. For example, administration of human cells to animals will often result in the rejection of the cells by the animal immune system. Innovative approaches are thus demanded, such as human cell culture systems to demonstrate in vitro proof of concept, or the use of homologous animal models where the respective animal cells are used instead of the human medicine. Such approaches could be used within the framework of what is known as the risk-based approach that is already part of the EU regulatory system. The current proposal does not appear to adequately reflect that background.

In the clinical development chapter it is suggested to educate the general public on the complexity of ATMPs. We do not understand the benefit of this approach. While it is of course important to educate medical professionals handling and administering ATMPs on the complexity and scientific background of such products, adequate information on the benefit and risks of a treatment with a specific ATMP appears more appropriate for patients than understanding the scientific background of the ATMP.

Regarding the manufacturing of ATMPs, emphasis is put on the development of platform technologies and the replacement of autologous cells by allogeneic cells modified to lower immunogenicity. Both approaches may create further options for the development of ATMPs but may be applicable only to a limited number of ATMPs with a similar mode of action and may rather take quite a long time. However, only a limited impact on the development of ATMPs is to be expected in the mid-term. Moreover, platform technologies may be associated with complex issues regarding intellectual property, which needs to be reflected before embarking on this strategy.

In our view, a major shortcoming of the development of ATMPs is the difficulty to acquire the funding needed to prepare and write a clinical trial application and to conduct the clinical trial when approved. It should be evaluated whether IMI may be suitable to address this issue.

Most issues addressed in the document are regarded to be crucial to facilitate the development of ATMPs. However, several issues, such as developing new non-clinical model systems, generating production platforms or replacing approaches based on autologous cells by allogeneic cells with lowered immunogenicity, may need quite some time to make significant progress. Thus these approaches rather support scientific research but are anticipated to impact only to a minor extent on the availability of ATMPs in the next few years.

On the other hand, supporting the generation of clinical data by improving funding for the preparation and conduct of clinical trials may be more promising to bring further ATMPs to the patient in the nearer future. In this context, it is also regarded beneficial to further elucidate and develop approaches to better use data from outside clinical trials, i.e. data from every-day-use of licensed or authorized ATMPs, to support the evaluation of safety and efficacy of ATMPs.

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.

Research into ATMPs is growing, as demonstrated by the 511 clinical trials have been conducted from 2011 to 2014 for 303 different ATMPs products^[A3]. However numerous factors complicate the translation from research and development into patient access.

- Product development in this field faces a number of unique challenges inherent to the complexity of ATMPs that differ from traditional development of new chemical entities or biologics, 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 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 clause (HE). According to the legislation, a HE is not granted is applicable when the ATMP is a non-routine basis according to specific quality standards and used in a hospital under the exclusive professional responsibility of a medical practitioner. While university- and clinic-based developers welcome this additional approach, it may be perceived as a disincentive to by small and big companies, which in at putting more standardised products on the whole EU market and thus have to achieve a centralized MA.
- Once marketing authorisation is granted^[A9], decisions about pricing and reimbursement take place at the level of each Member State in the context of the national health systems. The value proposition for novel and often costly ATMP-based 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 six seven ATMPs (Status: 5/2016) been granted a marketing authorisation in the EU. Two of these products have been taken off the market due to a closure of the manufacturing site or other commercial reasons, mited uptake in clinical practice. At this time

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 Sentence incorrect:
 Not therapies are covered, but medicinal products

Comment [A2]: It is not clear what this is referring to; not all ATMP contain cells.

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Comment [A4]: Commercialization/reimbursement is a self-standing issue that should be listed separately, not under "product development"

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Comment [A5]: HE does not specify that only a limited number of persons may be treated but that the ATMP is prepared on a non-routine basis

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Comment [A7]: Please clarify what unregulated application of HE means

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 This chapter should be reflected and reworded.

-On which basis a growing number of HE has been verified?

- HE is an alternative tool for regulated and supervised ATMP therapy, clearly not an unregulated situation

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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 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 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.

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Please check with HTAs before making this statement: At least in Germany, reimbursement of other ATMPs such as Glybera has been granted.

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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. In specific cases it may be necessary to evaluate large animals that are comparable in both scale and physiology to human patients (e.g. pigs and dogs). The interaction with the field of veterinary sciences may be beneficial. Whenever feasible, it is requested that safety is investigated in disease/mechanistic animal models where survival can be monitored.

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

However, for many cell-based medicinal products suitable animal models are not available. For example, administration of human cells to animals will often result in the rejection of the cells by the animal immune system. Innovative approaches are thus demanded such as human cell culture systems to demonstrate in vitro PoC, or the use of homologous animal models where the respective animal cells are used instead of the human medicine. Such approaches could be used within the framework of the so-called risk-based approach that is already part of the EU regulatory system.

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 and transmission 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 the impact of this technology on the safety (and efficacy) of products must be considered.

Regulatory considerations

At least pivotal 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 may be a need to adapt regulatory requirements to what is feasible, 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 hints for 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 potential clinical efficacy.

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: 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).

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, and 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 reduce 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 approaches (registries, HE, compassionate use) in Europe as well as the type of data available in those programs 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 challenging, e.g. from a scale and consistency point of view. There is a lack in common best practices, analytical tools and 'automated' production platforms. This hinders the translation of therapies to cost-effective commercial production.

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, adequate quality and supply of raw materials can be challenging because often only research-grade reagents with variable levels of purification and quality control in an pharmaceutical QMS embedment is available. The variability of the raw materials may influence the quality of the product, e.g., cell

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culture media, with or without serum or other supplements are decisive for the critical quality attributes of the ATMP. The ATMP manufacturers suffer from the fact that their demand for raw materials is insignificant for vendors 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 parts there may be a lack of manufacturing knowhow, regulatory sciences and Current Good Manufacturing Practice (CGMP) standards adjusted to ATMP characteristics. More education and training 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 gene therapies the purification of the viruses is problematic and cumbersome. During infection of the producer 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 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 is regarded to facilitate development of ATMPs based on this platform. 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 cell, as well as iPS cell- derived products, CAR-T-cells...). Overall control of consistency of the production process of these cells should be achievable (Targeted Product Profile, Critical Quality Attribute). Autologous cell therapy approaches usually struggle with inherent patient derived cell variability and laborious manufacturing of the single, patient-specific product batches. The more 'universal' allogeneic cell therapies, where many patients could be treated with cells from the same source could provide a solution. However, immunogenicity may create an enormous limitation in this scenario. Genetic re-engineering of the cells to lower the immunogenicity is only beginning to emerge and a additional research is necessary. A consortium with the academic specialists would be beneficial to move this field forward.

A lot of the current manufacturing methods are developed at universities, hospitals or in SMEs. Based on the scientific focus, it can be difficult to transfer/scale up to commercial pharmaceutical process. Automated & closed processes/platforms are expected to 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 sensitive and robust analytical tools are not only beneficial for QC control, but also for manufacturing itself. As sampling volumes is currently often a major concern (e.g. the needed testing sample volume may take up a considerable part of the final product. There is also 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.

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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 clinical development (EUDRA CT data), with 60% of development is executed by research centers, and hospitals – none of them with any commercial capability. However, sometimes the research centers perceive them as transplantation and transfusion products – there is no interest to act as pharmaceutical supplier of an EU market or even some reservation to industry commercialization.

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 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

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Whole section is headed as pricing and reimbursement. Therefore, this part should be reconsidered to discuss respective topics related to header more specifically.

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 Centers of Excellence:

- Define opportunities for cross-border health care delivery
- Optimisation of care delivery for ATMPs.

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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.

Document reference: IMI2/OUT/2016-01321

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Nevertheless the growing number of unregulated application [A1][A2]of HE (which does not require long and costly demonstration of safety, quality and efficacy according to European legislation demonstrations) acts

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This chapter should be reflected and reworded.

-On which basis a growing number of HE has been verified?

- HE is an alternative tool for regulated and supervised ATMP therapy, clearly not an unregulated situation

- unregulated situation is in contrast when Point-of care ATMPs are produced and administered solely under the practitioners responsibility

-HE is an important tool for university hospital-based patient treatment and development

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limited uptake in clinical practice

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Purpose of this sentence in this section unclear. There are no distinct manufacturing approaches for GTMP and CBMP but a huge overlap, e.g. for genetically modified cells.

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es that are needed for the market