FIT FOR ATMPs?

Creating an EU Regulatory Framework that Works for Transformative Therapies

Event hosted by the MEP Interest Group on Transformative Therapies
16 June 2022

#MEPsforATMPs

European Alliance for Transformative Therapies

EVENT REPORT

Executive Summary

On 16 June 2022, the TRANSFORM MEP Interest Group held an online event with the TRANSFORM Alliance and other selected regulatory experts, representing patients, clinicians, research institutes, academia, regulators, pharmaceutical industry and EU institutions.

The event launched the TRANSFORM Alliance's Policy Asks on the Regulatory Framework for ATMPs. These Policy Asks represent the position of the TRANSFORM Alliance as of June 2022. This may be further refined and developed in light of external policy and legislative developments, culminating in a final and integrated set of Asks in a Charter to be launched in the European Parliament in October 2022.

During the event, the forthcoming legislative proposals that could impact the ATMP regulatory framework (including the Blood, Tissues and Cells (BTC), the Orphan Medicinal Products Regulation and General Pharmaceutical Legislation) were discussed, and opportunities to improve the regulatory processes identified. Given ATMPs' complex nature, attendees agreed that a robust framework safeguards patient safety. At the same time, balancing the regulatory framework against the need for flexibility, particularly around clinical trials, is important to the competitiveness of Europe as a hub for R&D – something that will ultimately benefit patients.

MEP speakers noted that regulatory clarity was key, and that the TRANSFORM MEP Interest Group will be reviewing the forthcoming legislative proposals that touch on the regulatory framework for ATMPs with these points in mind.

Opening words

Developing appropriate regulatory frameworks to ensure patients' safe and timely access to ATMPs

Ondřej Knotek MEP (Renew Europe, Czechia), Co-Chair of the TRANSFORM MEP Interest Group, highlighted:

- ATMPs are complex, so deserve a special regulatory framework for three reasons: to address patient unmet need; to attend to patient safety requirements; and to create an innovative environment to motivate development of further ATMPs to offer potentially curative, transformational treatment including for rare and neglected diseases.
- There is review, and potentially revisions, of the EU General Pharmaceutical Legislation and Blood, Tissues and Cells (BTC) legislation, as well as the proposal for a European Health Data Space. With those files, several bottlenecks and issues have already been identified, for example around evidence generation, and how to improve classification of therapies.
- The Policy Asks and discussion will support the MEP Interest Group in these legislative discussions.

Meeting patient safety and patient access needs; Building a flexible, robust and predictable framework in Europe

Simone Boselli, Public Affairs Director at EURORDIS, highlighted:

- The regulatory framework has worked well, including when we consider the EMA's PRIME scheme.[1] However, it is important not to lose sight of the overall ecosystem that goes before and comes after regulatory authorisation. There are three key aspects:
    a. Learning the lessons from the COVID-19 pandemic around different ways of conducting clinical trials and the potential to exempt ATMPs from the environmental assessment for clinical trials with cell and gene therapies under GMO legislation.
    b. Implementation of the Hospital Exemption (HE) in a way such that there is a level playing field.
    c. Providing for consistent patient involvement throughout the regulatory pathway, from clinical trials, ethics committees and HTA.

Alexander Natz, Secretary-General of EUCOPE, highlighted:

- A robust regulatory framework is needed to ensure Europe remains competitive and is attractive for companies to launch their ATMPs.
- The EMA is an agency that is globally renowned and demonstrated capacity to adapt to changing technologies to ensure they are available to European patients.
- However, ATMP R&D has been going to China and the US in recent years, so the European Commission must maintain a future proof system. This includes (a) getting the BTC legislation right, as BTC may be starting materials for cell and gene therapies and (b) allowing the EMA to leverage alternative data sources to support assessment of marketing authorisation applications.

Overview of the regulatory landscape

The review of the General Pharmaceutical Legislation and Blood, Tissues and Cells Directives to ensure a future-proof regulatory framework for ATMPs

Stefaan Van Der Spiegel, Head of Sector – Health Innovation, DG SANTE, European Commission, highlighted:

- The Commission is revising the BTC framework as, for example, it lags behind innovation and there needs to be more clarity on when BTC rules should apply. Addressing shortcomings in the current legislation should facilitate the supply of BTC as starting materials for ATMPs. The reported complexity of identifying borderline criteria and obtaining guidance leads to unclarity of classification. Developers of innovation, both in the pharma and in the BTC framework, need and want clarity. However, as the criteria for ATMP classification are in the pharmaceutical legislation, not the BTC legislation, aspects such as substantial manipulation, non-homologous use, industrial process or intention to place on the market will not be considered as part of the BTC review. He noted the introduction of an advisory board under the BTC legislation, to support national competent authorities, where needed with a joint mechanism to coordinate views between medicinal products, medical devices and BTC.
- The Commission's objective when looking at the General Pharmaceutical Legislation will be to promote innovation, affordability and ensure access to innovative medicines for patients, with special attention to enhancing security of the supply across the EU. When it comes to ATMPs, ideas being put forward include: (a) review and futureproofing of ATMP definitions and concepts (e.g. bedside manufacturing); (b) streamline for ATMPs the environmental assessment for clinical trials with cell and gene therapies under the GMO legislation; and (c) examine the possibilities for revision of the Hospital Exemption.

[1] A scheme introduced to offer enhanced support for the development of medicines that target an unmet medical need. It offers enhanced interaction and early dialogue between developers and the EMA.

The relevance of the medicine legislation for ATMPs: similarities and differences with other medicinal products?

Ana Hidalgo-Simon, Head of Advanced Therapies, EMA, highlighted:

- Advanced Therapies are game changers with enormous potential, but they are also very complex and need strong regulatory oversight. ATMPs have specific characteristics that make them different from traditional medicines in many aspects. When talking about transformative or curative therapies, you cannot take them home, they are difficult to copy, and administration requires qualified medical staff. Additional specific safety and efficacy considerations need to be examined. The long persistence of the product makes it impossible to stop treatment in case of a safety issue or non-response, but it also requires long-term monitoring for rare side effects that may appear long after administration, meaning that they require special oversight. At the same time, there needs to be flexibility in the system as science moves fast.
- The EMA provides dedicated support to ATMP developers through different procedures (EMA-HTA parallel consultation, ATMP classification, ATMP certification, …), early access framework (PRIME), guidelines and incentives including fee incentives.
- Now is a good time to look at the ATMP regulatory framework holistically; there is an opportunity for more coordination between the different pieces of legislation/guidelines, taking into account all stakeholders (traditional and less traditional) in the ecosystem.

Exchange of views between TRANSFORM MEP members and regulatory experts: New approaches to foster safe and timely patient access to ATMPs in Europe within the context of the general pharmaceutical legislation – Regulatory processes

Panel 1: The regulatory approval pathway for ATMPs: the General Pharmaceutical Legislation and EMA processes

- **Radka Maxová MEP (S&D, Czechia), TRANSFORM MEP member**
- **Dr Paula Salmikangas, Director of Biopharmaceuticals and ATMP at NDA Group AB; Former Chair of EMA's Committee for Advanced Therapies (CAT)**
- **Dimitrios Athanasiou, Board Member of World Duchenne Organization and member of the EMA's Paediatric Committee (PDCO)**
- **Marcello Milano, Director R&D and Regulatory Policy EU, BioMarin**

- **Radka Maxová** stated that ATMPs are complex medicines and must undergo a different evidence generation pathway compared to traditional medicines. This has an impact on the availability of data, so this means we must adapt regulatory processes to accommodate the specific characteristic of innovative therapies.
- **Marcello Milano** said that industry needs more opportunities for iterative engagement with the EMA, and ATMP developers would benefit from earlier access to the PRIME scheme. Ideally, the EMA would serve as a regulatory 'one stop shop' for ATMPs and facilitate interactions with all relevant stakeholders; including aligning – to the extent possible – on evidence generation across the full development pathway. This will require adequate resourcing for the EMA. Streamlining the Centralized Procedure and expediting the Commission's decision-making would be welcome. The Commission and EMA should ensure that the Clinical Trials Information System (CTIS) portal is fully functional and that all Member States implement the Clinical Trial Regulation promptly and without adding requirements not foreseen in the Regulation.
- **Dimitrios Athanasiou** said that regulatory work must answer issues around access to ATMPs for patients. Whilst safety is important, so is efficacy. Moreover, there is a need to streamline throughout the process, so data collected in regulatory work can answer reimbursement questions too. We must keep Europe attractive for clinical trials, as it means faster access for patients and we also need resources for policymakers, which means funding and education. For patients, what still lacks is a full understanding of how the voice of the community is

reflected in the regulatory and drug development process, and a broader understanding of how evidence from DARWIN EU is working with European Reference Networks, the European Health Data Space, the Clinical Trials Regulation etc..

- **Dr Paula Salmikangas** said that, since ATMPs are very complex, with no comprehensive knowledge on their safety and efficacy long-term, revisions of the legislation must be proportionate to the associated risks. The revisions should also aim for a harmonization of requirements globally. Undertaking clinical trials in the EU is a challenge for ATMP developers. The new Clinical Trials Regulation will bring about more centralization and common understanding but it remains to be seen whether this will be sufficient to make Europe more attractive for ATMP development. Problematic points like GMOs should be properly addressed inside the European Commission, as it seems that different units are not driving things to the same direction. Good cooperation between the Commission and the EMA is required to enhance authorization of ATMPs in the EU.

Panel 2: Ensure appropriate use of the Hospital Exemption

- **Dr Stefano Ferrari, Head of Research & Development at The Veneto Eye Bank Foundation, on behalf of the European Alliance for Vision Research & Ophthalmology (EU EYE)**
- **Dr Martin Telko, Global Public Affairs Director for Biomedical Innovation, Novartis**
- **Stefaan Van Der Spiegel, Head of Sector – Health Innovation, DG SANTE, European Commission**

- **Dr Stefano Ferrari** said that the Hospital Exemption (HE) can help deliver a new product where there is no authorized product. It can be used to build up information and expertise to work towards a marketing authorization. HE should be used even when an equivalent centrally approved ATMP is on the market to guarantee access to therapy in cases of limited national budget or withdrawal of authorised products from the market. Having a European registry is important for the success of the HE in producing ATMPs. Requirements such as GMP manufacturing and use of registries should be enforced. The Commission should define terms like 'non routine basis application' to support more harmonized use of the HE.
- **Dr Martin Telko** stated that industry is not against the HE, but they want to see it used appropriately. It is unknown currently whether the HE is working well for patients, what the short term and long-term impact is, or how many patients are receiving treatment under the HE, because the system in Europe is so fragmented. This lack of transparency is not in the interests of patients. Treatments offered under the HE has not undergone clinical trials or been approved by regulators and are not subject to GMP standards. Wherever possible, patients should benefit from authorized treatments.
- **Stefaan Van Der Spiegel** also contributed to the discussion by adding that the Commission will explore the HE in the General Pharmaceutical Legislation review. We need to keep in mind that the end objective is for EU citizens have access to safe and effective therapies. He therefore underlined the important role that public and academic actors play in offering innovative therapies to patients. He clarified there is a need to distinguish between cost and price, with a direct impact on access for patients, and called for a discussion on this point. He stated that evidence is key to ensure safety and efficacy, and there are a lot of registries in the transplant sector to explore.

Panel 3: Classification of ATMPs and BTC - the relevance of the Blood, Tissues and Cells legislation to the safety, administration and monitoring of transformative therapies

- **MEP Ondřej Knotek (Renew Europe, Czechia), TRANSFORM MEP Co-Chair**
- **Dr Vincenzo De Angelis, Director, Italian National Blood Centre; Coordinator of the GAPP-Joint Action**
- **Prof Giulio Cossu, Professor of Regenerative Medicine at the University of Manchester, on behalf of the Federation of European Academies of Medicine (FEAM)**
- **Dr Androulla Eleftheriou, Executive Director, Thalassaemia International Federation (TIF)**

- **Ondřej Knotek** said the BTC legislation is relevant for ATMPs as they are often used as starting materials for ATMPs, but this can lead to legal uncertainty. He summarized two key takeaways from the discussion so far, broadly: first, regulatory clarity is needed in legislation on classifications; and second, the EU is facing the risk of withdrawal of therapies from the EU market, and this needs to be borne in mind with the forthcoming legislation.
- **Dr Vincenzo De Angelis** said that, from the Italian competent authority point of view, the different regulations are difficult, and having a new advisory board to support competent authorities with the BTC legislation will be important. This will help with timing and quicker authorization of different products.
- **Dr Androulla Eleftheriou** stated that for patients with transfusion dependent beta-thalassemia, the BTC legislation is very important. Dr Eleftheriou noted a recent ATMP for beta thalassaemia, which was a product that was developed from BTC and then infused into the patient. She reflected on how complex the treatment's administration was, and concerns from patients around the coverage of standards and safety from the beginning of the administration process all the way to re-infusion of the therapy. There is a need for a European level mechanism so that all European countries have the same safety regulatory standards for ATMPs.
- **Prof Giulio Cossu** noted that harmonization among regulatory agencies in Europe is necessary. He noted that lifesaving therapies are being withdrawn from the market due to poor negotiations or industry decisions. This needs to be looked at from a European point of view, so if a company decides to withdraw, there is a way for governments to produce that therapy.
- **Stefaan Van Der Spiegel** also contributed to the discussion by adding that the final decision on applicable rules for BTC lies at the national level, and Member States can come to different conclusions for similar therapies. However, he said that by trying to coordinate and come with common views on topics, the EU can support Member States' decisions.

Conclusions and next steps – Aligning on a TRANSFORM position in the context of the Pharmaceutical Strategy for Europe

Nicolás González Casares MEP (S&D, Spain), Member of the TRANSFORM MEP Interest Group, highlighted:

- The objective of regulatory policy is to ensure patient safety and maintain quality and efficacy standards in the delivery of advanced therapies. ATMPs are complex, non-conventional products, so having a robust regulatory framework for their marketing authorization, monitoring and administration is critical.
- There is also a need to balance the regulatory framework against ensuring Europe remains a hub for clinical trials with ATMPs, and they are swiftly approved to enable timely patient access.
- The European Health Data Space should be leveraged to support data interoperability and enable real-world evidence to be used in assessment decisions.
- The TRANSFORM MEP Interest Group will be reviewing the forthcoming legislative proposals that touch on the regulatory framework for ATMPs with these points in mind.

About the European Alliance for Transformative Therapies (TRANSFORM)

We invite you to join the TRANSFORM Community on Twitter and LinkedIn and keep an eye on the website to continue this important discussion online and to stay updated about the TRANSFORM MEP Interest Group and Alliance of experts' 2022 plans.

If you did not attend the event or if you wish to re-watch the discussion, you can access the recording here:

https://www.youtube.com/watch?time_continue=6368&v=vSZiQiAaM1A&feature=emb_logo

You can read the TRANSFORM Policy Asks on the Regulatory Framework for ATMPs launched on 16 June 2022 here:

https://transformalliance.eu/wp-content/uploads/2022/06/TRANSFORM-Policy-Asks-on-Regulatory-Framework-for-ATMPs_FINAL_June2022.pdf

You can read the TRANSFORM Policy Asks on Access to Authorised ATMPs launched on 31 March 2022 here:

https://transformalliance.eu/wp-content/uploads/2022/03/TRANSFORM-Policy-Asks-for-Access-to-Authorised-ATMPs.pdf

You can read the TRANSFORM MEP Interest Group Policy Asks on Cross-Border Healthcare launched on 10 November 2021 here:

https://transformalliance.eu/wp-content/uploads/2021/11/TRANSFORM-MEP-Interest-Group-Five-Asks-on-Cross-border-Access-to-ATMPs-1.pdf

You can read the TRANSFORM Recommendations for Actions in the context of the Pharmaceutical Strategy for Europe launched in June 2021 here:

https://transformalliance.eu/wp-content/uploads/2021/06/TRANSFORM-Recommendations-Version1.0_June2021-1.pdf

The European Alliance for Transformative Therapies (TRANSFORM) is a multi-stakeholder Alliance that connects Members of the European Parliament (MEPs) and policy-makers with patient groups, medical experts and associations, scientists, researchers, industry actors, networks and other relevant stakeholders. TRANSFORM aims to foster effective dialogue and provide evidence-based policy recommendations to enable safe and timely patient access to cell and gene therapies, whilst ensuring sustainability of healthcare systems.

The work of the TRANSFORM Secretariat, provided by FIPRA, is enabled by funding from EUCOPE and its members, BioMarin, CSL Behring, Gilead Sciences, Miltenyi, Novartis, Novo Nordisk, PTC Therapeutics, Santen and Vertex Pharmaceuticals.

The European Medicines Agency is an Observer to the Alliance.

EFNA – European Federation of Neurological Associations

RI – Retina International

WDO – World Duchenne Organization

IPOPI – International Patient Organisation for Primary Immunodeficiencies

TIF – Thalassaemia International Federation

EHC – European Haemophilia Consortium

EURORDIS – Rare Diseases Europe

EPTRI – European Paediatric Translational Research Infrastructure

CCI Europe – Childhood Cancer International Europe

SIOP Europe – the European Society for Paediatric Oncology

EAHAD – European Association for Haemophilia and Allied Disorders

EU EYE – European Alliance for Vision Research and Ophthalmology

EUCOPE – European Confederation of Pharmaceutical Entrepreneurs