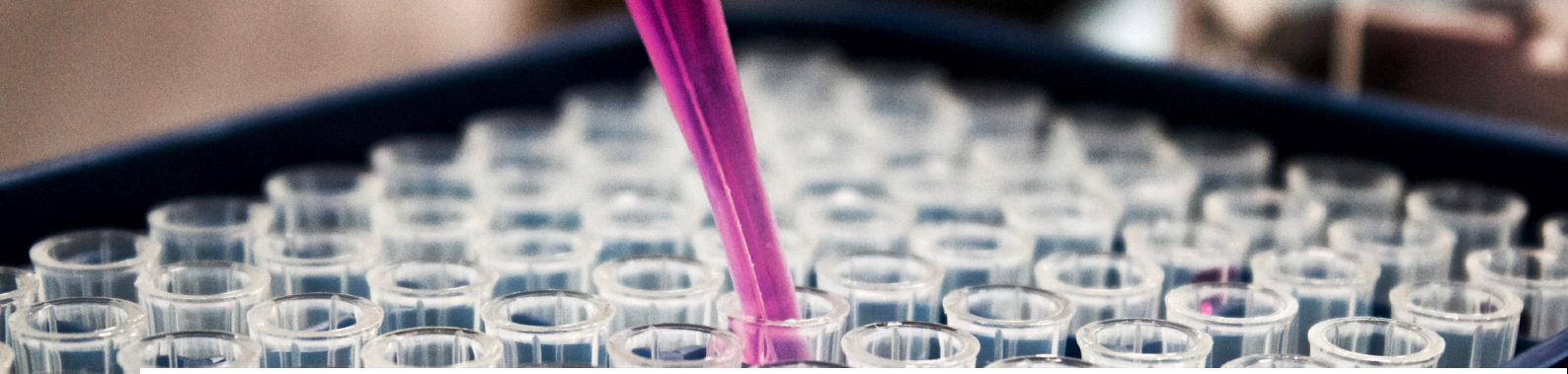
Policy Asks on the Regulatory Framework for ATMPs

Ensuring the Regulatory Framework is fit-for-purpose for ATMPs

#MEPsforATMPs

European Alliance for Transformative Therapies



These Policy Asks reflect the position of the TRANSFORM Alliance as of June 2022. The Asks will be integrated into a TRANSFORM Charter to be launched in the European Parliament on 13 October 2022.

The European Alliance for Transformative Therapies' (TRANSFORM) Policy Asks[1] advocate for a regulatory framework that enables safe and timely patient access to transformative therapies, building on the 2021 TRANSFORM Recommendations for Action.

ATMPs are complex medicines, and even small differences in DNA construct, the cellular composition of the final therapy, manufacturing steps, or route of delivery can have a significant impact on their clinical profile and performance. Having a robust and facilitatory regulatory framework for ATMPs' marketing authorisation, monitoring and administration is therefore critical to uphold patient safety and maintain quality and efficacy standards. At the same time, this must be balanced against the need to ensure that Europe remains attractive for clinical trials with ATMPs, and such therapies are assessed and, where appropriate, swiftly approved to provide EU patients with timely access to medical innovation.

The European Commission has highlighted the importance of adapting the regulatory framework to the specificities of innovative medicinal products, including ATMPs.[2] With the increasing number of cell and gene therapies for both rare and prevalent conditions coming to the market with the potential to transform patients' lives, notably many young patients' lives, the TRANSFORM Alliance welcomes the Commission's commitment to further build expertise in the European Medicines Agency (EMA), Health Technology Assessment bodies and national competent authorities on innovative and new medicines. Public confidence in the regulatory pathway will be key to long-term success.

A holistic review of the EU Pharmaceutical legislation must have patients at the centre of decision-making, and streamline regulatory processes where possible. The joint review of the Orphan and Paediatric Medicinal Products legislations, the revision of the rules governing Blood, Tissues and Cells (BTC) (which are sometimes used in the manufacturing of ATMPs), the implementation of the Regulation on Health Technology Assessment (HTA), within the context of the revision of the EU General Pharmaceuticals legislation will be critical in ensuring a clear interplay between the different legislative regimes and a level playing field for all stakeholders active in this area. Classification with a clear delineation between BTCs and ATMPs is central to defining their regulatory requirements and pathway.

The TRANSFORM Alliance has developed these Policy Asks with a view to ensuring a science-based and future-proof ATMP regulatory framework that is agile, flexible and proportionate to the associated level of risk. This requires aligning patient access demands with patient safety requirements, as well as establishing a predictable, efficient regulatory environment conducive to R&D investment in the ATMP sector.

[1] The Policy Asks have been developed through a process of finding points of common agreement and majority consensus amongst Alliance members. A stakeholder meeting was held on 5 May and three rounds of consultation took place between May and June 2022.

[2] See Commission's reaction to Parliament's report on pharma strategy, published 18 March 2022: Procedure File: 2021/2013(INI) | Legislative Observatory | European Parliament (europa.eu)

Policy Asks on the Regulatory Framework for ATMPs

POLICY ASK 1 — Ensure that Europe's regulatory framework remains fit for ATMP clinical trials

Challenge – Europe's attractiveness for ATMP R&D is stagnating

Running clinical trials in Europe directly benefits patients. These studies are a critical pathway to ensuring patients can access more ATMPs, and quicker, as it is a crucial step in the R&D process. Yet Europe is lagging behind other world regions in the number of clinical trials initiated with ATMPs. In 2019, there were 845 new clinical trials with ATMPs initiated in North America and 736 in Asia, compared to 323 in Europe. Moreover, between 2014 and 2018 the number of clinical trials with ATMPs initiated in Europe declined by 2%, whereas it grew by 36% in North America and 28% in Asia.[3] The expertise of and skills of clinical centres and HCPs, the speed of approval and quality of review were among factors that influence the selection of a clinical trial site identified in a study.[4]

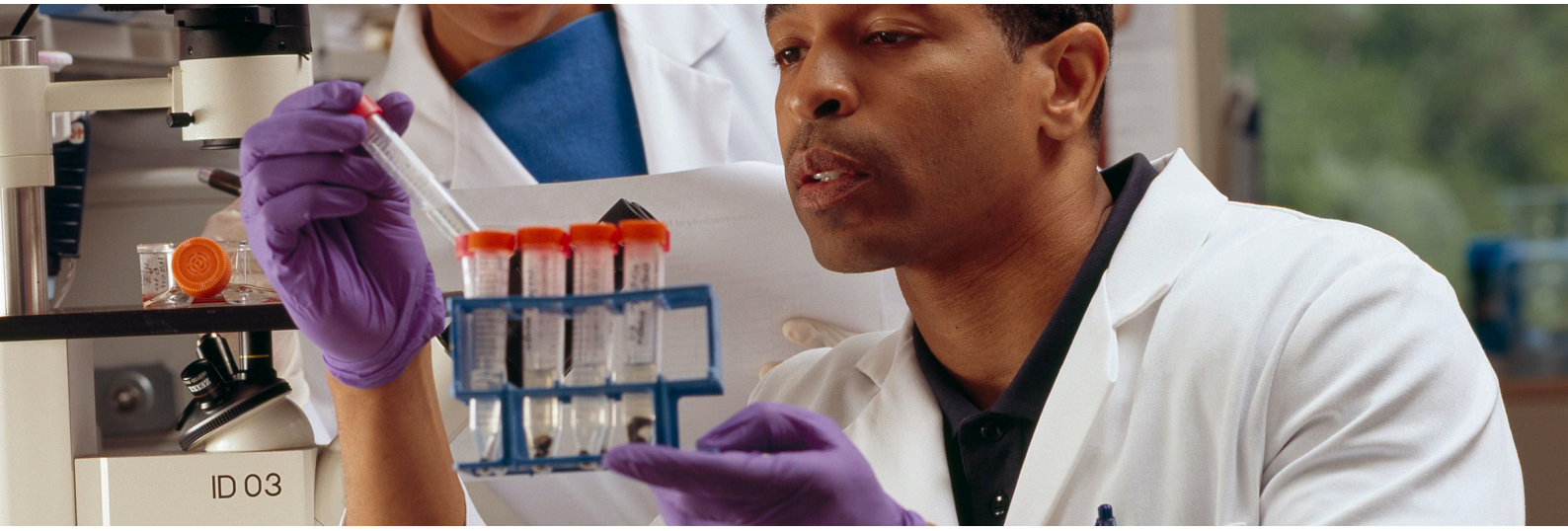
Policy Asks

1.1	**Ensure that the Clinical Trial Regulation is fully implemented and adhered to in all Member States**, and the introduction of additional national requirements for clinical trials outside of the Regulation is avoided.
1.2	**Ensure all relevant documentation can be submitted via the Clinical Trials Information System (CTIS)** and reducing the documentation requirements.
1.3	**Ensure harmonised national implementation of current EU guidelines on the required level of certification of cell therapy handling for ATMPs at the clinical site.** The minimal manipulation or handling of cell therapies prior to treatment in patients should be subject to Good Clinical Practice or Good Tissue Practice, as is currently in the EU guidelines. This should be clarified at EU level to ensure harmonised implementation across Member States.
1.4	**Support national competent authorities, by ensuring sufficient expertise and resources for assessing an increasing number of clinical trials with complex ATMPs**, for example by offering EU-level training and resources.

[3] https://alliancerm.org/wp-content/uploads/2019/10/Trends-in-Clinical-Trials-2019-Final_Digital.pdf These trends have continued in 2019, 2020 and 2021 as shown by ARM at the Meeting on the Med in April 2022.
[4] *Ibid*

Rationale / Explanation

Greater harmonisation between Member States on clinical trial requirements will remove complexity that does not exist in other (more homogenous) markets, and will contribute to making clinical evidence for European regulatory evaluations more readily available. Further building skills and expertise among national competent authorities will also go some way to make EU clinical trials more attractive to developers. For patients, the direct consequence of having more European ATMP studies will be access to more of these therapies, and faster.



Challenge – GMO requirements are complex

Most ATMPs currently in development meet the definition of, or include, genetically modified organisms (GMOs) and must comply with the EU GMO legislation. These rules are complex, vary by Member State, and require an environmental risk assessment (ERA) review by GMO national or regional authorities, independently from the review by the health regulatory authorities. However, such extended ERAs were not primarily intended, and different from ERA intended for medicinal products. The different reviews and timelines for approval (clinical trial approval by health authorities versus written authorisation for clinical trials involving GMOs) have not been anticipated or managed in the implementation of the Clinical Trial Regulation (CTR).

Policy Asks

1.5	**Exempt ATMPs from, and/or simplify the environmental assessment for clinical trials with cell and gene therapies under GMO legislation.**
1.6	**Consider adapting the Clinical Trials Information System to account for ATMPs falling under the definition of GMOs**, i.e. requiring additional review and approval by GMO authorities, so that at least one portal can be used for all submissions/documents related to a clinical trial application, including the GMO application.

Having simplified rules for medicinal products like ATMPs under the EU GMO legislation would support more and faster clinical trials in Europe, and faster access to more innovative therapies for patients.

A (temporary) exemption from GMO legal requirements was granted for COVID-19 vaccines and therapeutics in clinical trials, meaning GMO compliance was delayed until full marketing authorisation for the vaccine/therapy was sought. This underscores the legal possibility of introducing a similar derogation for ATMPs. A Risk Based Approach should be sufficient during clinical development.

POLICY ASK 2

Review the regulatory approval pathway for ATMPs, with a view to ensuring the marketing authorisation process for these therapies is fast, flexible and agile

Challenges

Cell and gene therapies are innovative therapies, based on novel technologies, which could require additional engagement with regulators to provide them with a solid understanding of the science behind the therapies. In addition, due to the unique nature of cell and gene therapies, they must undergo evidence generation pathways that differ from 'traditional medicine' such as biologics and small molecules. Therefore, earlier and iterative engagement with regulators can ensure the appropriate lifecycle data generation plans are developed and avoid unnecessary delays further in the approval process.

The eligibility criteria for some early access pathways (such as PRIME) can make it challenging for developers to successfully access these pathways and support at the most beneficial and timely point in the development pathway – i.e. early and limited data, yet insufficient evidence of clinical promise to facilitate support, or late and mature data yet too late to change the development plan.

The development process for ATMPs is dynamic and often more fast-paced than the development process for traditional therapies, such as biologics and small molecules. As transformative therapies, ATMPs can have a significant impact on patients' lives, especially when they apply to young patients and/or address debilitating or life-threatening conditions. However, despite the nature of their possible long-term medical benefit, ATMPs will often possess limited data and evidence to prove long-term clinical benefits at the time of approval.

Misalignments remain between regulators and HTA bodies in their evidence requirements such as: addressing the use of surrogate endpoints, considering expectation of life's years, small patient populations, non RCT trial designs, acceptable RWE and long-term efficacy/effectiveness. This is despite progress in and across Member States towards convergence and alignment on evidence requirements.

Policy Asks

2.1 **Reflect on the role of PRIME and update its scope, entry point and the possibility of a specific pathway for flexible, scientific interactions** with the aim of practically accelerating approval timelines.

More specifically:

- The EMA should act on the recommendations highlighted in the 5-year report[5] in the areas of flexibility of scientific advice provision and knowledge building to enable accelerated assessment, in addition to the scope and time of entry.
- The eligibility criteria for PRIME should be enlarged to allow all ATMP developers an early entry point so that designation can be obtained without the need to submit preliminary clinical efficacy data, which is currently only an option for academia or SMEs.

[5] https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

Rationale / Explanation

Enlarging the eligibility criteria for PRIME will ensure that if a product is promising and the need for support is justified, broad access for ATMPs to the scheme will be available.

Broadening access to PRIME can potentially accelerate patient access to transformative therapies. In 2020, ATMPs that benefitted from PRIME support and were granted marketing authorisation had on average shorter active assessment time and clock-stop duration than the average assessment time for all types of new active substances.[6]

2.2. Create opportunities for **earlier, more frequent, interactions between developers, the EMA, HTA bodies and patients**, to support and align on evidence generation across the full development pathway, including on the design of paediatric investigation plan (PIP) (when relevant), conditional authorisation, the use of real-world evidence (RWE) and the potential for conditional reimbursement.

This could be supported by:

- Setting up early dialogue and interaction between EMA and HTA bodies and including academic experts and patient representatives.[7]
- Enhancing the availability and use of untapped Member States' scientific expertise by creating communities of ATMP experts.
- Considering establishing a single point of contact for SMEs and academic developers at the EMA to provide speedier guidance at all development stages.
- Including national payers in these early discussions when appropriate. Regulatory bodies and payers have distinct objectives in their assessments of the same therapy, and full harmonisation of evidence requirements may not be possible; however, the early identification of the needs for the different stakeholders, with convergence of requirements where possible, should be encouraged as much as possible.
- Considering the opportunity for more informal meetings between ATMP developers and regulatory authorities. For instance, by enabling sponsors to obtain preliminary informal consultation for innovative investigational products at an early stage of development before the initial clinical trial application.

Establish **an iterative dialogue scheme** involving a series of official and unofficial interactions between the developer and each of the key stakeholders potentially involved (i.e. CHMP, COMP, PDCO, CAT, PRAC, HTA authorities, etc). In order to increase efficiency, not all members of the Discussion Group would need to attend all meetings (i.e. specific topics could be discussed with specific members) and meetings could take place in a parallel and staggered manner.

Rationale / Explanation

Early, frequent and informal dialogue provides developers with the reassurance they need to be confident in bringing a treatment through the European system. Increased early advanced dialogue facilitates swifter approval timelines; i.e. in Japan review timelines are accelerated to just 6 months.[8]

[6] Ibid
[7] Reineke A. Schoot, Maria A. Otth, Gerardus W.J. Frederix, Hubert G.M. Leufkens, Gilles Vassal, 'Market access to new anticancer medicines for children and adolescents with cancer in Europe', European Journal of Cancer, Volume 165, 2022, Pages 146-153, available at: https://doi.org/10.1016/j.ejca.2022.01.034
[8] Nagai S. (2019). Flexible and Expedited Regulatory Review Processes for Innovative Medicines and Regenerative Medical Products in the US, the EU, and Japan. International journal of molecular sciences, 20(15), 3801. https://doi.org/10.3390/ijms2015380

As innovative technologies with unique evidence generation requirements emerge, ensuring early engagement to highlight evidence uncertainties and to align where possible on the required pre- and post- Marketing Authorisation evidence generation plans and evidence requirements can avoid unnecessary delays in approval and access. This will help to ensure that RWE generated for regulatory purposes in the pre- and post-authorisation settings is also acceptable for value assessments by national authorities, as it serves as a key opportunity to find evidence generation alignment. Ensuring that Joint Scientific Advice under the EU HTA Regulation is offered to all developers will be an essential element in facilitating such engagement.[9]

Supporting this ambition with a more dynamic community of experts can offer a more flexible and agile response to the ATMPs coming through the pipeline in real-time.

The INTERACT program in the US (**IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s) proved to be very helpful for ATMP developers. It generally consists of one informal and non-binding consultation and is intended for innovative investigational products that introduce unique challenges due to the unknown safety profiles resulting from the use of complex manufacturing technologies, development of innovative devices, or cutting-edge testing methodologies. A similar procedure could be established in Europe.

2.3 Consider the introduction of a Master File for biological raw materials and starting materials for ATMPs.

Rationale / Explanation

The EU already has a well-functioning active substance master file (ASMF) system that allows for confidential information in the case of chemical APIs.

A Master File (MF) for biological raw materials for ATMPs (e.g. cytokines, media, reagents) and starting materials (e.g. viral vectors) can facilitate the administrative burdens for regulators and developers of ATMPs by avoiding the need for multiple assessments by every national competent authority each time these materials are used by developers of ATMPs, and reduce additional delays.

If Master Files for such products could be accepted by European regulatory authorities, as is already the case in the USA,[10] the EMA and regulatory authorities would receive comprehensive information and insight into the raw/starting materials used, getting all the necessary details directly from the supplier of the raw/starting materials, including commercially sensitive and proprietary information, and ATMP manufacturers could reduce their qualification activities.

There are no pharmacopeial monographs for many of the biological raw materials used in the manufacture of ATMPs since their quality cannot be ensured solely on the basis of physico-chemical and biological testing. This means that ATMP manufacturers who use biological raw materials need to qualify them, a complex and resource-intensive activity.

[9] Another example is the UK's Innovative Licensing and Access Pathway (ILAP). ILAP acts as a pathway to support innovative approaches to the safe, timely and efficient development of medicines, and involves interactions with both the regulatory body MHRA and the UK HTA bodies. It also includes patients in the review of the target product profile. ILAP includes multiple entry points, which means that all developers can apply at pre-clinical stages, thus benefitting more from the system.
[10] The United States of America has established a system of Drug Master Files which accelerate and streamline the review of ATMPs.

POLICY ASK 3 Bolster the EMA's work on innovative and new medicines

Challenges

Compared to other regions, the EU has one of the slowest approval timelines for new therapies.[11] This has trickle-down implications for access, as patients wait for transformative therapies to undergo the approval pathway which could be safely accelerated. Rare and paediatric patient populations, with some of the highest unmet medical needs, are particularly affected by delays.

Moreover, there is concern that the EMA does not have adequate resourcing to deliver everything that is within – or may soon be added to – its remit as the central marketing authorisation agency in the EU.

When comparing accelerated regulatory review processes across markets, in 2020, the EMA had an extremely low percentage (37%) of new active substances approved via expedited reviews, compared to other regions of the world (74% in the United States, 61% in Switzerland, 56% in Australia).[12] This illustrates Europe's capacity challenge, and the fact that therapies are not able to benefit from existing pathways.

The Scientific Advice process has also come under pressure in recent months, with many procedures delayed due to resource constraints in the EU regulatory network.

Policy Asks

3.1 **Introduce an overall streamlining and acceleration of the Centralised Procedure**, including the European Commission decision-making process, which could shorten the EU's approval timeline to 170 days.

This could include, for example:

- A more flexible, iterative data review process during the scientific advice procedure.
- The EMA becoming a so-called 'one-stop shop' or 'hub' for innovative therapies seeking development support and approval, facilitating interactions with all involved agencies.

Rationale / Explanation

The EMA as a 'one-stop shop' refers both to development support and the assessment of a therapy, given ATMPs require diverse expertise and may require, for example, use in

[11] https://cirsci.org/publications/cirs-rd-briefing-81-new-drug-approvals-in-six-major-authorities-2011-2020
[12] EFPIA report, 'Evidence MIX (Measures, Insights and eXamples): Evaluating the regulatory system', p.13, available at: https://www.efpia.eu/media/636564/evidence-mix_final-9-dec-2021.pdf

combination with an in vitro diagnostic, or a device. Navigating different frameworks, and different authorities, is a recognised challenge for developers.

Streamlining the approval process for EU marketing authorisation for innovative therapies, whilst upholding quality, safety and efficacy standards, will ensure they can be assessed and, where authorised, be available to patients as quickly as possible.

3.2 **Ensure appropriate resourcing for the EMA and the wider European medicines regulatory network** in order to appropriately deliver against their high demands and to have sufficient internal expertise available to assess the increasing number of ATMP applications. This could include the creation of Multi National Assessment Teams (MNAT).[13]

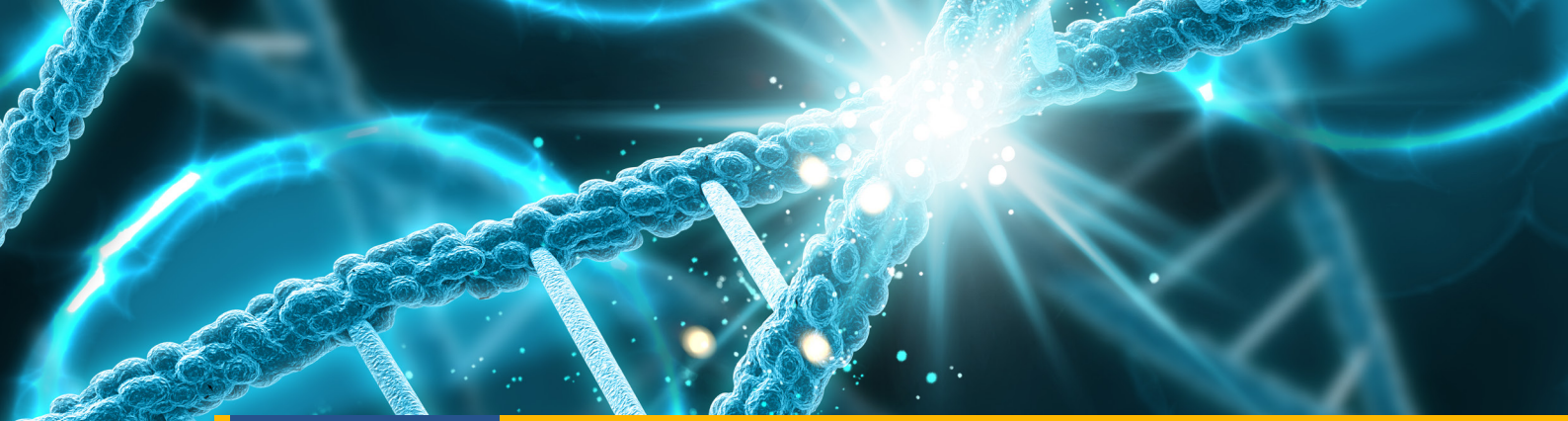
Rationale / Explanation

The EMA's mandate has recently been extended in the context of the COVID-19 pandemic: in March 2022, a regulation reinforcing the EMA's role in crisis preparedness and management of medicinal products and medical devices came into force, expanding the EMA's role significantly. The EMA has also been playing a significant and new role in the implementation of the Clinical Trial Regulation.

As noted in these policy asks, there are also areas for ATMPs where the EMA could take a larger role, and the Commission is considering how to build expertise in innovative therapies within the Agency.

Considering this general trend towards an expansion of its remit, having a well-resourced and experienced EMA is critical to public confidence in regulatory processes. MNAT could support the expertise within the regulatory network and help address some of these resourcing challenges.

[13] https://www.ema.europa.eu/en/documents/other/multinational-assessment-team-concept-next-phase-broadening-concept-post-authorisation-phase_en.pdf



POLICY ASK 4 Ensure the patient perspective is included in the full regulatory pathway

Challenges

The EMA has acknowledged that, currently, patient and patient representatives' input in scientific advice procedures and in the assessments of marketing authorisation applications is included in a qualitative, non-systematic way. However, the agency recognises a need to involve patients and patient representatives in a more structured way, including via patient preference studies, in regulatory decision-making processes.[14]

Policy Asks

4.1 **Ensure that patients and the patient perspective are actively included throughout the full regulatory pathway**, including more patient-oriented clinical trial design and risk/benefit assessment. There should be transparency on how the patient input/experience/preference was factored in in benefit/risk assessments, or in providing advice on drug developments.

4.2 **Strongly encourage all national competent authorities to systematically seek and integrate patient representatives' input** in their national scientific advice and clinical trial application processes.

Rationale / Explanation

As key stakeholders with a unique perspective on novel therapies, it is essential that the patient voice is reflected during the development and assessment of novel therapies, both during the Marketing Authorisation assessment and joint clinical assessment under the EU HTA Regulation. The participating patient associations should be determined on a case-by-case basis, to reflect the appropriate expertise.

TRANSFORM notes the IMI project, PREFER, which in April 2022 published its recommendations for a framework to include patient preferences in regulatory decision making.[15] The EMA and HTA bodies/payers are involved in this project.

[14] Draft Qualification Opinion of IMI PREFER - for public consultation (europa.eu)
[15] https://www.imi-prefer.eu/recommendations/

4.3 **Include Young Persons Advisory Groups (YPAG)**[16] in the assessment process to consider young patients' opinions.

Rationale / Explanation

Young Persons Advisory Groups, composed of youths actively advising researchers in various research projects, can help researchers develop research questions, design trials, improve communication with young patients, and brainstorm methods for dissemination of findings.

4.4 **Provide EU-level support for education and training on ATMPs** for patients, patient representatives and Health Care Professionals (HCPs).

Rationale / Explanation

It is important that patient representatives are properly educated about ATMPs so that they can make informed contributions. Organisations like EUPATI[17], SIOP Europe[18] and the TEDDY Network[19] are working to achieve this. The same applies for HCPs, which act as a vital link in facilitating access and understanding of ATMPs.

[16] https://www.teddynetwork.net/ypag/
[17] https://eupati.eu/
[18] https://siope.eu/activities/education
[19] https://www.teddynetwork.net/

POLICY ASK 5

Ensure a level playing field for all stakeholders, with no discrepancies in classification of BTC and ATMPs in Europe

Challenge

Blood, tissues and cells (BTC) can be the raw/starting materials (whether they are autologous (i.e. from the patient themselves) or allogeneic (i.e. from a donor)) for ATMPs. BTC are then modified to create a human medicinal product - an ATMP.

The revised EU BTC legislation – which the European Commission is currently drafting - is expected to lay down a process for authorisation of novel or innovative applications of BTC: preparation process authorisation (PPA).

ATMPs and BTCs are governed under different legislative regimes, reflective of their potential risk and impact on patients. As BTCs evolve, applications will become more advanced with increasingly novel preparation processes, making it probable that there will be more therapies on the borderline between the definitions of ATMPs and BTCs. The Commission has already noted the difficulties in classification between BTCs and ATMPs, pointing to the case of keratinocyte grafts as one example of re-classification.[20]

The applicable regulatory requirements for any type of product should be proportionate to their risks and based on science, aligned with the current definitions of ATMPs or other available legislation. For novel applications of BTC, it is imperative that the applicable regulatory regime is clear and adhered to by all stakeholders.

Policy Ask

5.1 **The regulatory requirements for BTC, ATMPs and medical devices should be proportionate to their risks, based on science, and aligned with the current definitions in the existing BTC and ATMP legislations, respectively.** The delineation of the regulatory frameworks should not be changed.

This can be achieved by:

- Establishing an EU level mechanism, within the framework of the EMA, to advise Member States on whether the BTC framework, the ATMP or any other framework(s) should be applied for borderline products based on tissues, cells or genes. Such advice from the EMA should be binding throughout the EU.
- Enforcing consistent standards for BTC across the EU, aligned with the pan-European classification.

[20] See Study supporting the evaluation of the EU legislation on Blood and Tissues and Cells, pages 111 and 121-122. Available: https://op.europa.eu/en/publication-detail/-/publication/c1c3414c-ec23-11e9-9c4e-01aa75ed71a1/language-en/format-PDF/source-106664789

Rationale / Explanation

The existing ATMP Regulation and Directive on medicinal products for human use already provide a clear definition for ATMPs with a robust and science-based optional classification pathway managed by CAT.[21] Since the revised BTC legislation will provide a specific framework for the authorisation of preparation processes of BTC (PPA), situations where, for instance, a product could be classified as BTC by a BTC Competent Authority in a country and as an ATMP by the medicines Competent Authority in another should be avoided to ensure all ATMP developers are held to consistent standards across the bloc.

Therefore, a mechanism should be put in place to ensure consistency of approaches within the EU, driven by science and based on the potential risks for patients. The establishment of a pan-European mechanism to advise on the classification has been discussed by the joint action on facilitatin**G** the **A**uthorisation of **P**reparation **P**rocess for blood and tissues and cells (GAPP-JA)[22] and could be introduced in the revised BTC legislation. This body could advise on the classification between BTC, ATMPs and medical devices as well as on the risk level for BTC.

It will be important to ensure that the advice from such pan-European classification body is consistently enforced across the EU, leaving no room for different interpretations at national or regional levels. It is therefore proposed that such advice should prevail over national BTC Competent Authorities.

Challenge

Point of Care BTC processing and Decentralised Manufacturing of ATMPs will likely become more prominent in the future, the implications of which are being considered by the European Commission under its Pharmaceutical Strategy for Europe.[23]

A relaxation of existing regulatory requirements for BTCs or ATMPs, as mooted by some stakeholders, should be avoided in order to maintain current quality, safety and efficacy standards.[24]

Where appropriate, decentralised manufacturing has the potential to speed up production and treatment times of ATMPs, but as noted by the Commission, such new manufacturing methods create new manufacturing models, which "*create new challenges in terms of appropriate quality, inspection and oversight*".[25]

5.2 **Apply similar regulatory and quality standards for Decentralised Manufacturing of ATMPs as for products manufactured centrally, by ensuring consistent implementation across the EU and consistent control by the national health inspectorates.**

The existing exemption for autologous grafts within the same surgical procedure should not be used for the Decentralised Manufacturing of ATMPs since this would imply a lack of regulatory oversight and lower quality standards to the detriment of patient safety.

[21] The ATMP Regulation defines a tissue-engineered product and combined ATMP. Directive 2001/83/EC Annex I Part IV defines gene therapies and somatic cell therapies.
[22] Good practice guideline to authorisation on preparation processes in blood, tissues and cell establishments, page 44. Available at: https://www.gapp-ja.eu/wp-content/uploads/2022/01/GAPP-volume-Guide-and-Technical-Annexes.pdf
[23] See page 19 of the Strategy, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN
[24] "Industry urged to share potential regulatory challenges to decentralized manufacturing", PinkSheet, 18/04/2022, available at: https://pink.pharmaintelligence.informa.com/PS146026/Industry-Urged-To-Share-Potential-Regulatory-Challenges-To-Decentralized-Manufacturing
[25] See page 19 of the Strategy, available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN

Reform to the BTC legislation and General Pharmaceutical Legislation should ensure that all ATMPs continue to be regulated by and uphold to the same standards, irrespective of where they are produced. All ATMP production should be subject to rigorous GMP manufacturing and testing standards irrespective of the manufacturer (academic or industrial), and irrespective of the manufacturing method (centralised or decentralised).

The EMA GMP Guideline for ATMPs already lays out some basic rules & obligations in case of Decentralised Manufacturing. However, they would need further elaboration because (1) an increased use of Decentralised Manufacturing is anticipated in the future (2) there are different interpretations and implementations of the requirements at national level. Additional guidance on Decentralised Manufacturing in the GMP for ATMP, as well as some training courses for inspectors coordinated at EU level would be helpful to ensure consistent implementation and control of the quality standards throughout Europe.

Rationale / Explanation

ATMPs are complex medicines. Even slight differences[26] in molecular structures, in the cellular composition of the final products, or in the different manufacturing steps that are necessary to ensure consistent high-quality products, can have a major impact on the clinical profile and clinical performances of ATMPs.

Ensuring that all ATMPs, irrespective of where they are manufactured continue to meet high quality standards is essential to ensure long-term patient safety and confidence in innovative therapies.

[26] EMA Questions and answers on comparability considerations for advanced therapy medicinal products: "When critical changes are made in the manufacturing of starting materials for ATMPs having an impact on the manufacturing process or the finished product, a comparability demonstration is required to ensure the consistent quality of the product and to ensure that the change does not have an adverse effect on the safety or efficacy profile of the product", 2019, available at: https://www.ema.europa.eu/en/questions-answers-comparability-considerations-advanced-therapy-medicinalproducts-atmp

POLICY ASK 6 Ensure appropriate use of the Hospital Exemption for ATMPs

Challenges

There are currently different implementations across Member States of the Hospital Exemption (HE) for ATMPs provided under the ATMP Regulation.[27] The HE is interpreted differently and used more liberally in some Member States compared to others, including in cases where a fully developed ATMP has been authorised at community level for the same indication.[28]

As ATMPs manufactured under the HE do not undergo central marketing authorisation approval, there are concerns around their oversight and safety. ATMPs are complex products, where small changes in manufacturing processes can have significant consequences.

Policy Asks

6.1 **Introduce EU regulatory guidelines, premised on a patient-centric approach, setting minimum standards for the HE-authorisation procedure at national level to ensure an efficient, clear, transparent and streamlined approach across EU Member States.**

Specifically:

- HE should be possible in areas of large unmet medical needs, including where the ATMPs may be life saving (e.g. rare disease settings, like paediatric cancer), when there are no centrally authorised ATMPs available to patients in the Member State for the indication, and there are no clinical trials available for the same indication with an ATMP in the Member State. HE should not be used to bypass marketing authorisation and/or clinical trials procedures in Europe.
- Guidelines should be published to define regulatory requirements on how HE should be documented, pre- and post-approval including details on how the safety and efficacy profile can be documented and better characterised pre- and post-approval to ensure an efficient, clear, transparent process, with a streamlined approach across the EU. Such guidelines should set minimum data requirements before granting a HE authorisation and request minimum efficacy data reporting after HE authorisation.

6.2 **Create European registries to provide transparency around the HE** with details of the products, hospitals, their uses/indications, number of patients intended to be treated, duration of the hospital exemption authorisations etc. Such registries should be regularly updated to report on the experience gained with products used under HE and the evidence regarding their

[27] "Hospital Exemption" refers to the exemption provided under Article 28 of Regulation 1394/2007/EC (the ATMP Regulation), which foresees the exclusion of certain ATMPs from the scope of Directive 2001/83/EC on medicinal products for human use. 'Any advanced therapy medicinal products which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient'.

[28] http://alliancerm.org/wp-content/uploads/2020/10/ARM-position-on-HE-final-Oct-2020.pdf

therapeutic value: the collected efficacy and safety data (e.g. case report form linked to outcomes) should be documented and reported in the registries.

Ensuring that such registries are publicly and easily accessible will help increase knowledge on HE-ATMPs and will facilitate patient access.

Rationale / Explanation

HE is a legitimate pathway to enable patients to receive an ATMP under controlled conditions in cases where no other medicinal product is available. However, it is important to ensure that patients are protected from unnecessary risks and that the HE is not misused to circumvent the applicable legal instruments for the marketing of safe and effective medicinal products in Europe. The HE principle provides for the use of ATMPs without a marketing authorisation under certain circumstances. As per the definition of the Hospital Exemption (see footnote 28), it applies to any ATMP which is prepared (a) **in a hospital setting under the sole responsibility of the treating physician, (b)** on a **non-routine basis, (c)** for an **individual patient**. Any change in standards to allow wider use of the HE could reduce patient confidence in this emerging field by introducing a two-tier system for ATMPs where therapies can be developed with significantly less regulatory oversight around quality, safety and efficacy. Liberal use of the HE may also act as a disincentive to seeking a marketing authorisation or enrolling patients in clinical trials, thus slowing the continued development of ATMPs.

Similarly as proposed by the League of European Research Universities (LERU), HE usage should be redefined and limited to situations where a centrally authorised ATMP is not available (e.g. because it is still undergoing consideration and has not yet been put on the national market) or as part of an ongoing clinical trial with an ATMP.[29]

[29] See LERU's paper on ATMPs published in August 2019. Available here: https://www.leru.org/files/LR-BP-ATMP.pdf

POLICY ASK 7 Support the use of real-world evidence in regulatory approval

Challenges

The characteristics of ATMPs are such that developers are oftentimes unable – or it is impractical - to produce the type of clinical data typically required by the EMA for marketing authorisation applications, particularly if they are SMEs or academic institutions that may lack the necessary resource and regulatory expertise.

Due to the nature of ATMPs, even post-authorisation data uncertainties remain, especially regarding the long-term efficacy. This underlines the importance of long-term follow up and monitoring of patient outcomes that should be tracked over many years. Real-World Evidence (RWE) can play a key role in measuring the long-lasting medical benefits of these therapies.

In addition, due to the technology of ATMPs, as well as practical and ethical limitations, randomised control trials (RCT) are not always a feasible approach to generate robust clinical evidence. This is due to a lack of comparators for clinical and economical evaluation, sometimes limited treatment centres to administer investigational products, and ethical considerations of not providing a curative treatment to a patient while their condition deteriorates.

There are also challenges related to patient retention over long periods of time, which can compromise the statistical quality of the evidence. For some therapy areas, RCT's can also be completely unviable due to small and dispersed patient populations.

Policy Asks

7.1 **Continue to build flexibility within the EMA's standards to allow for other forms of data generation.** This could include:

- Offering more guidance to developers of what real-world data may be acceptable to regulators, and under what context.
- Bringing in new experts in real-world data to advise the EMA on what types of data could be used as evidence.
- Listening more to patients in each disease area as to what real-world data would be practical and acceptable to collect and analyse, to help with a decision-making process.
- Continued dialogue around including non-traditional clinical trial designs, for example adaptive trials (where modifications are allowed during the course of the trial) and single-arm using external control (e.g. natural history) for context.
- Giving consideration to the use of wearable devices as an additional data source.

Rationale / Explanation

Randomised clinical trials are seen as the gold standard in clinical trial design. However, for ATMPs non-traditional clinical trial designs such as open-label single-arm studies, with

supportive comparator data via real-world evidence, are often the only feasible alternative.

While the potential therapeutic value of gene therapy is clearly very high, their full benefit is not easily quantified. When the duration of the therapeutic effect is anticipated to be sustained in the long term, even with continued evidence collection there will be uncertainty as to the duration of effect and long-term safety. Other challenges faced by all rare disease treatments include limited data on natural history, heterogeneous patient populations, delayed diagnosis, lack of established clinical endpoints and little or no consensus on current treatment.

Recognising the data constraints for ATMP developers and a more flexible approach to providing guidance on acceptable approaches will support more marketing authorisation applications for ATMPs in the future.

Furthermore, health data stemming from wearable devices should be given consideration as an additional data source.

7.2 **The EMA's approval requirements should be updated to recognise RWE as an acceptable and standard form of supporting evidence in Marketing Authorisation assessments of ATMPs, as well as post-approval.**

This could build on the EMA's current work under DARWIN EU. Its Coordination Centre, which was set up in February 2022 and is led by Erasmus University Medical Centre, will play a key role in providing timely and reliable evidence on medicines from RWD databases across the bloc.[30] In order to ensure the best possible use of DARWIN, it is important that all stakeholders, including drug developers, have access to the database and contribute with data from their clinical trials.

Rationale / Explanation

A recent analysis shared at the CAT Interested Parties meeting in October 2021 indicates that for all ATMP approvals between 2018 to date CAT considered RWE as part of the regulatory decision-making process leading to authorisation, and imposed RWE generation in the post-approval phase. However, some resistance remains in the system to move on from the tightly controlled, golden standard of randomised controlled trials, when justified.

The Commission should drive this evolution of the regulatory standards. In order to respond to the challenges outlined and ensure that access is not further delayed by regulatory processes, alternative evidence such as RWE must be routinely accepted by regulators.

A multitude of stakeholders should be included in the ambitious DARWIN project. ATMP developers and researchers for example, who generate important RWE, should be involved during the development of the system to assess its validity, reliability and utility.

Ideally, the data and analytic tools should be accessible to all stakeholders in the healthcare ecosystem.

These Policy Asks will be included in the TRANSFORM Charter, to be launched in the European Parliament in **October 2022**.

[30] https://www.ema.europa.eu/en/news/initiation-darwin-eur-coordination-centre-advances-integration-real-world-evidence-assessment

About the European Alliance for Transformative Therapies (TRANSFORM)

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.

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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