

# Shifting the paradigm for ATMPs:

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Adapting reimbursement and value frameworks  
to improve patient access in Europe

January 2022

# Shifting the paradigm for ATMPs

Advanced Therapy Medicinal Products (ATMPs) are at the forefront of global scientific innovation in healthcare. These pioneering treatments, which include gene therapies, somatic cell therapies and tissue engineered products, have the potential to transform patients' lives, providing new therapeutic options for diseases for which there may be limited or no available treatments, and in some instances being potentially curative. In the context of the recently published Pharmaceutical Strategy for Europe, the European Commission recognises ATMPs as a generational milestone and acknowledges the need for new pricing and reimbursement frameworks that help address the shift from payment over time for chronic treatments to upfront costs for these often one-time therapies. With multiple approved products and numerous more in the pipeline, the timing is now to collectively build a future-proof innovation model for ATMPs. This White Paper identifies key challenges ahead and proposes a set of recommendations to start collectively building that future-proof innovation model.

ATMPs fundamentally change the value assessment framework, being usually associated with a single upfront payment, despite benefits extending many years into the future and spreading to societal areas beyond savings in the healthcare system. Moreover, the current evidence package of ATMPs at launch may not address all questions posed in traditional Health Technology Assessments (HTA), demonstrating cost-effectiveness can be challenging and the holistic value of ATMPs is not being consistently recognised. This new generation of ground-breaking treatments calls for a two-pronged paradigm shift, enabling the advent of a new wave of innovation and delivering better health outcomes for patients. Such a change requires a collaborative, multi-stakeholder environment.

EFPIA members have come together to propose a concrete list of recommendations that could increase patient access and accelerate the availability of innovative, potentially curative ATMPs. They address the challenges identified, focusing on two pillars:

- Promoting patient access to ATMPs while supporting payer decision-making
- Ensuring sustainable ATMP access for healthcare systems and patients

A broader, holistic value assessment is anticipated to enable timely patient access to ATMPs. Collaboration between industry, the European Medicines Agency (EMA) and Health HTA agencies is needed to harmonise evidence requirements and facilitate greater acceptance of ATMP evidence, including indirect treatment comparisons, surrogate endpoints, and real-world evidence (RWE). Innovative payment models can help address payers' remaining evidentiary questions while helping to spread the upfront cost of ATMPs, securing timely patient access and alleviating the financial burden. A longer distribution of costs over time and the restructuring of existing budget silos could also tackle sustainability concerns. Horizon scanning is another key element of the ATMPs access toolbox, as it allows to inform financial commitments ahead of landmark launches and prevent delays in access and uptake.

As we welcome this new generation of therapies, we hope that this White Paper will serve as a roadmap towards identifying the steps that are necessary at EU and Member State level, to ensure the full value of ATMPs is realised and patients can benefit from unprecedented opportunities. A paradigm shift is never an easy task and we are convinced that collectively, we can rise to the occasion and deliver on the shared commitment of our industry and the healthcare systems for patients.

Nathalie Moll  
EFPIA Director General

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# RECOMMENDATIONS

## Promoting patient access to ATMPs while supporting payer decision-making

I

### Utilise outcomes-based innovative payment models for ATMPs

Use outcomes-based models as a means towards securing timely patient access while addressing payer concerns and maintaining incentives for innovation. To ensure schemes are fit for purpose, clear alignment should be achieved on the uncertainty to be addressed and the metrics measured. Industry and payers should work together to ensure the necessary infrastructure and healthcare professional engagement is in place to enable high quality data collection.

II

### Harmonise evidence requirements across regulators and HTA agencies

Collaboration between industry, the European Medicines Agency (EMA) and Health Technology Assessment (HTA) agencies is needed to harmonise evidence requirements and facilitate greater acceptance of ATMP evidence including indirect treatment comparisons, surrogate endpoints, and real-world evidence (RWE). EFPIA advocates for sufficient capacity to enable high-quality HTA advice, as well as the establishment of robust EU joint clinical assessments and scientific consultations that avoid duplicative processes and inconsistent patient access.

III

### Ensure an inclusive, multi-stakeholder approach to ATMP value assessments

Include patients, healthcare professionals and Centres of Excellence during HTA to capture a holistic view of treatment value and fill evidence/knowledge gaps. Provision of sufficient training is needed to ensure stakeholders can provide meaningful contributions throughout the process.

IV

### Consider holistic ATMP value in HTA appraisals

Allow for data during the HTA process that captures the lifetime value of ATMPs to supplement assessments, including educational and societal benefits, improved healthcare system resilience and the impact of single administration on treatment burden and non-adherence.

V

### Adapt the cost-effectiveness frameworks used to assess ATMPs

Use cost-effectiveness threshold modifiers and/or specialised pathways that account for the rarity and severity of ATMP indications, in addition to revising discounting methods to ensure ATMPs are not placed at a disadvantage to non-ATMP treatments.

VI

### Efficient collection of high-quality ATMP RWE

Provide further investment to improve and maintain the digital and human infrastructure needed for high-quality RWE collection to support HTA decision-making and outcomes-based agreements. Data should be collected at an EU rather than national level when possible and appropriate standards for developing and using RWE in assessments should be established.

VII

### Selective application of value-based iterative assessments to address outstanding HTA questions

Use iterative assessments only when required to address important clinical and economic uncertainties. Assessment timelines should consider the nature of the individual ATMP, the specific uncertainty to be addressed and the availability of meaningful new data.



# RECOMMENDATIONS

## Ensuring sustainable ATMP access for healthcare systems and patients

I

### **Increase use of innovative payment models that distribute costs over time**

Alleviate the financial burden of upfront costs by utilising models such as annuity payments. EFPIA is willing to work with European and national stakeholders to identify and overcome accounting and/or legislative barriers to engaging with these models.

II

### **Maintain a collaborative environment for developing innovative payment models through co-creation and shared learnings**

Industry and payers should engage collectively to share learnings of successful engagements and identify necessary areas for change and policy reform, while respecting the necessary confidentiality and commercial sensitivity of agreements. Development of innovative payment models should be grounded in a co-creative process that could begin at the point of early dialogue to identify uncertainties and appropriate models as well as infrastructural requirements.

III

### **Enhance horizon scanning**

Conduct robust horizon scanning through collaboration between industry, HTA agencies, payers and patient organisations that appropriately informs upcoming ATMP launches and associated funding and healthcare service requirements. Best practices of well-functioning horizon scanning systems should be shared to support the enhancement of other Member States' processes.

IV

### **Implement adaptive budget impact analyses**

Adapt budget impact analyses to capture a holistic view of both ATMP costs and savings over the patient lifetime. Ensure budget impact analyses include time horizons and innovative payment models that reflect the nature of single administration curative treatments and their reimbursement conditions to provide a clear picture of short- and long-term affordability.

V

### **Reconfigure budget silos**

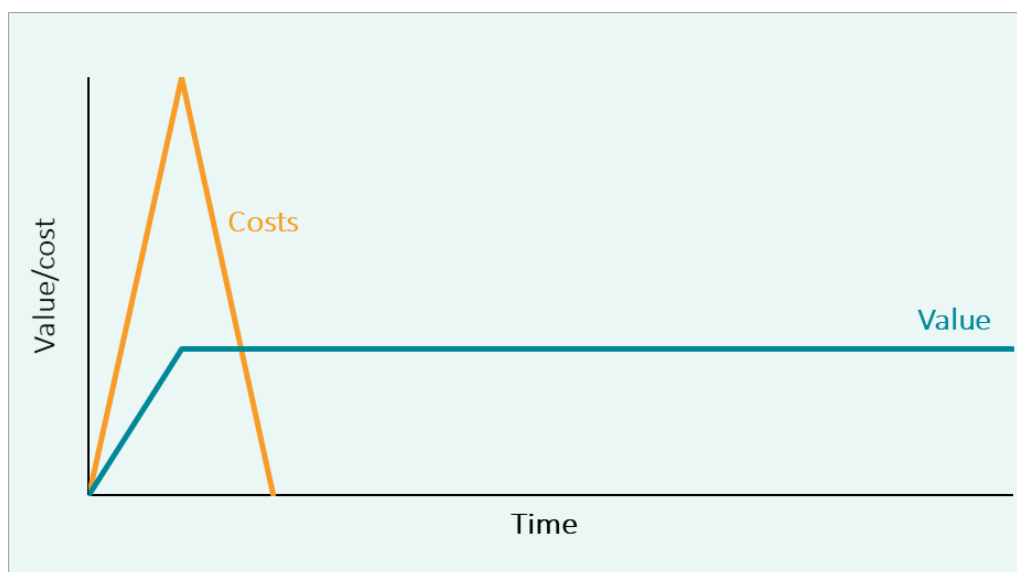
Configure budgets to ensure funding allocated to pharmaceuticals incorporates the savings made in the wider health and social care system resulting from ATMP benefits. EFPIA is willing to work with stakeholders to identify ways to co-create an integrated, patient-centric budget system and promote efficient healthcare funding allocation and expenditure for advanced therapies.

## ATMPs represent a fundamental change to the healthcare and biopharma value and innovation model

Advanced Therapy Medicinal Products (ATMPs)<sup>i</sup> are at the forefront of global scientific innovation in healthcare. Since the approval of the first ATMP by the European Medicines Agency (EMA) in 2009, these pioneering therapies have been growing in importance to patients, the industry and healthcare systems. This has been recognised in the recently published Pharmaceutical Strategy<sup>1</sup> for Europe by the European Commission, which highlights the development of these treatments as a major milestone since the turn of the millennium and calls for a new business model to adapt to their specificities.

ATMPs represent a significant breakthrough in health outcomes for patients, providing the opportunity for long-term value and in some instances curative potential, after a single administration. These therapies are usually associated with a single upfront payment, despite benefits extending many years into the future. Broadly then, ATMPs are characterised by two paradigm shifts:

- i. **Long-term benefits to patients and society**
- ii. **Higher upfront costs to healthcare systems**



*Figure 1: Conceptual illustration of ATMP value and costs over time*

Pricing and reimbursement (P&R) mechanisms in Europe have long since provided a framework for the assessment of pharmaceutical innovations' value, economic efficiency, and budget impact. Although not without challenges, this system has generally allowed for the successful negotiation and reimbursement of non-ATMP therapies. While ATMPs provide great opportunity for patients and healthcare systems, their characteristics raise challenges that necessitate a reconsideration of health technology assessment (HTA) and P&R processes to ensure access. The outcome of the recent price

<sup>i</sup> For the purpose of this white paper, the definition of an ATMP proposed by EFPIA is used and includes ATMPs including but not exclusive to those targeting rare diseases. EFPIA defines an ATMP as medicinal products which are either: 'a gene therapy medicinal product or a somatic cell therapy medicinal product or a tissue engineered product'.

negotiation for the one-off gene therapy Zynteglo in Germany provides an example of some of the challenges that arise for ATMPs in pricing and reimbursement negotiations. Price negotiation in arbitration led to a request for significant discounts on the Zynteglo launch price. The assumptions made when calculating the new price did not account for the anticipated life-long benefit of treatment. Ultimately, the outcome of negotiations did not result in patient access to Zynteglo<sup>2</sup>.

It is critical that stakeholders across Europe come together to ensure the potential of these life-altering therapies is realised and a sustainable environment for continued innovation maintained. The need to facilitate positive policy reform has been recognised by the formation of several ATMP-specific initiatives, not only representing industry but also those led by patient organisations, and scientific or medical societies<sup>3, 4, 5, 6, 7</sup>.



	Approved indications		Example therapy areas in development
✓	Haematological cancers	☐	Solid tumours
✓	Spinal Muscular Atrophy	☐	Haemophilia A & B
✓	Beta-thalassemia	☐	Diabetes
✓	Inherited retinal disease	☐	Cardiovascular disorders
✓	Severe combined immunodeficiency	☐	Pain
✓	Complex perianal fistulas in Crohn's disease	☐	Neurological disorders
✓	Cartilage disease	☐	Sickle cell disease
		☐	Neoplasms and pancreatic cancer

Figure 2: Therapy areas with ATMPs approved or in development as of May 2021<sup>8</sup>

## ATMPs provide an opportunity for unprecedented long-term benefits to patients and society...



...however, the evidence package of ATMPs at launch may not address all questions posed in traditional health technology assessments...

To date, ATMPs have targeted rare and severe disorders, offering a step change in treatment benefit for areas of high unmet need. The presence of small populations often with no effective alternatives coupled with the unprecedented value provided by ATMPs raise practical and ethical challenges to utilising the historical “gold-standard” randomised-controlled trial design<sup>9</sup>. In response, the use of indirect treatment comparisons (ITCs) is growing. However, the formal acceptability of such evidence varies across HTA agencies and closer alignment is needed.

The ATMP value proposition is grounded in a long-term or curative benefit, therefore the length of patient follow-up required to demonstrate such efficacy is far greater than a typical trial duration. Further, the use of well-established or hard endpoints such as overall survival to determine long-term effect is not always feasible due to the chronic, severe, or poorly understood nature of the indications

ATMPs often target<sup>10</sup>. The use of surrogate outcomes is thus often necessary in ATMP trial designs. Some surrogate endpoints are well-established and objectively measurable; however, particularly in rare diseases where clinical experience or pharmacological research is more limited, surrogates may not be extensively validated or considered subjective. As a result, these endpoints are not consistently accepted in pricing and reimbursement decision-making. In addition, the willingness to accept surrogate endpoints varies by country and may pose significant issues during ATMP appraisals<sup>11</sup>.

The EMA grant marketing authorisation once the positive benefit-risk ratio of a drug has been robustly established in the target population. In contrast to HTA agencies where assessments based on launch data can prove challenging, the EMA applies a more flexible approach recognising both the therapeutic potential and need for ATMPs, utilising expedited processes such as conditional marketing authorisation<sup>ii</sup> and/or accelerated assessment through PRIME<sup>iii</sup> designation<sup>12</sup>. In 2020 alone the EMA granted PRIME eligibility to 9 ATMPs across several therapeutic areas<sup>13</sup>, with recommendations given to products offering major therapeutic benefits and addressing a significant unmet need. The difference in evidence requirements between regulatory and HTA agencies may in part be explained by the fact that EMA marketing authorisation is based on the benefit-risk ratio and level of unmet medical need, whereas HTA agencies are tasked with assessing comparative efficacy, budget impact, and/or the cost-effectiveness of a therapy. ATMP manufacturers can ultimately face lengthy, complex assessments and negotiations with HTA agencies and payers that are unique to each country. This fragmentation results in resource intensive negotiations for both industry and healthcare systems that can prolong time to patient access and often conclude with demands for further evidence collection<sup>14</sup>.

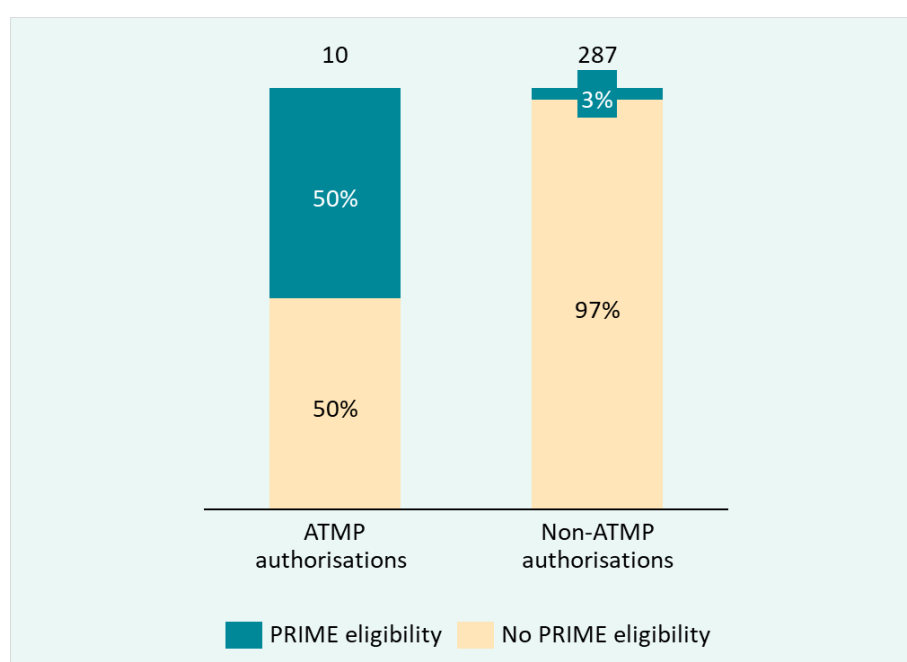


Figure 3: Products approved by EMA with PRIME designation 2016 – May 2021<sup>8</sup>

<sup>ii</sup> Conditional marketing authorisation is a pragmatic tool used by the European Medicines Agency (EMA) for the fast-track approval of a medicine that fulfils an unmet medical need.

<sup>iii</sup> PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. Through PRIME, the EMA offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications.





...demonstrating cost-effectiveness can be challenging...

Cost-effectiveness analyses are a key element of the value assessment process in several Member States. ATMPs to date have targeted rare and severe diseases; both smaller patient populations as well as greater complexity of manufacturing mean achieving cost-effective status at a commercially viable price can be particularly challenging. In the case of orphan/ultra-orphan medicines, it has been highlighted that cost-effectiveness thresholds may need to be higher in order to allow prices that provide a return on investment that is comparable with non-orphan medicines<sup>15</sup>. Rarity and/or disease severity are two variables incorporated into cost-effectiveness decision-making by a few countries, including Norway, Sweden, and England. These can take the form of modifiers or separate pathways in order to facilitate a higher willingness-to-pay for such conditions. However, these practices are not uniformly considered by all countries. Further, the stringent criteria and limited capacity of pathways like the National Institute for Health and Care Excellence (NICE) Highly Specialised Technology (HST) programme can limit their use in practice<sup>16</sup>.

To capture the full value of ATMP treatments there is a need to extrapolate over long-time horizons in cost-effectiveness analyses. Incremental cost-effectiveness ratios may be deemed uncertain in some instances due to a lack of comparative data or the use of surrogate outcomes and can be compounded further by data extrapolation. This can impact price negotiations. Initial reimbursement at a lower net price, with an adaptive pricing model and commitment to re-evaluate once new evidence has been developed, has recently been proposed as a solution to challenges in demonstrating cost-effectiveness with data available at launch<sup>17</sup>.

Discount rates can have a significant impact on the value of a health gain or cost incurred in economic evaluations<sup>18</sup> and have a disproportionate effect on ATMPs with higher upfront costs, yet long-term benefits<sup>19</sup>. Approaches to discounting vary in Europe. Rates of 3-5% are the most commonly used<sup>20</sup>, however different rates and a variable use of differential discounting between costs and benefits exist at country level<sup>20v</sup>. The impact of different discounting rates is generally explored through sensitivity analyses, and some HTA agencies offer a measure of flexibility in its application. For example, in England, lower discounting is considered for treatments deemed likely to have a significant impact on patient health over a long period of time. However, the application of this flexibility has been limited in practice<sup>16</sup>, and the differential effect on transformative medicines vs. chronic treatments has not yet been addressed.



...and the holistic value of ATMPs is not consistently recognised.

Existing value frameworks used in European HTA tend to focus on the impact of a treatment on survival, morbidity, quality of life and healthcare cost savings to determine the value of an innovation. However, the outcomes associated with a one-time treatment offering curative potential can yield significant additional value for patients, families, and healthcare systems. Other value components may include patient and caregiver productivity gains, reductions in treatment administration burden and improved adherence, the value of hope provided by a cure, reduced healthcare utilisation due to

<sup>iv</sup>3 – 5% is also a much higher interest rate than observed on average EU government debt over the last 10 years.

long-term disease remission and increased health system resilience by reallocation of savings gained to elsewhere in the health system. These value elements are not widely recognised during HTA, despite the magnitude and extent of benefit that can be provided by ATMPs due to their curative potential. Some countries include a wider perspective when considering the value of an innovation. For example, in New Zealand, the Pharmaceutical Management Agency considers the savings, suitability and health benefits of an innovation on the patient's family, wider society and/or health system. However, in Europe, there is still a lack of consistent recognition of holistic value.

## EFPIA recommendations: Promoting patient access to ATMPs while supporting payer decision-making

Value assessment frameworks need to evolve in order to promote a positive environment for ATMP innovation and timely patient access in Europe, while also ensuring uncertainty is addressed using appropriate mechanisms. To achieve this goal, EFPIA recommends the following:



### Utilise outcomes-based innovative payment models for ATMPs

Outcomes-based payment models provide a useful method of sharing risk between the manufacturer and payer in the presence of uncertainty, giving confidence to payers that the cost of treatment is aligned with anticipated benefits which may facilitate greater patient access. The use of outcomes-based models is growing, and several such agreements have been reached for cell and gene therapies in countries including Spain, Italy, and Germany<sup>21</sup>.

EFPIA believes that outcomes-based payment models should not be used as a substitute for robust, appropriate ATMP HTA or considered the default when negotiating reimbursement. However, EFPIA does advocate for the use of these models as a means towards securing timely patient access while balancing healthcare system sustainability and maintaining incentives for innovation. This echoes proposals by several other organisations, including ARM<sup>v</sup> and EUCOPE<sup>vi</sup>, who call for application of outcomes-based schemes to increase payer confidence and enable patient access<sup>5, 6, 7</sup>. To guarantee these schemes are fit for purpose, clear alignment must be achieved upfront on the uncertainty driving the need for their implementation and the metrics that will be measured. Flexibility should be applied to ensure the metrics that will be measured are appropriate within the context of the disease area, innovation, and uncertainty to be addressed. Early multistakeholder dialogue and collaboration should take place to guarantee this is achieved. Further, industry is willing to work with payers to ensure the necessary infrastructure (see below), capacity and healthcare professional engagement is present to overcome existing obstacles in data gathering and analysis and enable high-quality data collection.

<sup>v</sup> The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organisation that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide.

<sup>vi</sup> The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) is a trade body for small to medium-sized innovative companies working in the field of pharmaceuticals and medical technologies.



## Harmonise evidence requirements across regulators and HTA agencies

To ensure wider and timely patient access, EFPIA calls for more harmonisation in evidence requirements across the EMA and HTA agencies. The importance of alignment between regulatory and HTA assessments, as well as across HTA bodies in Europe, has been recognised by other initiatives including RARE IMPACT<sup>vii</sup> and RESTORE<sup>viii,22,23</sup>. The new Work Plan published by the EMA Committee for Advanced Therapies (CAT) has identified guidelines on quality and requirements for ATMP clinical trial applications, and the use of Real-World Evidence (RWE) in regulatory decision-making, as key activities for 2021<sup>24</sup>. However, more coordination is needed to align value assessments at the Member State level. To facilitate improved ATMP access for patients, greater acceptance of ITCs, surrogate endpoints and RWE in decision-making is required. Unified guidance on these topics would help to streamline early advice processes, while consensus between the EMA and HTA agencies on what constitutes relevant, acceptable evidence within the context of a given disease or therapy setting would act to increase consistency and predictability during appraisals. To achieve this, industry is willing to work with regulators and HTA agencies to facilitate alignment with regards to evidence requirements. We believe that the positive, flexible approach to ATMP innovation and access demonstrated thus far by the EMA should remain central to any harmonisation process.

One of the most effective tools to promote dialogue between manufacturers and regulators/HTA bodies has been the EMA-EU<sup>net</sup>HTA Parallel Consultation process. With EU<sup>net</sup>HTA coming to an end in 2021, EFPIA strongly advocates for sufficient capacity to be put in place both at regulator and HTA level to ensure companies can request and receive high quality advice, including for the EU joint clinical assessment to be established by the EU HTA regulation. In line with the regulation, we support a state-of-the-art system of EU joint clinical assessment and scientific consultations, so long as unnecessary duplication between EU and national assessments is avoided. For ATMPs, this is all the more important as they will fall in scope immediately, together with oncology products. For this system to be a success, meaningful participation and contributions from manufacturers must be ensured. Until such a time that optimal procedures for this framework can be implemented, we welcome HTA initiatives that minimise duplicative processes and inconsistent patient access across Member States.

HTA methodologies and processes should be responsive to the evolving innovation landscape and regulation paradigms, with an integrated approach to evidence development building on a constructive EMA/HTA interface. To facilitate these changes to the HTA landscape in Europe, there should be effective EU-level engagement with stakeholders including regulators, patients, medical associations, and academia.

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<sup>vii</sup> RARE IMPACT is a collaboration chaired by EURORDIS and involves a consortium of manufacturers of gene and cell therapies and umbrella organisations such as EFPIA and EUCOPE focused on enabling and improving patients' access to ATMPs.

<sup>viii</sup> RESTORE is a large-scale research initiative focused on making the promise of advanced therapies a reality for the benefit of patients and society.



## Ensure an inclusive, multi-stakeholder approach to ATMP value assessments

EFPIA advocates for a robust, inclusive approach to stakeholder engagement in ATMP HTA in order to capture the full value of treatment and mitigate uncertainty. The involvement of patients and healthcare professionals is crucial to ensuring their unique perspective is considered throughout the HTA process. Where additional evidence generation is required, HTA agencies and manufacturers should work with patient organisations to relay the importance of follow-up in understanding treatment benefit and securing access. As ATMPs are specialised technologies, it is important to also engage clinical specialists with ATMP expertise, as well as Centres of Excellence who are key stakeholders in their delivery. Collaboration between HTA agencies, patient organisations and clinical experts to identify best practices for successful stakeholder involvement is therefore required. To ensure key stakeholders can actively engage and meaningfully contribute to the HTA process, sufficient training should be provided, as noted in the Quality Standards for Patient Involvement in HTA by the HTAi Interest Group for Patient and Citizen Involvement<sup>ix,25</sup>.



## Consider holistic ATMP value in HTA appraisals

EFPIA believes that value assessment frameworks should recognise the holistic lifetime benefits of ATMPs. Curative therapies return patients to a disease-free state, allowing them to pursue or resume educational/professional commitments and contribute to national economies. In turn, this can provide value to caregivers, improving their quality of life and productivity. Improving the long-term health of patients can also minimise healthcare resource utilisation and improve system resilience, particularly where ATMPs might target more prevalent conditions such as cardiovascular disease or diabetes. This is a focus of the new Pharmaceutical Strategy in Europe and an area of particular importance following the COVID-19 pandemic<sup>1</sup>.

ATMPs offer the potential to eradicate the treatment burden of chronic conditions which can positively impact patient quality of life and alleviate adherence issues. The value of a one-off administration and patient preference for less burdensome treatments is not typically recognised in value assessment frameworks. Further than providing better convenience over a current standard of care, ATMPs go beyond moving to a simpler dosing regimen by eliminating the need for chronic treatment. This should be taken into consideration through patient questionnaires and physician testimony, considering many established quality-of-life instruments do not have the specificity or sensitivity to capture benefits stemming from reductions in treatment burden. Beyond patient benefit, the cost of non-adherence to chronic therapy could be taken into account when evaluating ATMP cost savings versus the comparator. One-off administrations may help to reduce the significant costs associated with non-adherence, estimated at €1.25bn annually in the European Union<sup>26</sup>

To support payer decision-making, manufacturers and HTA agencies should work together to ensure quality evidence is collected in a robust and standardised manner. A first step in this process would be to bring together stakeholders including patient organisations, healthcare professionals, industry,

<sup>ix</sup> HTAi Interest Group for Patient and Citizen Involvement in HTA is an interest group comprised of patients and citizens, clinicians, HTA agencies, industry, and other stakeholders with a focus on patient and citizen involvement in HTA.

HTA bodies and Health Economics and Outcomes Research (HEOR) experts to understand barriers and solutions to incorporating other value elements into HTA.

One approach to capturing holistic benefits in HTA is the use of multicriteria decision analysis (MCDA) frameworks. MCDA frameworks provide a methodological process to capture wider elements of value for a more inclusive, value-based assessment<sup>27</sup>. However, the application of an MCDA framework requires robust methodology and establishment of practical processes. To expedite this, further research should build on the existing frameworks such as EVIDEM<sup>x</sup> and the proposals of ORPH-VAL<sup>xi,28,29</sup>.



### Adapt the cost-effectiveness frameworks used to assess ATMPs

In the absence of ATMP-specific pathways or cost-effectiveness threshold modifiers, industry welcomes the use of mechanisms that allow for greater flexibility to be built into cost-effectiveness frameworks. Disease severity/rarity modifiers are employed in England and Sweden through the NICE end-of-life criteria and TLV solidarity principle, respectively. EFPIA encourages the wider application of similar methods in Member States that employ a cost-effectiveness assessment. However, EFPIA notes that specialised pathways such as the HST programme can have restrictive eligibility criteria and suffer from capacity constraints<sup>16</sup>. A more integrated approach may therefore be preferable to meet the demands of the ATMP pipeline, as well as account for ATMPs targeting more prevalent conditions. Where pathways are utilised, they must be adequately resourced to allow for the required numbers of appraisals.

A revised method of discounting needs to be considered to ensure ATMPs are not disproportionately affected compared to non-ATMP treatments that often form comparators. To this end, EFPIA welcomes the recent commencement of the NICE methods review<sup>30</sup>, and the acknowledgment that reform may be needed to ensure effective assessment of ATMP cost-effectiveness. This includes the consideration of lower discounting<sup>xii</sup>, as well as further guidance on data extrapolation and the replacement of the current end-of-life modifier with a more holistic disease severity modifier. Industry is willing to work with HEOR experts and HTA agencies to identify areas of methodological reform that are needed to guarantee fair and robust assessments of ATMP cost-effectiveness. To monitor and review the impact of these reforms, multi-stakeholder groups could be established to assess whether the new methodological frameworks are and continue to be fit-for-purpose.

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<sup>x</sup> EVIDEM is a multicriteria decision analysis framework that promotes transparent and efficient decision-making through systematic assessment and dissemination of the evidence and values on which decisions are based.

<sup>xi</sup> ORPH-VAL is a working group of European rare disease experts including patient representatives, academics, politicians, regulators, payers, and industry, focused on improving patient access to orphan medicines through the formation of common principles to underpin P&R processes in Europe.

<sup>xii</sup> In their ongoing methods review, NICE are considering lowering the reference-case discount rate for both costs and health effects in line with the UK Treasury recommended discount rate of 1.5%.



## Efficient collection of high-quality ATMP RWE

RWE can be a powerful tool, providing new insights into patient benefits in a context different to that of a clinical trial. It can support evidence development plans at the point of early dialogue and inform assessments of efficacy, budget impact and cost-effectiveness for initial reimbursement and reassessment decisions. RWE is also essential to the success of outcomes-based agreements. Evidence generation should be targeted and objectives for data collection should be clearly stipulated and understood by all stakeholders. Early scientific advice should be sought to ensure RWE generation plans both pre- and post-launch will address outstanding data gaps. Data should be collected at a European rather than national level, when possible, particularly for ATMPs targeting rare conditions with small patient populations. However, any country-specific context regarding the administration of treatment e.g., patient eligibility and treatment patterns, should be made transparent to ensure any heterogeneity in the sample is understood<sup>31</sup>. EFPIA welcomes the DARWIN EU<sup>xiii</sup> project run by the EMA which will strengthen EU-wide real-world data and evidence to support regulatory, HTA and healthcare professional decisions<sup>32</sup>.

While digitised health is allowing for the promise of RWE to become a reality, variability in data collection between countries and limited infrastructure can pose challenges to high quality, consistent evidence generation. Significant administrative burden and inconsistent data reporting can also raise barriers. EFPIA therefore calls for further investment to improve and maintain digital and human infrastructure for RWE collection, where funding could be shared between healthcare systems and the companies involved. We recommend a clear protocol for data collection is established according to accepted scientific standards. Standardised electronic health records could help to improve the quality of the evidence collected, and an independent process or third party could be used to assess evidence quality following collection<sup>31</sup>. Industry is willing to work with stakeholders to ensure alignment between HTA agencies and regulators on the appropriate standards for developing and using RWE in decision-making. This is aligned with the recent recommendations made by the RWE4DECISIONS<sup>xiv</sup> initiative, which calls for greater alignment between HTA agencies and prevention of duplicative evidence generation<sup>33</sup>. Best practice guidelines between agencies and regulators will help to drive efficiencies in the collection process. Countries leading in the collection of RWE, such as Italy, Spain, and Sweden, may provide a starting point for development of EU level best practice methods.



## Selective application of value-based iterative assessments to address outstanding HTA questions

Iterative health technology assessments may help to address questions surrounding data available at launch and provide HTA agencies with more flexibility in decision-making when dealing with clinical and economic uncertainty. There has been a recent movement towards this approach in some

<sup>xiii</sup>The EMA Data Analysis Real World Interrogation Network (DARWIN) EU aims to deliver a sustainable platform to access and analyse healthcare data from across the EU.

<sup>xiv</sup> RWE4DECISIONS is a multi-stakeholder initiative commissioned by the Belgian National Institute of Health and Disability Insurance and comprising of multiple stakeholders including policy makers, HTA bodies, payers, regulatory agencies, clinicians, patient groups and industry.

countries, for example, the Transparency Committee in France has committed to re-evaluating new CAR-T data on an annual basis, while most ATMPs approved in Germany have a time-limited resolution set by the G-BA<sup>34xv</sup>. Iterative methods impose a time burden on both manufacturers and HTA agencies and therefore should only be utilised in instances of high clinical and economic uncertainty. For example, adaptive pathways at the regulatory level have been proposed as a basis to determine the need for application of iterative pathways in HTA<sup>35</sup>. ATMP reassessments should be carried out at an appropriate time, dependent on the nature of the innovation and the specific uncertainty to be addressed, to allow for meaningful discussions based on important new data. Alignment on these parameters should be discussed upfront. Decision-making should be based on the best quality data available at time of re-assessment. Further, for iterative pathways to be truly value-based, EFPIA believes pricing negotiations should allow for a price to increase or decrease, dependent on the latest value proposition of the innovation. This is in alignment with a recently proposed adaptive pricing model linked to new evidence in Sweden, to ensure price reflects the data available over time<sup>17</sup>.

## ATMPs are associated with higher upfront costs to healthcare systems...



...leading to sustainability concerns at both the individual ATMP level and at the aggregate level...

ATMP development has seen a period of exponential investment and growth in recent years (figure 4). In 2021, a promising pipeline includes almost 400 ongoing clinical trials with European sites<sup>13</sup>. NICE in the UK expects to consider approximately 30 ATMPs by 2023, while in the US, the Food & Drug Administration (FDA) predicts approval of 10 to 20 per year by 2025. Although only a percentage of the pipeline may achieve marketing authorisation and reimbursement, this is an area of the biopharmaceutical sector experiencing significant growth. The upfront cost associated with these therapies alongside the growing number in development, as well as the economic fallout of the COVID-19 pandemic, has led to concerns regarding the affordability of advanced therapies and healthcare expenditure in general. Medicine affordability concerns are echoed by the European Commission, in parallel to their recognition of the potential of ATMPs and the need for a sustainable business model for one-time treatments<sup>1</sup>. The delivery of affordable treatments to ensure health system financial and fiscal sustainability is one of the key initiatives of the EU Pharmaceutical Strategy<sup>1</sup>.

<sup>xv</sup> The Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany.



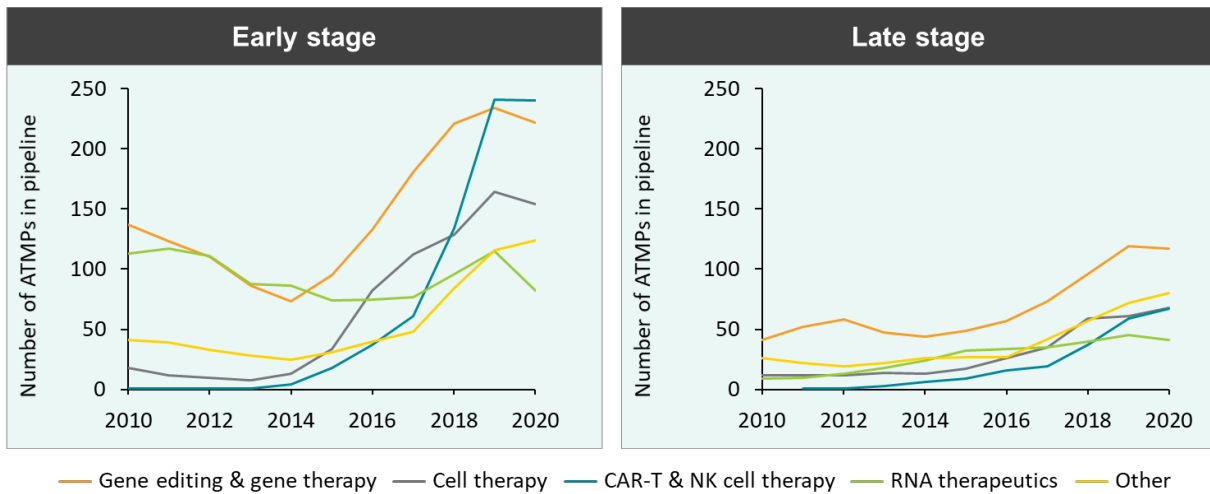


Figure 4: ATMP early- and late-stage pipeline by mechanism<sup>8</sup>

Questions about the prices and affordability of ATMPs can be viewed at the discrete and aggregate level:

- I. Prices of individual ATMPs, i.e., ‘sticker shock’
- II. Aggregate affordability of ATMPs as a class

Nonetheless, it is important to recognise that significant interdependencies exist between these issues (figure 5). Willingness to pay for an individual ATMP is governed by the belief a price is reflective of value, but also the ability to pay for the innovation within budget constraints. Further, the prices of ATMPs often highlighted in the media can drive concerns regarding overall sustainability of a health system’s expenditure. Although it is not possible to differentiate entirely between the price of the individual medicine and aggregate affordability, it is important to explore the root cause of stakeholder concerns and ensure they are addressed, while maintaining a sustainable model for biopharmaceutical innovation and access for patients.

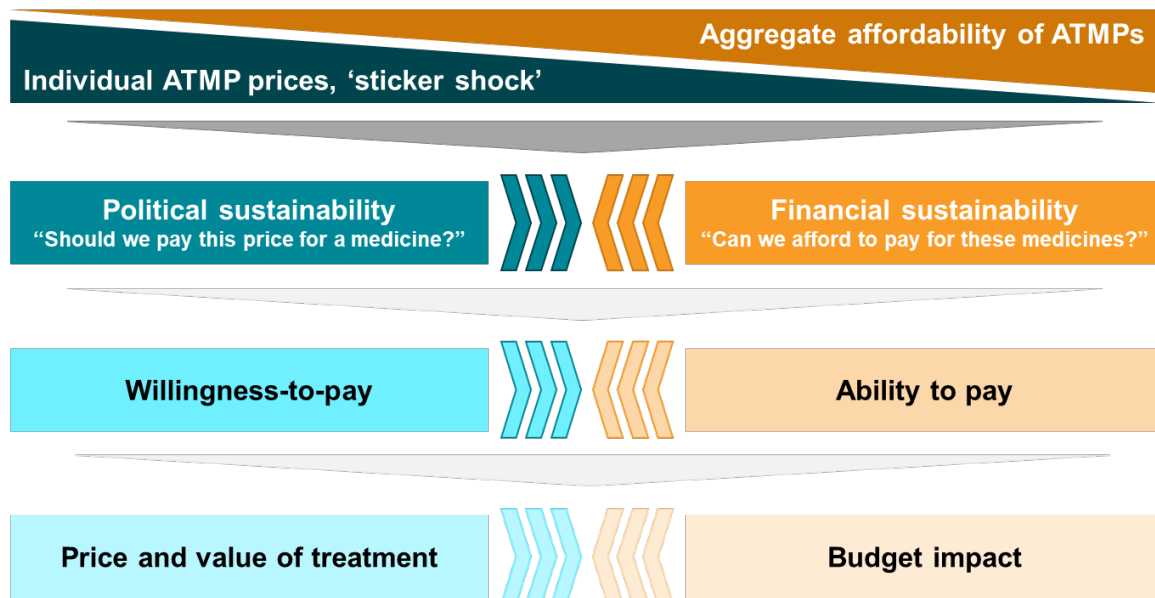


Figure 5: Illustration of interdependencies between individual ATMP prices and aggregate affordability



### ***Individual ATMP prices***

At launch, the payment for single-administration ATMPs is condensed into a single figure and drives concerns regarding the individual price of ATMPs. However, the price of a single treatment in isolation cannot be considered a risk to the financial sustainability of healthcare systems. The issue posed by 'sticker shock' of individual ATMP prices is therefore one of political sustainability, with governments in some instances required to justify their willingness-to-pay over one million Euro on a one-off treatment for a single patient. Media headlines coining Zolgensma "the world's most expensive drug" are reflective of the intense public attention and political pressure surrounding the price of ATMPs<sup>36</sup>. Therefore, while the individual prices of ATMPs contribute to an aggregate picture, concerns also exist as to whether these treatments can be considered value-for-money in isolation of their budget impact.

During price negotiations ATMPs are formally or informally benchmarked to a current SoC that could include other innovative medicines, poor-performing treatment options or best supportive care. When comparisons are made between the price of ATMPs vs. non-ATMPs, it is important that the overall cost of chronic treatment is considered. Pricing plays a vital role in ensuring the economic viability of drug development and in turn, continued sustainable innovation, particularly for treatments such as ATMPs that target small populations. This innovation leads to improvement in health outcomes. Pricing concerns can drive complex and protracted discussions; however, it is important that these are based on value and focused on achieving access for patients.

### ***Aggregate affordability of ATMPs***

The broader issue of financial sustainability is driven by whether budget-holders believe they have the ability to cover the cost of medicines in both the short- and long-term as new treatments come to market. Despite existing concerns over healthcare expenditure, recent studies suggest that European payers have proven capable of managing aggregate spend on pharmaceuticals through commercial agreements and effective competition in the off patent market<sup>37,38</sup>. Nevertheless, the sustainability of aggregate expenditure, of which ATMPs are one element, is an important topic. To make informed decisions regarding the affordable reimbursement of ATMPs, assessments must be able to accommodate for their unique characteristics. However, at present, these systems are not always appropriately configured to reflect the nature of single administration curative therapies.

To determine ability to pay for a new medicine, payers will often consider the impact a therapy will have on the overall pharmaceutical or healthcare budget. Time horizons typically cover the first 1-3 years post-ATMP launch, despite payer recognition that lifetime horizons are more appropriate to capture the long-term benefits and savings offered. With high upfront costs and the largest treatable population present in the first few years post launch, costs are significantly greater in the short- vs. long-term. Further, the scope of budget impact analyses may not account for the reduction in healthcare resource utilisation or savings beyond the pharmaceutical, or even healthcare budget. Thus, current budget impact analyses may be ineffectual in providing a clear picture as to the true long-term affordability of ATMP reimbursement.

Budgets allocated for pharmaceutical expenditure can be disconnected from the wider healthcare budget, further hindering holistic reimbursement decision-making for ATMPs. Pharmaceutical budget silos may produce inefficiencies across the entire healthcare system. For example, budgetary decisions made at pharmaceutical level, rather than therapeutic or patient level, hinder the allocation of resources to fund services that offer the highest value within a given disease area<sup>39</sup>. Further, the existence of budget silos means savings gained in primary or tertiary healthcare services because of an ATMP cannot be easily recognised or reallocated to fund future advanced therapies, or innovations

in general. The aggregate cost of ATMPs may therefore be placed entirely on the pharmaceutical budget. Despite promises of efficiency gains and wider healthcare savings, these will not be reflected in budgets to support continued affordability of ATMPs.



...while multiple barriers exist to innovative payment models that could facilitate access.

Innovative payment models, including outcomes-based schemes, such as those agreed for CAR-Ts Kymriah and Yescarta<sup>21</sup>, are becoming more widely accepted in recent years. These payment models can help to share the risk of evidential uncertainty between payers and manufacturers while helping to spread the upfront cost of ATMPs, alleviating the financial pressure of reimbursement. Despite their advantages, there is still a limited capacity to negotiate such schemes in some countries, with simple discounts or price-volume agreements preferred.

EFPIA has previously identified three main barriers to engaging in innovative payment models that, if addressed, would help to mitigate challenges of uncertainty and affordability<sup>40</sup>:

- I. Legislative barriers
- II. Infrastructure barriers
- III. Need for system change

Legislative barriers include legal and regulatory frameworks that have not been updated to accommodate dynamic innovative agreements between payers and industry. Financial systems are built around annual or short-term budgets with limited vision, which are driven by the European Accounting Rules (ESA)<sup>41</sup>. National legislation can also pose issues; for example, in Germany, sick fund accounting is conducted on an annual basis, while legislation in Sweden prevents governments from passing on financial obligations to succeeding political parties<sup>42</sup>. In France, costs must be booked in the year of treatment even if payment is spread over multiple years, however, French legislation may change in the future presenting the opportunity for ATMP split payments<sup>43,44</sup>.

Sufficient digital and human infrastructure is critical to supporting agreements and collecting high-quality data. A lack of patient registries, electronic patient records, payer databases and human capacity can prevent effective implementation of innovative payment models. However even when sufficient infrastructure exists, a paucity of defined governance frameworks on data sharing, privacy laws such as GDPR, quality standards and processes for undertaking data analysis or interpretation can present obstacles.

In addition to legal and infrastructural constraints, payers and industry today find themselves at the beginning of a learning process around a novel approach to reimbursement. Current systems do not easily accommodate innovative payment models and without a change in approach or willingness to experiment, barriers to innovative payment models will remain. Stakeholders are often sceptical of the mutual benefit provided by agreements to healthcare systems and manufacturers. In the absence of long-term evidence on their benefits there can be a reluctance to engage, particularly when best practices and optimal approaches are still uncertain.

## EFPIA recommendations: Ensuring sustainable ATMP access for healthcare systems and patients

Approaches to pricing and reimbursement decision-making need to evolve to alleviate financial pressure on healthcare systems and give confidence to payers that the treatments they reimburse represent value for money, while promoting sustainable investment and innovation for ATMPs, and timely access for patients. In order to achieve this goal, EFPIA recommends the following:



### Increase use of payment models that distribute costs over time

Building on our previous recommendation to utilise innovative payment models with an outcomes-based element, EFPIA calls for increased use of payment models that allow for the cost of an ATMP to be distributed over time to address specific affordability concerns linked to the upfront cost of an ATMP. Annuity payments are one example that focus on the timing of payments rather than clinical outcomes to distribute the financial burden of innovative therapies. Spreading the cost over time reduces the initial budget impact of treating all prevalent patients in the first-year post-launch, while still ensuring access to an ATMP for all who could benefit. Financial based payment models can be used in isolation or paired with an outcomes-based component, which may provide more certainty to payers that benefits are aligned with their willingness-to-pay and a value-based price.

Industry acknowledges that legislative and accounting barriers currently exist to payment models spanning multiple years in some countries and are willing to work with payers and policy makers to find appropriate solutions, while still adhering to accounting laws. To this end, EFPIA welcomes the measures included in Article 15 of the new Accord Cadre in France, which present the possibility for ATMP split payments, subject to change in the necessary legal frameworks. Innovative payment models that have been established for CAR-Ts Yescarta and Kymriah<sup>21</sup> are indicative that legislative and accounting challenges can be addressed. These successful agreements may provide a template for industry, payers and policy makers working to overcome these issues.



### Maintain a collaborative environment for developing innovative payment models through co-creation and shared learnings

To facilitate increased use of effective innovative payment models, EFPIA calls for a robust method of shared stakeholder learnings and best practices, leveraging case studies of successful engagements and the specific uncertainties addressed. Meetings could be held among payers, policy makers and industry to discuss insights from recently agreed innovative payment models and identify necessary areas for change and policy reform. EFPIA notes that any shared learnings process should respect the necessary confidentiality and commercial sensitivity of these arrangements. It is also acknowledged that the needs of one situation may differ from another, however, greater cooperation and alignment is needed to facilitate agreements.

These recommendations are aligned with the proposals of other initiatives. RESTORE have suggested that a series of workshops could take place with European payers, umbrella patient organisations and

industry stakeholders to share experiences and identify priority areas for implementing change to enable innovative payment models<sup>23</sup>. In parallel, RARE IMPACT and the European Alliance for Transformative Therapies<sup>xvi</sup> call for the dissemination of best practices on innovative payment models that can support national governments, through leveraging the structure of past agreements<sup>22,45</sup>.

EFPIA acknowledges the important role industry must play in developing mutually acceptable and effective payment models that serve the patient, healthcare system and manufacturer. We therefore support increased co-creation and collaboration between payers, regulators, and industry to develop innovative agreements that ensure all stakeholder perspectives are considered. Co-creation could begin at the point of early dialogue, to identify uncertainties and potential innovative payment schemes, including any infrastructural requirements to address them. The ongoing NICE methods and processes review suggests the use of technical engagement prior to the first appraisal meeting for technologies requiring additional support, to discuss evidence gaps and potential resolutions<sup>30</sup>. This provides an example of collaboration between payer and manufacturer that not only supports co-creation of innovative payment models but may also reduce time to patient access.



### Enhance horizon scanning

Healthcare service and budget planning requires a thorough understanding of the pipeline to assess funding requirements at the national and local level and identify support services and infrastructural needs. We advocate for robust horizon scanning at the national and supra-national level, in line with our public policy principles, to appropriately inform upcoming ATMP launches and ensure associated funding and healthcare service preparations are made. All relevant stakeholders including industry, HTA agencies, patients, and healthcare professionals should be involved in holistic discussions on how access to these treatments can be facilitated. Horizon scanning is particularly pertinent for ATMPs given their higher up-front costs and potential needs for infrastructure reconfiguration, to support both effective service delivery to patients and potential implementation of innovative payment models. Beyond funding and infrastructure planning, horizon scanning can support HTA agencies and manufacturers in identifying ATMPs likely to face challenges during the appraisal process and plan for contingencies. Industry acknowledges the important role it has to play in supporting horizon scanning processes and is willing to collaborate and proactively contribute to support HTA agency and health service planning, to promote institutional readiness and ultimately prevent delays in access and uptake. A recent OECD report noted that the Netherlands, Norway, and Sweden have robust horizon scanning frameworks<sup>46</sup>. The practices of well-functioning systems should be shared to support the enhancement of other Member States' processes.



### Implement adaptive budget impact analyses

EFPIA calls for the adaption of budget impact analyses to capture a holistic view of both ATMP costs and savings over the patient lifetime. Budget impact analyses should consider costs and savings beyond the pharmaceutical or healthcare budget, to include the long-term societal cost offsets of curative treatments. Reconfiguration of pharmaceutical budget silos, as discussed in the subsequent

<sup>xvi</sup> The European Alliance for Transformative Therapies is an informal interest group with a focus on fostering effective dialogue around gene and cell therapies and provide evidence-based policy recommendations.

recommendation, would allow for budget impact analyses to consider a wider scope of costs and savings. Further, time horizons that go beyond 3-5 years, considering lifetime costs, benefits and savings associated with ATMPs are needed to reflect the nature of single administration curative treatments. Where innovative payment models have been agreed, inclusion of the anticipated savings from these schemes in budget impact calculations is warranted and provides a more accurate indication of the budget impact of an ATMP. RARE IMPACT has similarly called for greater sophistication in ATMP budget impact analyses such as longer time horizons, assessment of societal budget impact and consideration of risk-sharing schemes<sup>5</sup>. Application of differentiated budget impact thresholds for ATMPs at launch would also allow for flexibility in budget impact analyses to account for the initial spike in cost post-ATMP launch, followed by a substantial drop over time once all prevalent patients have been treated. The provision by Italy's AIFA of a payback exemption to drugs classed as 'innovative' is an example of an adaptive budget impact threshold dependent on innovation level<sup>47</sup>. Methodological improvements to budget impact analyses could be regularly reviewed by multi-stakeholder user groups to ensure adaptations are appropriately capturing a holistic view of ATMP costs and savings.



### Reconfigure budget silos

EFPIA supports the reconfiguration of budget silos to ensure funding allocated to pharmaceuticals incorporates the savings made in the wider health and social care system as a result of using an innovative therapy, such as an ATMP. It is more efficient for budgetary decisions to be made in the context of the patient care pathway, rather than within a pharmaceutical silo. Reconfiguration of budget silos to follow the patient pathway, for example, increases patient-centricity and flexibility in fund allocation for therapies that offer greatest value, while allowing for a reduction in funds for less effective services. Savings gained as a result of ATMP use through reduction of costs related to chronic disease treatment and management, as well as healthcare resource utilisation due to long-term disease remission could subsequently be reallocated to finance future transformative therapies, facilitating affordability of these high cost, but high value medicines. Although theoretically this approach to fund allocation is favourable, EFPIA acknowledges the challenges in practice, with limited real-world examples of successful budget silo reconfiguration available to reflect upon. EFPIA is willing to work with stakeholders to identify ways to co-create an integrated budget system and promote efficient healthcare funding allocation and expenditure for advanced therapies.

## EFPIA commitment to ATMP access in Europe

ATMPs represent a huge breakthrough in medical science for healthcare stakeholders and have potentially life changing, long-term benefits to patients. With the field and R&D pipeline rapidly evolving, now is the time to ensure Europe fosters a positive yet sustainable environment for ATMP innovation and patient access. As the voice of the research-based pharmaceutical industry in Europe, EFPIA is ready to collaborate with key stakeholders at the European, multi-national and national level to achieve a future where ATMPs are widely available to the patients who need them.

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