WHITE PAPER

In an Already Challenging Cell and Gene Therapy (CGT) Market Access Environment, are You Ready for New European HTA Regulations?

Five actions to consider as you plan for an EU CGT submission

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Advanced therapy medicinal products (ATMPs), including cell and gene therapies (CGTs), have the potential for transformational health gains beyond our traditional pharmacological armamentarium, but the challenges of developing the optimal evidence package and payer value proposition are significant.[1]

Developers of CGT therapies must navigate complex issues throughout clinical development, including the most intricate clinical value chain in modern medicine, long and nonlinear patient journeys, and efficacy and safety questions requiring many years of study.

Market access assessments for these novel and often high-cost treatments also pose unique challenges. Typically, pharmaceutical reimbursement for chronic conditions is spread out over years, however, the cost of a gene therapy would usually incur a single large payment.[2] In addition, the principle value drivers of these therapies—their long-term (>5-10 years and possibly life-time) benefits and safety—are difficult to establish in traditional clinical development life cycles. CGTs are often positioned where there are no other treatment options, creating practical challenges when conducting randomized controlled trials as there may be no comparator for patients facing end-of-life care or for hereditary conditions without existing treatments. CGTs may also offer a "cure" which can mean different things to different stakeholders, and there are also often complex questions about the durability of effect and limited knowledge of effectiveness in larger patient cohorts. This blend of concentrated cost and unclear long-term outcome has led to uneven patient access globally.[3]

Adding to the uncertainty is a critical need to understand and prepare for continual changes and updates in regulations and requirements affecting development, market access, and commercialization plans for all treatments, including CGTs. Regulation (EU) 2021/2282 on health technology assessment (HTA) will be applied starting in **January 2025 with cancer treatments and ATMPs planned as the first therapeutic areas to be impacted.** With the consultation almost complete on methods key for CGT development, we will see the development of a new EU HTA and market access ecosystem emerge in the next few years. The regulation will be fully implemented in 2030.

The changes are anticipated to have far-reaching implications, including potentially a tightening of evidence requirement. As one of our clients has stated: "this could be the biggest change since the establishment of NICE [National Institute for Health and Care Excellence] in the UK in 1999."

What is HTA?

HTA seeks to improve the efficiency and equity of the healthcare system by informing priority setting and resource allocation.[4] It guides health coverage policies, including benefit coverage, quality improvement interventions and quality standards. HTA assessments overlap with traditional regulatory reviews, but they are multidisciplinary, covering several dimensions including clinical effectiveness, safety, costs and economic implications, ethical, social, cultural and legal issues, and organizational and environmental aspects. They also consider wider implications for the patient, relatives, caregivers, and the population. The assessment may require evidence not collected during clinical trials, such as aspects of costs, treatment patterns and quality of life to convey a therapy's value story.

Background on EU HTA regulation

Each of the 27 Member States of the EU perform their own clinical assessments and have experienced challenges resulting from a lack of coordination. According to the HTA Commission:[4]

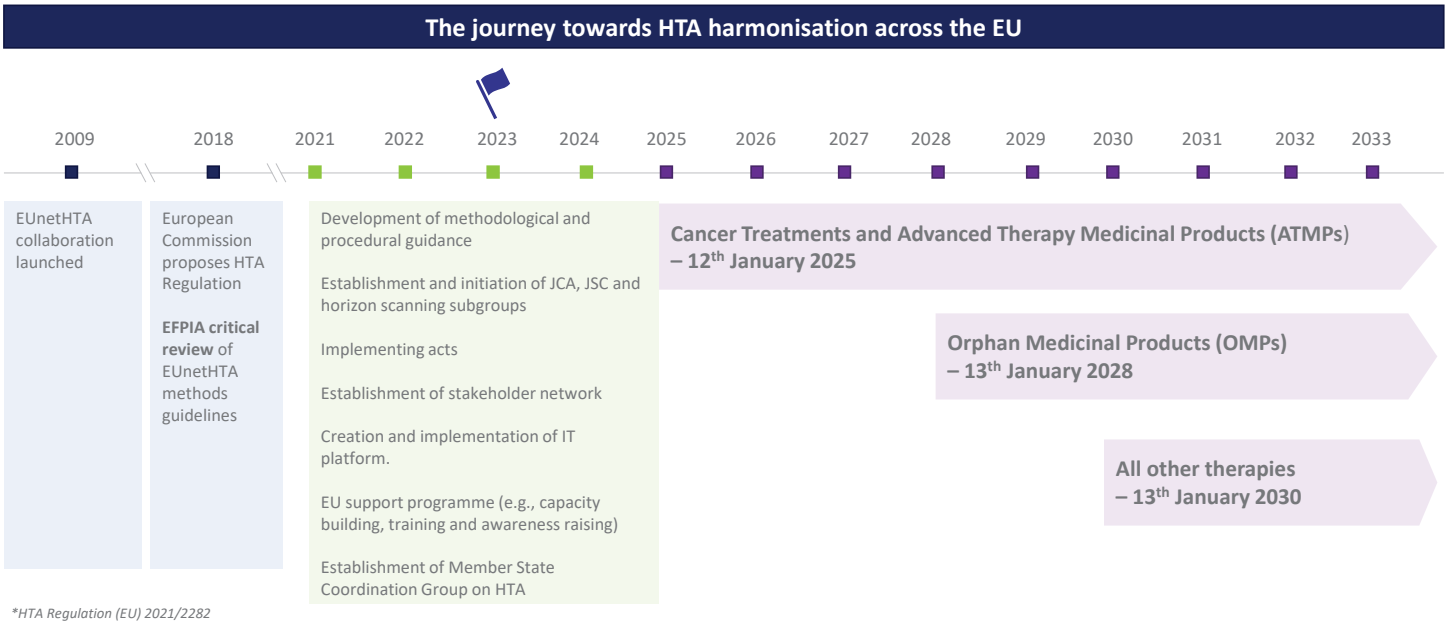
"Currently, market access for innovative technologies is impeded and distorted due to differing national or regional processes and methodologies for HTA across Europe. This situation also contributes to lack of business predictability, higher costs for industry, delays in access to technologies, and negative effects on innovation. Moreover, it can result in duplication of work for national HTA bodies, inefficient use of resources and limited transparency for patients."

In December 2021, the European Commission announced the new regulation for health technology evaluation and contracted a consortium of 13 HTA agencies (EUnetHTA21)[5] to replace Joint Actions EUnetHTA a 20-year voluntary network of national authorities. The stated aim of EUnetHTA21 is to:[5]

- Make vital and innovative health technologies more widely available to EU patients
- Ensure efficient use of resources
- Strengthen the quality of the HTA across the EU
- Save national HTA bodies and industry from duplicating efforts
- Reassure business and ensure the long-term sustainability of EU HTA cooperation

The new regulation includes four pillars[4]

1. "Horizon scanning" exercises will identify, at an early stage, promising health technologies, to help health systems prepare for them
2. Joint Scientific Consultations (JSC) advise technology developers on clinical study designs that generate appropriate evidence. This is an opportunity to receive non-binding scientific advice before the start of pivotal clinical trials (after feasibility/proof of concept study), in order to improve the robustness and appropriateness of the data
3. Member States' HTA bodies will conduct Joint Clinical Assessments (JCA) of new medicines and certain high-risk medical devices focusing on clinical aspects of HTA (i.e., the relative clinical effectiveness and relative clinical safety of a new health technology as compared with existing technologies). This is the key output of the regulation, that is, the EU HTA dossier
4. Member States may also engage in further voluntary cooperation, e.g., on health technologies other than medicines and medical devices or on economic aspects of HTA



HTA Regulation (EU) 2021/2282

Abbreviations: ATMP: Advanced Therapy Medicinal Product; EFPIA: European Federation of Pharmaceutical Industries and Associations; EUnetHTA: European Network for Health Technology Assessment; HTA: Health Technology Assessment; JCA: Joint Clinical Assessments; JSC: joint Scientific Consultants; mAb: Monoclonal antibody; OMP: Orphan Medicinal Product

IMPACT SUMMARY: What we currently know and don't know about the upcoming change

With a 2025 implementation date set for ATMPs and a call to action anticipated in 2023, CGT developers will have limited time to identify risks and develop mitigation strategies.

The full consequences of this new regulation are uncertain. With clinical added value, pricing, and reimbursement of products remaining at the country level, we do not know how stakeholders within and beyond the EU might use the JCA outputs. Will some countries adopt the JCA for every product versus those that adopt some JCAs—or even only portions of some JCAs—and ignore others? If so, country submission requirements might continue to vary greatly from country to country.

The immediate impact on technology developers will also vary

- Developers with advanced evidence generation activities may consider accelerating to launch before the change, or they might determine they have time to mitigate risks before their submission
- Developers with pivotal studies underway that now require major redesigns will need to quickly pivot
- Developers who have not yet started pivotal studies might have a window to assess the new challenges and redesign their studies
- All will need to act quickly to strategically approach the new HTA environment

Five Potential Challenges and Related Opportunities or Actions

The new regulation introduces a number of potential challenges and related opportunities and key actions that could impact your internal organization, how you engage with HTA bodies, and your development and market access planning.

CHALLENGE ONE
Limited Early Engagement

A Joint Scientific Consultation (JSC) allows technology developers to engage early and obtain input from HTA bodies in parallel with EMA scientific advice on the clinical development program, pivotal trial design, and evidence development planning in preparation for the future JCA.[6] Prospective and timely advice may allow the applicant to integrate specific HTA and regulatory needs into the development plan very early on, ideally fulfilling the evidence requirements for both regulators and HTA bodies at the same time.

However, the availability of procedures for JSC is extremely limited and, while intentions have been stated to increase capacity for advice to create more availability for JSCs, it is unclear if more slots will become available.[6]

Related Opportunity or Action

Timing is a key consideration. It is important to receive advice early enough so that the design of the pivotal trials can still be influenced, but late enough to be able to provide a solid position of the proposed approach, ideally in the form of a draft study protocol.

If a JSC spot is available, choosing to engage—or not engage—is another strategic decision. Before engaging, you might seek pre-advice from an external source with insights about other JSC projects to analyze your clinical development plan and pivotal study design against the EUnetHTA 21 guidelines[7] to identify potential issues and constraints. If scenarios emerge in which it appears you may not wish to follow anticipated advice, then seeking a JSC might not work to your advantage as there could well be a cost to seeking and then not following advice. Even though the consultation outcomes are not made public, the JCA assessors will be aware of who did/did not follow JSC advice. It is unclear what if any impact not following the advice will have on subsequent JCA outputs.

On the other hand, there are some clear advantages to seeking and following advice and aligning on EU consensus during this evolving process. Engaging early, that is, at a point when the feedback can be taken on board to influence pivotal trials designs, is critical as these decisions will have consequences—for good or for ill—that will impact an asset throughout its life cycle. A JSC, as discussed in more depth in the next section, can also be of great value in instances where more risk is anticipated if alignment can be reached on approaches, especially as it relates to scoping (see challenge two) and methods (see challenge four).

CHALLENGE TWO
Scoping

Scoping is a critical initial step in HTA process as it defines the research questions. EUnetHTA defines the role of the PICO (Population, Intervention, Comparator, Outcomes) question as the formulation of a defined research question that should be answered by the assessment.[8]

As proposed, technology developers will not be involved in the scoping exercise, and it is not yet clear what role, if any, healthcare professionals and patients will play. It appears likely that each Member State may be asked to submit PICOS that they consider relevant for their country.

"Because of different policy questions from different partners (e.g., due to differences in standard of care) or because of different research questions within the complete approved indication of a specific treatment (e.g., due to different lines of therapy), it is possible that more than one PICO is required to define the research questions to be answered in a given assessment. In this document, an individual set of PICO elements which together define a research question is called a PICO question. Thus, within a given assessment there might be the need to elaborate on one or more PICO questions."[8]

In fact, this could end up creating a great many PICOS for CGT assets which would not be practical for most technology developers to address.

Related Opportunity or Action

When designing the pivotal study, a range of potential PICOs should be assessed. This analysis is key for all assets, but it is critical when studies are required to assess long-term clinical outcomes, a typical requirement for CGT studies. A JSC may help gain advice and alignment on an approach to de-risk approaches for those cases where potential issues have been identified early, for example:

- Multiple PICO questions are anticipated from different Member States (or for other reasons)
- The analysis provided by the PICO at scoping is not anticipated to cover all evidence needs
- The data will include real-world data or indirect treatment comparisons versus a randomized controlled trial

If it is later discovered that the evidence needs at scoping were not completely covered, it is unknown how an evidence gap will be addressed in value assessment and pricing negotiations at the country level. Nevertheless, it is clear that a gap will make the negotiations more difficult. If the shortfall in evidence can be acquired in a reasonable amount of time, it may be beneficial to delay the launch or accept a lower price in exchange for the development of additional data. The developer could also consider designs where the active trial arms and placebo are added to the existing standard of care (SoC). This data can then be analyzed for different comparators and populations. However, to gain meaningful data, large multi-country studies with sophisticated statistical analyses would likely be necessary, which does not meet the goal of simplicity that the regulations are aiming for.

CHALLENGE THREE
Overlapping Assessments/Timelines Between the EMA, The JCA, and Member State HTA Bodies

The harmonized JCA dossier aims to reduce duplication of effort for both national HTA bodies and industry, thus, increasing efficiency and decreasing development costs. Nevertheless, as the organization of health services, allocation of resources and reimbursement, and pricing decisions remain the responsibility of Member States, the degree to which countries accept the JCA remains to be seen. If views do not align with the joint EU view, or if the clinical assessment doesn't provide the analysis they want, countries may choose to conduct their own assessment. They may also decide to accept parts of a JCA rather than the whole, requiring technology developers to understand why an analysis did not meet their needs and potentially provide additional clinical evidence generation.

It also remains to be seen whether the HTA regulation will put in place effective mechanisms for cooperation between the EMA and the Coordination Group to ensure relevant information is shared to avoid duplication of assessments.

EMA and HTA do take different approaches when assessing a new technology. EMA evaluates the asset alone, determining if the benefits of its use are greater than the risks and downsides clinically in the treatment of a specific condition. Generally, more risks are acceptable for severe disease versus self-limiting conditions. HTA, on the other hand, evaluates the value of a technology with questions that include: is it better than current options and how will it impact resources available for other conditions? While there is overlap, the two approaches require distinct considerations. For instance, endpoints that are acceptable for regulatory purposes may not be suitable to show an added benefit for HTA purposes.

EMA and HTA timelines are also likely to overlap, thus, leaving only a short time for the dossier submission after scoping. Significant resource use will be required for the submissions of EMA and EU HTA, especially on a rapid timeline, which may cause competing needs, threatening to overextend existing resources (e.g., biostats, medical writing, etc.). This challenge may be particularly acute for smaller CGT developers with limited resources.

Related Opportunity or Action

Early engagement is key to help make informed decisions about comparators and outcomes that help bridge the perspectives of the EMA, the JCA, and Member States. Developers can ensure their approach continues to make sense in an evolving environment by monitoring Member State views and analyzing any discrepancies in the advice provided by the JSC.

Internally, technology developers should proactively analyze their organization to avoid siloed approaches and, instead, coordinate action to limit duplications of efforts for functions including biostats, medical writing, health economics, and regulatory.

Developers may also consider creating a JCA Champion role to help bridge regional and global internal teams who may or may not be accustomed to working closely together and to bring an informed understanding of the changing JCA to facilitate its expeditious implementation in different therapeutic areas and business units.

CHALLENGE FOUR
Conservative, Inflexible Methods

As the EU HTA methods consultation results become available, a concern is growing that the proposed methods guides are too methodologically conservative and not sufficiently flexible for novel or pragmatic state-of-the-art methods. CGTs are most often positioned in disease areas without a SoC treatment (e.g., rare orphan diseases, hereditary conditions, or in oncology), creating practical challenges of conducting trials with a comparator group, widely considered to be the "gold standard" of randomized controlled trials. These studies may also face ethical challenges, for example is a randomized placebo-controlled study appropriate for a terminal condition for which no other treatment option beyond palliation is available? Often, CGT developers apply novel solutions (e.g., real-world data and historical controls) for patients facing end-of-life care or for hereditary conditions without existing treatments.

As discussed in Challenge Two, CGT assets, may also need to contend with multiple PICO question at the onset, followed by many years of follow-up studies. Patients may require follow-up for 15 years or more to study the durability of the benefit, placing burdens on patients, caregivers, investigational sites, and technology developers, and potentially delaying access to treatments to those in great need.

The impact of the new advice process on the national HTA advice procedures remains to be seen. How will the JSC handle divergent views between participants as well as Member States? To date, we've tracked that many comments calling for changes to the method guides have not been taken onboard, and so a concern is also growing that divergent points of view are not being integrated. Notably, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) have raised similar concerns:[9]

"We are firmly convinced that the input from patient organizations, healthcare professionals, industry and HTA experts and societies enriches the quality of the methodological guidance and processes that will govern the functioning of the HTA Regulation. We are concerned that comments to the various guidance documents by EUnetHTA21 remain largely ignored."

EFPIA and EUCOPE urge that the outcome should align common European methodologies and information requirements and harmonized HTA criteria versus consolidating national practices which would "undermine the goals of the Regulation."

"The approach proposed by EUnetHTA21 merely exports today's fragmentation in requirements to the European level. Also, health technology developers with their unique insights as main contributors of evidence for a joint clinical assessment should be given the opportunity to bring in their perspective during the scoping process."

Related Opportunity or Action

A lack of methodological flexibility may require larger and longer clinical trials due to stringent evidence needs. Here again, aligning on evidence needs early — either by gaining a JSC engagement or, if that is not possible or advisable, by soliciting national scientific advice from Member States — may help gain alignment that may pave the way to acceptance of novel approaches.

CHALLENGE FIVE
Delays in Patient Access

Though the new regulation's overall impact on time-to-patient access — not to mention equity or equality — is yet unknown, there may well be a potential for a delay in access as a result of the new regulation being implemented.

The impact for CGT developers will depend on the target condition. There is a clear first-to-market advantage for treatments for rare conditions with great unmet needs as there is likely to be a pool of patients waiting for treatment and then a relatively smaller incident population once the existing patients are treated.[10] As well, non-responders to the first-to-market product cannot be re-challenged by the following CGTs entrants if they use the same viral vector. Later entrants will be competing for the incident population only. In conditions of greater incidence, being the first to bring a "game changing" therapy to patients creates a powerful "halo" effect, impacting later entrants who will need to establish why treatment should change.

Even if a delay in time to patient access is observed across the EU as a result of the new regulation's implementation, in theory, some EU countries with limited resources available for HTA will gain access to high-quality assessments via the JCA to support their decision-making, potentially reducing time to access in 'second wave' markets.

Related Opportunity or Action

Early engagement, including a JSC, if available and appropriate, may be an opportunity to accelerate patient access by 1) aligning early with HTA bodies in parallel with EMA scientific advice, 2) producing a feasible number of PICOS, and 3) creating an early evidence generation plan that would, in turn, help strategically allocate internal resources to build an integrated core EU dossier so that the main analysis can be conducted in advance.

CGT developers may also consider conducting a mock run of a JCA dossier to review the level of integration of your regulatory and HTA teams to perform Integrated Scientific Advice. A dedicated internal JCA Champion role may also help anticipate and mitigate issues to avoid delays.

Other Global HTA Reform

Beyond the EU HTA reform, momentum toward harmonization and collaboration across HTA shareholders globally could potentially bring about additional changes for CGT developers. In the U.K., Innovative Licensing and Access Pathway (ILAP) is a partnership bringing together The All Wales Therapeutics and Toxicology Centre, The Medicines and Healthcare products Regulatory Agency (MHRA), National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), among others, to provide an accelerated infrastructure for certain medicinal products, including CGTs.[11]

NICE has also recently announced another partnership with HTA bodies from three continents to boost collaboration on a range of shared opportunities and challenges.[12] Partners will, for example, exchange ideas on how HTA processes could better anticipate technological and methodological challenges and explore the feasibility of recognizing or using each other's HTA information and running a pilot for a joint clinical assessment in the UK, Canada, and Australia.

Conclusion

New EU HTA regulation is poised to change the market access ecosystem in the EU. While the impact of the new regulation remains to be seen — especially in regard to whether the JCA will overtake or supplement country-specific HTA regulations and appraisals — CGT developers planning to submit to the new EU-HTA infrastructure in the early phases of its implementation are now on a short runway to plan and prepare their data for submission.

Early engagement with HTA bodies — whether this takes the form of a JSC or occurs with individual Member States — may help gain early insights to drive decisions. As well, it is important to closely track all draft guidance documents developed under EUnetHTA 21 — including comments from public consultations — to glean insights that can help shape your approach and plan.

Even if an EU submission is not in your near future, it will be important to closely track and analyze outcomes for other CGT developers as you can expect to be navigating the implications for your pipeline for many years to come.

References

1. Besley S, Henderson N., Towse A. & ColeA. (2022) Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose? OHE Consulting Report. Accessed December 28, 2022. https://www.ohe.org/publications/health-technology-assessment-gene-therapies-are-our-methods-fit-purpose#.
2. Palmer S. HTA Challenges for Cell and Gene (C&G) Therapies. Presented at: CDDF Spring Conference 2020; February 10, 2020. Accessed December 28, 2022. https://cddf.org/wp-content/uploads/2020/02/1700_Stephen-Palmer.pdf
3. Tunis S, Hanna E, Neumann PJ, et al. Variation in market access decisions for cell and gene therapies across the United States, Canada, and Europe. *Health Policy*. 2021;125(12):1550-1556. doi:10.1016/j.healthpol.2021.10.003
4. Q&A: Commission proposal on Health Technology Assessment. European Commission — European Commission. Accessed December 28, 2022. https://ec.europa.eu/commission/presscorner/detail/el/MEMO_18_487
5. Health Technology Assessment Regulation. European Commission — European Commission. Accessed December 28, 2022. https://ec.europa.eu/commission/presscorner/detail/en/ip_21_6771
6. Joint Scientific Consultations (JSC) - EUnetHTA. Published November 5, 2021. Accessed January 24, 2023. https://www.eunethta.eu/jsc/
7. Joint HTA Work. Published November 8, 2021. Accessed February 3, 2023. https://www.eunethta.eu/jointhtawork/
8. PICO FAQ - EUnetHTA. Published March 3, 2021. Accessed December 30, 2022. https://www.eunethta.eu/pico/
9. Joint Statement Pharmaceutical industry concerns over the implementation of the EU HTA Regulation. Accessed December 31, 2022. https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/joint-statement-pharmaceutical-industry-concerns-over-the-implementation-of-the-eu-hta-regulation/
10. Pharma's first-to-market advantage | McKinsey. Accessed January 1, 2023. https://www.mckinsey.com/industries/life-sciences/our-insights/pharmas-first-to-market-advantage
11. Innovative Licensing and Access Pathway. GOV.UK. Accessed January 2, 2023. https://www.gov.uk/guidance/innovative-licensing-and-access-pathway
12. NICE partners with international health technology assessment bodies to boost collaboration on shared opportunities and challenges | News | News. NICE. Accessed January 2, 2023. https://www.nice.org.uk/news/article/nice-partners-with-international-health-technology-assessment-bodies

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