EXECUTIVE INSIGHTS

EUnetHTA 21 — Transition to EU-wide HTAs: Implications for Pharma

Key Takeaways

1. Set by the EU health technology assessment (HTA) regulation 2021, joint clinical assessments (JCAs) will gradually become mandatory for health technologies registered centrally via the European Medicines Agency: products containing a new active substance, class IIb or III medical devices, and class D in vitro diagnostic devices.
2. Implementation will be gradual: JCAs will become mandatory for advanced therapeutic medicinal products and oncology products in 2025, for orphan drugs by 2028, and for all other products by 2030.
3. JCAs will provide an assessment of clinical evidence while non-clinical evidence assessments will remain the responsibility of the member states.
4. Member states will continue to make the final decision on pricing of and reimbursement for a health technology, but they are expected to include the clinical evidence of the JCA in their decision-making.
5. In the short term, navigating JCAs will be cumbersome for pharma companies, requiring them to actively dialogue with JCA stakeholders, in addition to national/regional HTA bodies; also, it is not clear how the existing provisions for conditional access with evidence development will be impacted.
6. In the longer term, harmonisation of HTA requirements across member states and greater transparency on HTA requirements are expected to accelerate time to market access for new health technologies.

Introduction

A Health Technology Assessment (HTA) aims to determine the value of a health technology in a given context, with the ultimate purpose of informing decision-making on reimbursement and pricing. In Europe, HTAs are conducted mostly at the national level: HTA approaches, including value frameworks, data requirements and timing, differ by country. The country-specific setup duplicates efforts and costs and might lead to delays and/or inequalities in patient access between countries, so in recent years, cross-country initiatives have begun to emerge to streamline decision-making (e.g. the Beneluxa initiative).

In order to improve the efficiency and quality of HTAs and increase transparency of HTA requirements, the EU HTA regulation, adopted in 2021, is seeking to create joint clinical assessments (JCAs) between member states and provide joint scientific consultations (JSCs) to applicants. JCAs will gradually become mandatory for relevant health technologies during the 2025-2030 period and will partially replace national HTAs for transferable (clinical) dimensions. JSCs will be offered to enable a dialogue between the applicant and the HTA agencies involved in the EUnetHTA network to provide early, non-binding scientific advice.

Substantial changes to the current approach to HTAs are expected from JCAs and JSCs, transitioning from the parallel interactions with national HTA bodies to a mix of EU-wide and national interactions. This *Executive Insights* outlines the key changes and implications for pharma companies.

Fifteen years of EUnetHTA work culminating in the EU HTA regulation 2021

EUnetHTA (European Network for Health Technology Assessment) was incepted after the European Commission and Council of Ministers recognised an "urgent need for establishing a sustainable European network on HTA" in 2004. Initially established with 35 partners, it grew to 82 national, regional and not-for-profit agencies from 29 EU member states and the UK.[1] The main goal of EUnetHTA is to provide a platform for HTA agencies across Europe to exchange HTA information and develop HTA methodologies in order to ultimately facilitate the harmonisation of HTA approaches across member states. In 2009, the initial EUnetHTA collaboration was organised into an operational network, and tools to harmonise HTA assessments (e.g. the HTA Core Model®) were produced. From 2010 to 2021, EUnetHTA focused on three sequential joint actions (JA1, JA2 and JA3[2]), resulting in the development of HTA principles, tools and methodological guidance, and in the creation of a permanent cross-border HTA working structure which connects national HTA agencies, research institutions and health ministries.

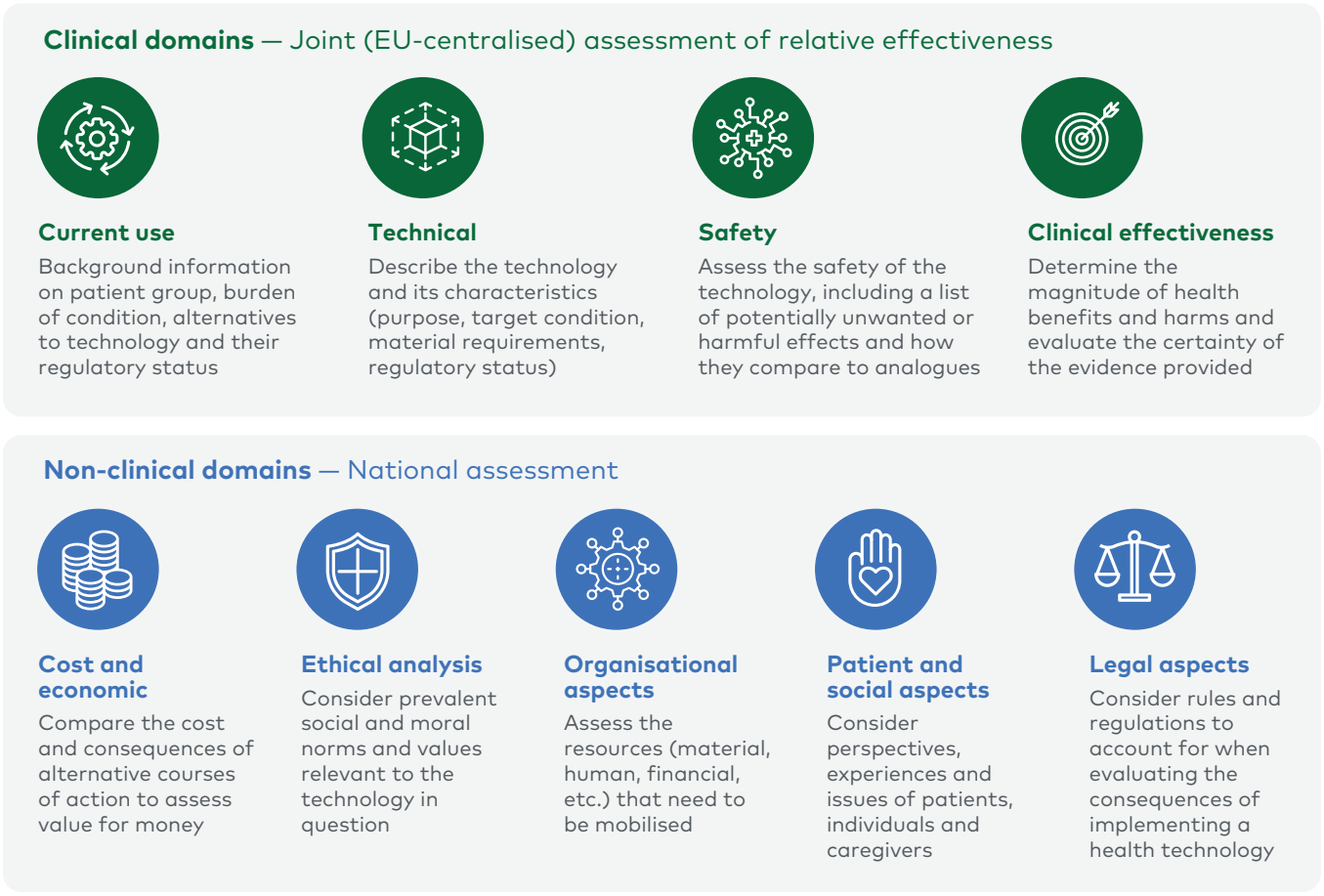
EUnetHTA actions resulted in the adoption of the EU HTA regulation[3] in 2021, which sets out the regulatory basis for JCAs and JSCs across EU member states (EUnetHTA 21).

JCAs as a non-binding assessment of clinical domains

The scope of a full HTA covers the assessment of nine domains (see Figure 1). Currently, all nine domains are assessed nationally by each member state. Under the EU HTA regulation, four (clinical) domains are considered transferable across borders and will be assessed at the EU level as part of a JCA. The remaining (non-clinical) domains will still be assessed by each member state in the context of its national policies and economic resources.

Figure 1
Nine (clinical and non-clinical) domains collectively form the basis of a full HTA

Domains of the HTA Core Model®



Source EUnetHTA; HTA Regulation (2018); L.E.K. research and analysis

Under the EU HTA regulation, JCAs are non-binding for EU member states, but results from JCAs cannot be ignored and member states should give them "due consideration" in their

appraisal. If a member state chooses to deviate from the evidence provided in the joint relative effectiveness assessment, it must deliver convincing justifications. While the JCA should replace the national assessment on clinical domains, national HTA bodies will remain free to demand additional analyses on clinical domains that were not evaluated in the JCA if deemed necessary to inform their reimbursement and pricing decisions (e.g., analyses related to national disease epidemiology). However, countries are not allowed to request a study that would yield the same data as what has already been submitted to a JCA. This aims to avoid the replication of efforts.

"A JCA does not decide how each member state uses its money. It is intended as an objective assessment of evidence that can be leveraged in each national body's decision-making process."

Former member of EUnetHTA Consortium Executive Board

The hierarchy of clinical and non-clinical domains in decision-making will remain the choice of each member state. As an example, it is expected that countries giving a lot of weight to cost-effectiveness studies will continue to do so (see Figure 2).

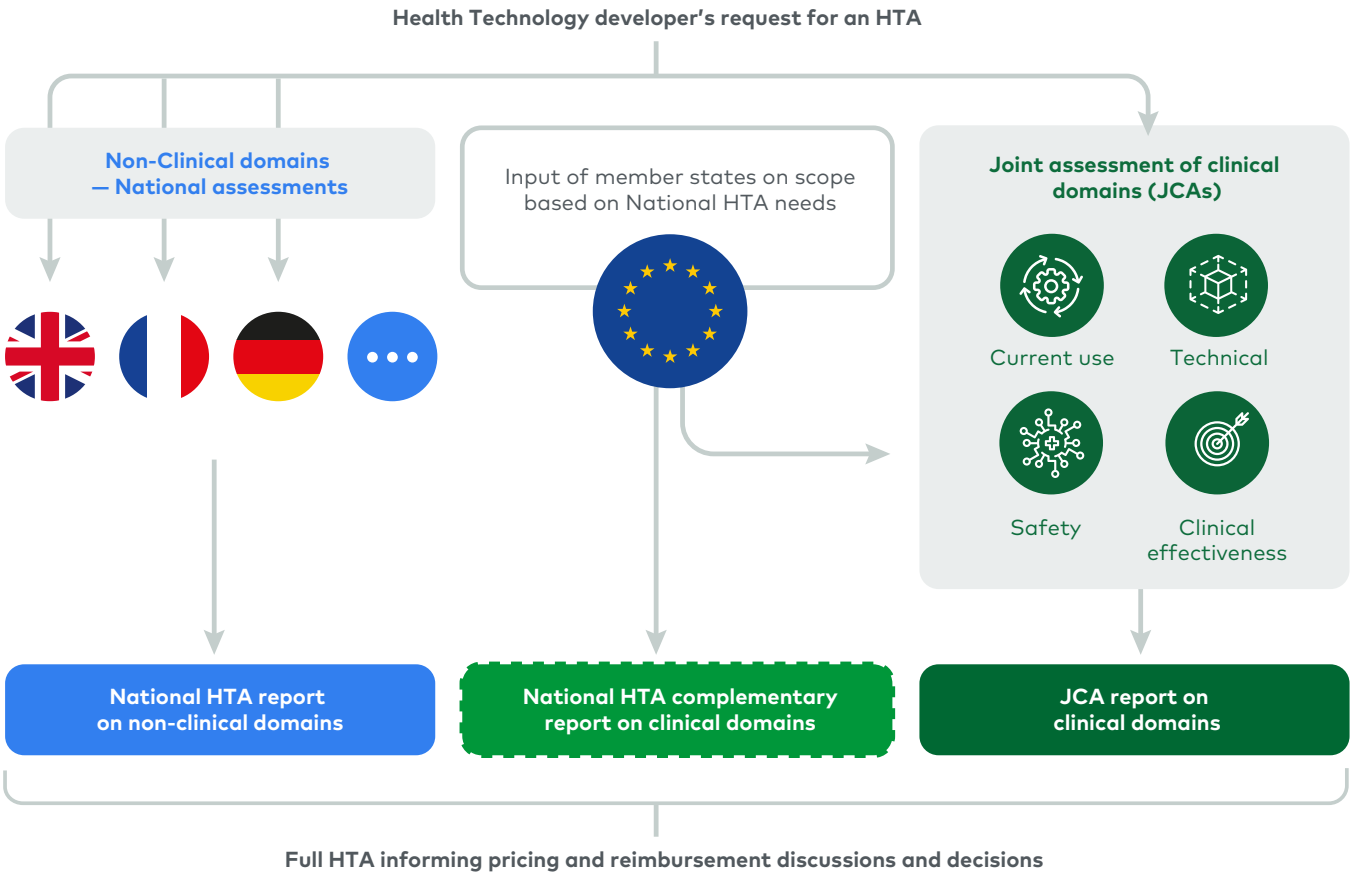
Health technologies subject to JCAs include those undergoing a centralised marketing authorisation that are medicinal products containing a new active substance and/or biotechnology products,[4] class IIb or III medical devices, and class D in vitro diagnostic devices (IVDs). At least four EUnetHTA partners from different EU countries must participate for a JCA to occur.

The JCA as a parallel HTA process to the EMA's centralised marketing authorisation

JCAs are carried out by a coordination group composed of representatives of national HTA bodies designated by member states. The coordination group allocates specific HTA authorities and bodies to subgroups to provide adequate technical expertise for the JCA. Assessors and co-assessors are appointed from the subgroups to conduct the JCA.

The JCA procedure starts with the scoping process, initiated by the subgroup. A PICO[5] survey is set up to provide each member state with the opportunity to communicate PICO parameters. Disparities between countries in terms of expected endpoints and comparators may initially result in a high number of PICO parameters, but answers are consolidated and condensed as far as possible.

Figure 2
JCAs will assess the four clinical domains. Member states might complement the clinical assessment and will assess the non-clinical domains



Source L.E.K. research and analysis

"The consolidation of PICO parameters is where I expect major harmonisation to occur, otherwise the system will not be functional."

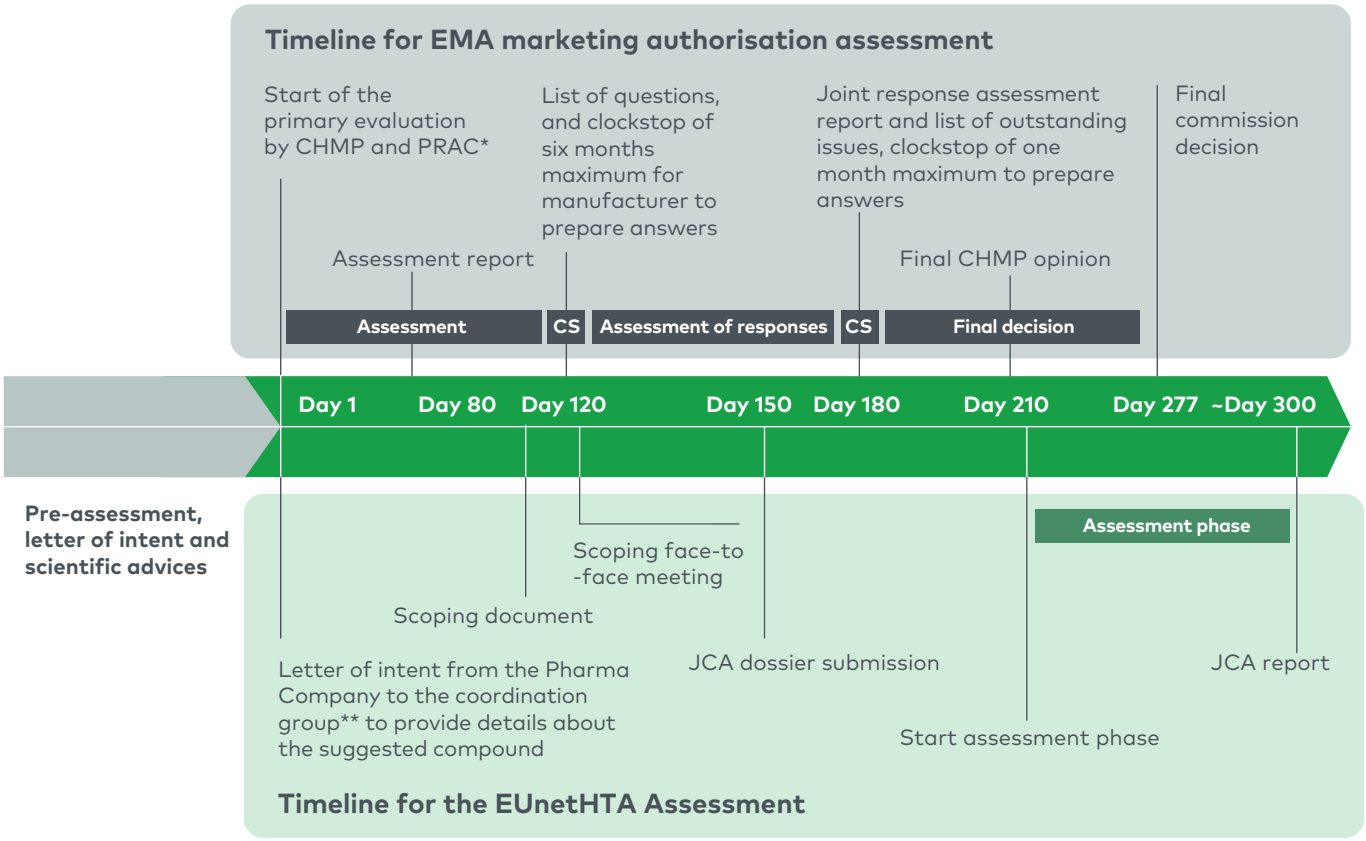
Former member of EUnetHTA Consortium Executive Board

The consolidated PICO requirements are transmitted to pharma companies to allow them to gather the necessary data. Assessors and co-assessors then evaluate the evidence provided and draft the JCA for publication by the European Commission.

A shortcoming of the PICO scoping process is that it occurs after the pharma company has applied for European Medicines Agency (EMA) approval, meaning that responses from the survey cannot be reflected in the clinical trial design. This highlights the importance of JSCs, which can occur ahead of clinical trials to make sure that inputs from national HTA bodies are considered in the design of clinical studies.

The timeline of the JCA procedure is concomitant with the EMA marketing authorisation application (MAA) timeline (see Figure 3), and the relevant assessments are performed in parallel. Whilst for the EMA, the final Committee for Medicinal Products for Human Use (CHMP) decision occurs at day 277, the JCA report is intended to be published two weeks after European Public Assessment Report publication (i.e. around day 300). The two clock stops included in the EMA process (maximum six months and one month) are expected to impact the JCA report publications by a similar delay.

Figure 3
The JCA timeline is synchronised with the EMA marketing authorisation assessment timeline



Note: EMA=European Medicines Agency; MAA=marketing authorisation application; JCA=Joint Clinical Assessment; CHMP=Committee for Medicinal Products for Human Use; PRAC=Pharmacovigilance Risk Assessment Committee; CS=clock stop

*The PRAC is the EMA's committee responsible for assessing and monitoring the safety of human medicines; the CHMP is the EMA's committee responsible for human medicines and conducts the initial assessment of EU-wide MAAs

**The letter of intent should be sent to the Joint Production Team of the EUnetHTA coordinating group in charge of producing joint assessments

Source EUnetHTA; Remap; Asphalion; EMA; L.E.K. research and analysis

JSCs: The most critical source of early input to prepare for JCAs

To ensure early input prior to an upcoming JCA, the HTA regulation has set up JSCs. JSCs provide non-binding early advice regarding the quality and appropriateness of data expected from clinical trials. They can take place prior to the start of pivotal clinical trials and in parallel with consultation with the EMA.

Eleven national HTA authorities[6] are part of the JSC standing committee, responsible for monitoring the eligibility of advice requests based on certain criteria (see Figure 4). An assessor from the coordination group is also involved to coordinate discussions between HTA bodies.

During the EUnetHTA 21 pilot phase, only a limited number of health technologies will receive JSCs, and a selection will be performed based on the nature and indications of the product.

> **"The current challenge is that JSCs are sponsored with public money — so availability is limited, and there are criteria for eligibility"**
>
> **Former member of EUnetHTA Consortium Executive Board**

It is currently uncertain whether JSCs will be offered for all eligible medicinal products after the pilot phase.

Figure 4
Criteria for selecting products for JSCs under EUnetHTA 21

Criteria for selecting from eligible requests for medicinal products and medical devices	Furthermore, EUnetHTA prioritises certain products, based on additional criteria
Unmet medical needs	Oncology products
First in class	ATMPs
Potential impact on patients, public health, or healthcare systems	Products for which there is no established guidance for clinical development (i.e. in absence of recent HTA evaluation in similar indication)
Significant cross-border dimension	
Major EU-wide added value	
EU clinical research priorities	

Note: JSC=Joint Scientific Consultation; ATMP=advanced therapeutic medicinal products; HTA=Health Technology Assessment

Source SKC; EUnetHTA; L.E.K. research and analysis

After a staggered implementation, JCAs will be fully mandatory in 2030

The EU Commission initially voted for the immediate, mandatory and binding implementation of JCAs in 2018. However, amendments resulted in a decision to implement JCAs in three phases: a pilot phase, an implementation phase and a mandatory phase (see Figure 5).

During the pilot phase initiated in 2022, the coordination group and the stakeholder networks are being formed. The stakeholder network is assembling healthcare stakeholders, including patients and care organisations, to dialogue with the coordination group.

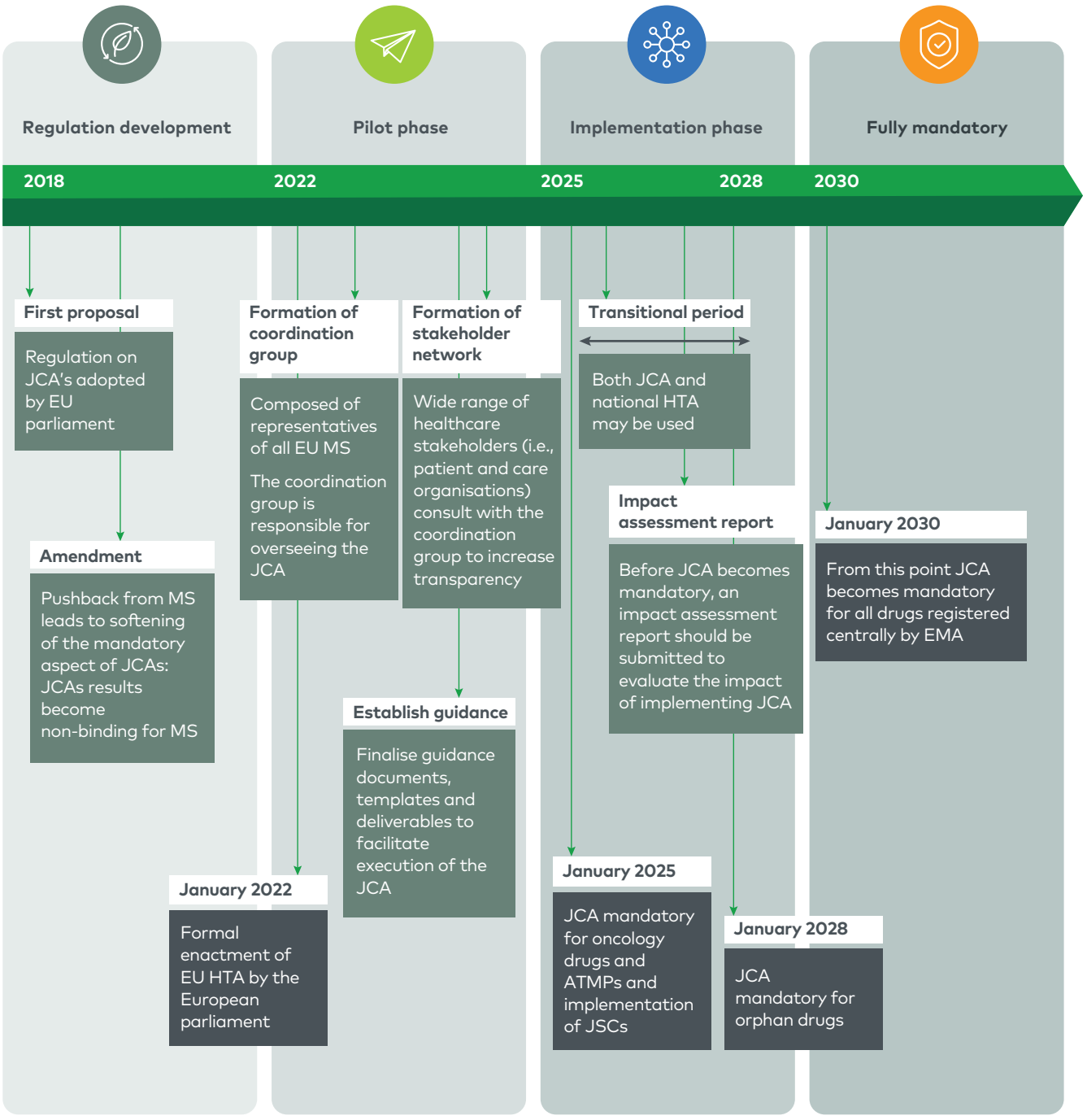
In addition, final guidance documents, templates and deliverables to facilitate the execution of JCAs are being produced.

"Patient associations are expected to play a bigger role in the future as they provide crucial inputs regarding disease burden and the perceived value of a new technology."

Former member of EUnetHTA Consortium Executive Board

The implementation phase is set to start in 2025, with JCAs becoming mandatory for all oncology drugs and advanced therapeutic medicinal products (ATMPs). During this phase pharma companies may choose to go either through a national process or through a JCA for all products that are not oncology drugs or ATMPs. However, once fully mandatory for orphan drugs in 2028 and then for all centrally registered products in 2030, relative effectiveness assessments will be conducted by designated HTA experts at the EU level and national HTA bodies will not be authorised to require the resubmission of information that has already been provided as part of the JCA.

Figure 5
Timeline of regulatory changes related to JCA implementation and adoption



Note: JCA=Joint Clinical Assessment; MS=member states; HTA=Health Technology Assessment; ATMP=advanced therapeutic medicinal product; JSC=Joint Scientific Consultation; EMA=European Medicines Agency

Source EUnetHTA; DIA Global Forum; Pharma Boardroom (2022); L.E.K. research and analysis

Implications for pharma: Short-term burden but long-term opportunity

Transition to a centralised model, with some national involvement

The approach to HTAs in EU countries is set to transition in the next five to 10 years to a mix of centralised JCAs of clinical domains and national assessments of non-clinical domains.

Managing parallel EMA, JCA and national processes is expected to be cumbersome and will require pharma companies to build additional resources. Adjusting to the EU-wide HTA dynamics will require specific market access expertise and structuring the team at the EU level.

It should be noted that the JCA report should be published closer to the CHMP decision than national HTA outcomes. JCAs might therefore decrease the time to HTA results, in particular for countries which give more weight to relative clinical effectiveness assessments, such as Germany, France, Austria and Slovenia, as these can rely to a greater extent on the data provided in the JCA. As a result, pharma companies should prepare to enter pricing and reimbursement negotiation discussions earlier.

Methodological changes to the HTA approach

The EU HTA regulation formulated a number of methodological changes such as the implementation of the scoping process, PICO surveys and JSCs. Pharma companies should prepare for these and aim to anticipate their challenges.

Preparing to answer PICO questions from each member state is key for a successful JCA. Experts anticipate challenges with PICO harmonisation across countries, which may lead to an initially long and burdensome list of PICO parameters. Changes to the way clinical effectiveness is measured are also expected as the aim is to reach a consensus on topics such as endpoints, off-label comparators and acceptability of surrogate endpoints across EU countries. A further challenge may be the limited opportunities to incorporate feedback from the PICO survey into clinical trial design due to the late timing of the survey.

To face such challenges, pharma companies should maximise advice from JSCs (as these occur before the PICO survey) and prepare to demonstrate eligibility for the JSC in the selection phase (e.g. demonstrating unmet medical need and expected positive impact on patients and healthcare systems; showing that the medicinal product addresses major EU clinical priorities; and applying for the JSC while phase II and III studies are still in the planning stage). In addition, anticipating PICO requirements through other routes will be critical for pharma companies, e.g. by engaging with national HTA agencies and other stakeholders such as medical organisations and patient associations early in the development process.

Increased involvement of various stakeholder groups

Ongoing harmonisation around operational aspects (e.g. selection of the country leading the JCA, inclusion of other countries) and scientific aspects (e.g. choice of population, comparators, use of surrogate endpoints, use of data not generated in randomised controlled trials) of the HTA regulation is critical to the success of JCAs.

Different stakeholder groups (e.g. patient associations, key opinion leaders, medical organisations) are expected to have a more prominent role in such HTA processes going forward. As such, their impact on future assessments will need to be carefully considered by pharma companies. Moreover, pharma companies will have the opportunity to interact with and obtain feedback from stakeholder groups and may contribute to shaping the JCA process via their participation in stakeholder network meetings and events.

Increased transparency and long-term opportunity for harmonisation and facilitated access

The HTA regulation was adopted in 2021 but will take time to implement. EU countries will formulate their HTA requirements and aim to harmonise their methodological approaches, facilitating EU collaboration and leading to greater transparency around HTA requirements. The regulation has created the basis for an EU-wide entity servicing HTA processes and providing advice in a fashion similar to the CHMP for drug approval. Pharma companies should prepare to interact with such a group and hold HTA discussions at the EU level in the long term.

In addition to increasing transparency and efficiency within the HTA process, JCAs will facilitate greater input from countries that tend to be less targeted by pharma companies currently, thus opening the door for broader access across Europe.

"Pharma companies will also have access to smaller countries (e.g. in Eastern Europe) that are not usually targeted as a priority. As these countries will be covered through the JCA, the EU HTA regulation will increase access to them."

Former chairman of the EUnetHTA Executive Committee

Uncertainties remain

JCAs have the potential to harmonise HTA processes across Europe. However, uncertainties around the implementation and interpretation of the regulation remain and will need to be carefully monitored by pharma companies.

The relative importance of JCAs in upcoming national appraisals might vary due to the non-binding aspect of the regulation and the freedom provided to national HTA bodies to augment JCA outcomes. Furthermore, it is to be expected that JCAs will not provide a firm yes/no recommendation, creating some uncertainty for national HTA bodies. Finally, the clarification of operational aspects and harmonisation of HTA methodologies will be critical for the future success of JCAs. This will hinge on the engagement of national HTA bodies and their ability to find common ground.

Another uncertainty comes when markets have varying local standards of care (SoC) and clinical practice. The position on interpreting the extent of benefit in this case would be impacted by different perceptions of the magnitude of benefit versus SoC, which will require resolution via PICO processes.

Despite these uncertainties, the EU HTA regulation will support a future joint HTA system, building on the achievements of the EUnetHTA joint actions and promising long-term benefits of greater efficiency and transparency.

How L.E.K. can help

We can provide perspectives on the implications of EUnetHTA for pharma companies, including changes in evidence requirements, stakeholder engagement, and time-to-access implications. To discuss the topic in more detail, please reach out to authors Verena Ahnert, at v.ahnert@lek.com and Elena Subbotina at e.subbotina@lek.com.

Endnotes

[1]The UK is no longer part of the EUnetHTA consortium and will not be participating in any joint actions proposed since its departure from the EU.

[2]Joint actions are multiyear projects to support the development and implementation of joint HTAs across Europe. They are funded by the EU and involve a consortium of partners from various countries coordinated by the EUnetHTA Secretariat. Joint Action 1 (JA1) (2010-2012) established the foundations and methodological guidance for EU HTA collaborations. Joint Action 2 (JA2) (2012-2015) strengthened the practical application of tools and approaches to EU HTA collaboration. Joint Action 3 (JA3) (2016-2021) implemented and encouraged voluntary EU HTA collaboration and supported healthcare decision-making.

[3] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

[4] Medicinal products containing a new active substance not yet authorised in the EU and/or obtained via biotechnology processes such as recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma, and monoclonal antibody methods.

[5] The PICO parameters include: Population: Identification of the relevant population(s) for the assessment scope, based on the claimed indication; Intervention: Combination of the intervention to be assessed and the indication or the intended use; Comparator: Pharmacotherapies and/or non-drug interventions that are relevant for the HTA for each of the populations of interest and that serve to determine the relative effectiveness of the health technology assessed; and Outcomes: Choice of endpoints of interest, and relative improvement necessary to demonstrate the relative effectiveness of the health technology assessed.

[6] AEMPS – Spain, AIFA – Italy, G-BA – Germany, HAS – France, INFARMED – Portugal, KCE/KCENIHDI – Belgium, NCPE – Ireland, NIPN – Bulgaria, NOMA – Norway, TLV – Sweden, ZIN – The Netherlands

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