The EU HTA Harmonization Initiative
What is the Significance to Manufacturers of the New Directive?

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Introduction

Comparative clinical benefit assessments are at the core of health technology assessments (HTAs) in Europe. HTAs are a multi-disciplinary process considering input and evidence from different areas, such as medical, social, and economic sources. These assessments are then used to inform the design of health policies that allow the safe and effective use of new technologies within individual health systems and their specific conditions.

Currently, HTAs are conducted separately by individual European countries using their own assessment criteria. This multiplicity of HTA methodologies can create considerable work for manufacturers, which currently need to submit HTAs to multiple European Union (EU) member states.

The idea of a pan-EU HTA has long been discussed, but has taken considerable time and effort to come to fruition.[1] On 31 January 2018, the European Commission (EC) requested EU Member States to adopt a new proposed Directive (2018/0018) which outlined several activities required for a European Health Technology Assessment (EU HTA). Despite being vetoed by Germany, France, the Czech Republic, and Poland, **the Directive was adopted on 3 April 2018 and is expected to be implemented on 30 March 2019.**

This white paper aims to outline the new Directive, highlighting the changes from existing HTAs, and to provide commentary on the potential impact of this legislation to key stakeholders, manufacturers in particular.


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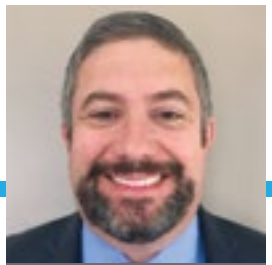
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Summary of the New Directive

- A major component is a **consistent, comparative, clinical efficacy assessment**, facilitated centrally for all EU member states and used for all European Medicines Agency (EMA) assessed pharmaceuticals, medical devices (within defined criteria), and diagnostics.
- This Directive specifies that **no separate comparative clinical assessment** may be carried out at individual member state levels.
- In contrast to the clinical assessment, the value assessment of **all non-clinical domains** (including social, economic, or organizational) and the determination of price will **remain with individual member states**.
- The EC outlines expectations of the new integrated approach, including increased transparency and potentially faster patient access to new technologies across the EU.
- It also sees benefits to the pharmaceutical and medical device industry, such as improved business predictability, enhanced competitiveness, and stimulating innovation.

As the implementation and methods associated with the Directive evolve over the short- and medium-term, it is vital for stakeholders, in both the public and private sectors, to understand the Directive's background and the proposed framework to prepare for the changes and leverage the opportunities this Directive presents.

Background

Recognizing that there are differences in the conduct of HTAs within the EU, a pan-European HTA has long been discussed as a fundamental method of harmonizing drug assessments within the member states. In 2004, the High-Level Group on Health Services and Medical Care, within the EC's Health and Consumer Protection Directorate, called for the development of an EU-level HTA network:

> *"[T]he usefulness of establishing a sustainable European health technology assessment network has been recognized. Such a network should address methods for developing common core information packages, methods to support transferability of assessments, methods for helping Member States to identify and prioritize topics and commissioning reports, tailoring common core information to national health policy processes and sharing methodologies, expertise and practice issues."*[1]

In response to the EC's call for action, the Danish Centre for HTA led a coalition of 35 organizations to develop the European Network for Health Technology Assessment (EUnetHTA) Project in 2005.[2] Since then, EUnetHTA has grown into a consortium of over 81 governmental and non-profit organizations from 29 countries (i.e., EU member states, EU-accession countries, European Economic Area countries, and European Free Trade Association countries) that collaborate on HTA – on a ***voluntary*** basis.[2] The movement for EU-wide HTA picked up steam in 2011, with Directive 2011/24/EU on patients' "cross-border rights." The push culminated in this year's developments, which shift participation from voluntary to ***mandatory.***

There has long been rumor of such a supra-nationalization, so readers may be skeptical that the regulation will be put into effect. A healthy skepticism is natural, but we advise against it in this case. Two-thirds of the 28 EU Member States' legislatures would have to lodge objections with the EC for the new initiative to fail. This means that 19 Member States would have to vote to oppose the Directive for it to fail. Only 4 Member states, Germany, France, the Czech Republic, and Poland vetoed the Directive. An additional 15 member states would therefore have to change their position, which is unlikely since many Member States, particularly those smaller ones with fewer resources to conduct clinical HTA themselves, stand to benefit from the regulation.

Manufacturers developing health technologies due to launch between 2019 and 2021 (i.e., the transitional period during which Member States participation remains voluntary), and especially those launching from 2022 onwards (i.e., at which point all Member States will be bound by the EU-level clinical HTA) should closely track developments and prepare accordingly.

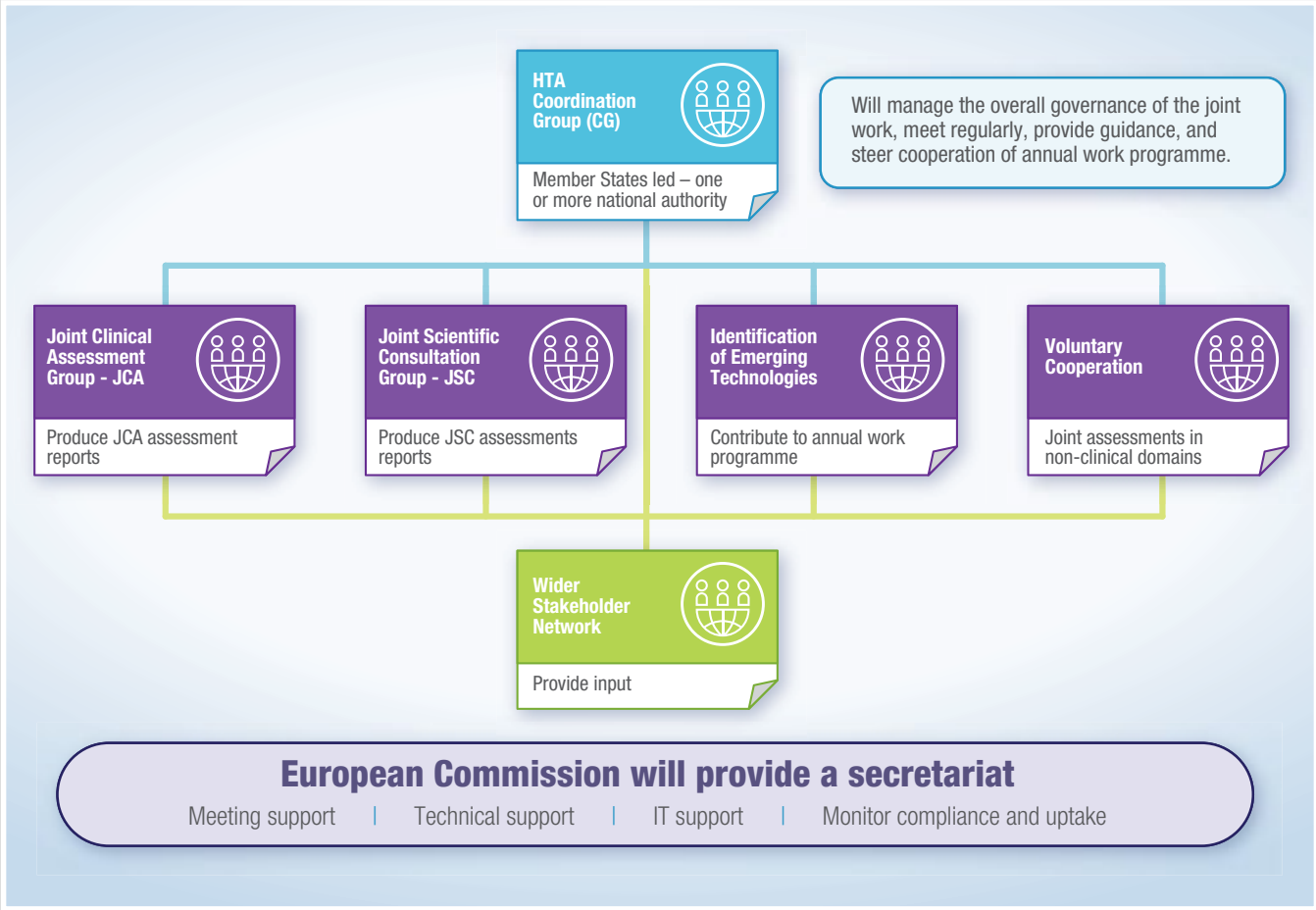
Structure of EU Clinical HTA Decision-Making

Article 3 of the regulation provides details on what it calls, "The Member State Coordination Group on Health Technology Assessment," or the "Coordination Group" for short.[3]

Structure and decision-making rules are as follows *(additional details can be found in Article 6).*[3]

- **Who?** The Coordination Group will be comprised of national HTA organizations designated by Member States.
- **How?** The Coordination Group will make decisions by consensus or, failing consensus, majority rule. There will be no representation based on relative Member State population; rather, each Member State will have one vote. The Group may create committees/subgroups for each type of health technology: drugs, devices, and "other health technologies." Each committee/

Figure 1. New Structure Designed to Facilitate EU HTA Harmonization Initiative



subgroup will appoint an assessor and co-assessor who will prepare the assessment report. In case the assessor requires additional evidence, he/she may suspend the assessment and request that the manufacturer submit those data. The manufacturer will have an opportunity to comment on the draft assessment report, as will patients and clinical experts, prior to finalization and publication.

- **Points to note**
  - "The Coordination Group shall …
    - ensure cooperation with relevant Union-level bodies to facilitate additional evidence generation necessary for its work;
    - ensure appropriate involvement of stakeholders in its work …"[3]
  - "The members of the designated sub-group shall provide their comments during the preparation of the draft joint clinical assessment report and the summary report. The Commission may also provide comments."[3]

This description raises more questions.

- **Cooperation with Union-level bodies.** It is unclear what this means. The EC may envision closer cooperation between the EMA and the Coordination Group. Does it envision joint regulatory and clinical HTA? Harmonization of additional evidence collection for regulatory and clinical HTA purposes?
- **Appropriate involvement of stakeholders.** Which stakeholders? What level of involvement is "appropriate"? What role will key opinion leaders (KOLs) play? Patient advocacy organizations? How will national-level organizations be handled versus EU-level organizations? Will the latter be privileged?
- **The Commission will comment?** It is not clear why the Commission should wish to reserve the right to comment on clinical HTA assessments, which are meant to be objective, technical, science-based reviews of evidence. In Article 25, the regulation also notes that the EC will co-chair Coordination Group meetings. It is unclear what role the EC envisions for itself in this process, though there are mentions in the regulation of a supervisory role for the EC to ensure the regulation is being executed appropriately.

Regulation's Scope

The scope of the Joint Comparative Clinical Assessments (JCA) includes:

Pharmaceuticals

- Medicinal products with central marketing authorization
- New active substances
- New therapeutic indications for existing substances

Medical devices - Class IIb and III

- For which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure

In vitro diagnostic medical devices - Class D

- For which the relevant expert panels have provided their views in the framework of the clinical evaluation consultation procedure

While *all drugs* with EMA approval are in scope, only those **devices and diagnostics** entering areas with the **following criteria** are in scope.

- Unmet medical needs
- Potential impact on patients, public health, or health care systems
- Significant cross-border dimension
- Major Union-wide added value
- Available resources

During the 3-year transition period (i.e., 2019-2021), 65 assessments are expected annually.[4]

Elements of the Joint Clinical Assessment

The Joint Clinical Assessment (the assessment hereafter) will cover four domains:[3]

- Description of the health problem and how it's treated today
- Description and technical specifications of the new health technology
- Comparative efficacy
- Comparative safety

Evidence quality, described by the regulation in Article 6, Section 5 as, "degree of certainty on the relative effects based on the available evidence," will factor into the assessment.[3] Manufacturers face many uncertainties based on this description.

- **Whose standard of care? Whose health care delivery system?** It is not clear how the assessment will handle variation in standard of care and health care delivery across Member States. Will the assessment consider all Member States' standards of care? All manners of delivering that care? If so, won't the assessment become unwieldy? If not, won't some Member States' status quo be ignored? Over time, the vision is presumably to homogenize standards of care across the Union, but what will constitute the baseline?
- **Role of real-world evidence (RWE).** It is not clear how RWE will factor into the assessment. What sorts of RWE will be acceptable to establish burden of illness? Treatment patterns? From which country or countries? How many countries are "enough" to represent the EU as a whole? Must some "key" countries be included? What study designs are required? How, if at all, do requirements in orphan disease differ from non-orphan?
- **Acceptability of indirect treatment comparison.** The Member States currently differ on acceptability and, thus, the use of indirect treatment comparison (ITC). Will the assessment's approach be stricter, like that of the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, or more accepting, like that of the National Institute for Health and Care Excellence (NICE) in the UK?
- **Endpoints and outcomes.** The Member States also differ significantly on the use of certain categories of endpoints, such as so-called "surrogate" endpoints. How will the assessment manage surrogates? The regulation does mention, "patient-relevant health outcomes chosen for the assessment," but does not specify how these outcomes will be selected.[3]

No National Clinical HTA as of 2022

Article 8 of the regulation specifically forbids Member States from conducting clinical HTA on technologies assessed by the Coordination Group, and requires that Member States "apply" the reports in their national HTA.[3] Member States must notify the EC of any national HTA on technologies assessed by the Coordination Group, and must tell the EC how the joint assessment report was used in their national HTA.

What is uncertain is the recourse Member States will have if the assessment fails to provide the evidence they need to carry out the other elements of their national pricing, reimbursement, and market access (PRMA) process? For instance, what if the standard of care selected for the comparative efficacy and safety analysis is not used in their country? The regulation currently offers no guidance on this point.

Restrictions during Transitional Period (2019-2021)

Coordination Group members from any Member State who opt out during the transitional period will not be permitted to act as assessors or co-assessors during that period, or to comment on or participate in approval voting on joint clinical assessments during that period (per Article 10 of the regulation).[3]

Early Scientific Advice (ESA)

ESA will be available from the Coordination Group, including parallel advice with the EMA (per Article 12).[3] The Coordination Group will prioritize for ESA health technologies that are likely to undergo joint clinical assessment.

Conclusion

The Directive is driving European HTA towards significant change and yet, as currently written, significant uncertainty remains around its implementation and potential impact.

Major unanswered questions include:

- How will the comparator be chosen?
- How will the assessors be determined?
- What will be the assessment methods?
- What are the expected timelines for the assessments?
- How will Member States apply assessment findings?
- What will Member States do if/when assessment findings don't apply to their specific circumstances?
- How will Member States incorporate assessments into those parts of the PRMA process for which they retain authority, including health economic assessment, access, pricing, and reimbursement?
- What is the role and importance of patient-reported outcomes?
- What is the role and importance of RWE?

As the industry watches for further developments, it is suggested that manufacturers take some immediate steps.

- **Pipeline and portfolio management.** Not only pipeline products, but also inline products gaining new indications from 2019, will be affected. Once these uncertainties are resolved, HTA-geared trial evidence and RWE plans may need to be revamped.
- **ESA strategy.** All ESA will be facilitated at the EU level. Market-focused efforts need to be retooled.
- **Price negotiation dynamics.** Well-understood price negotiation dynamics (e.g., in France, negotiating with the Economic Committee for Health Products [CEPS] based on the improvement of medical benefit assessment [ASMR]) will be upended. Preparations must be made to negotiate based on the assessment report.
- **Expertise evolution.** There will be a shift in required expertise from knowledge of decision-making by bodies like IQWiG, to experience and expertise in pricing, contracting, and tendering.
- **Dual assessments during the transitional period.** During the transitional period, manufacturers of in-scope technologies should prepare for dual clinical assessments – particularly for countries likely to opt out of the assessment process during this time (i.e., Germany, France, Poland, Czech Republic). ■

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