NDA Whitepaper

Joint Clinical Assessments – Mandatory EU-Level Evaluations for Health Technology Assessment

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About the author

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Sigrid is an expert in clinical oncology with extensive regulatory experience working in the European Medicines Agency (EMA) system. She spent 14 years at the Swedish Medical Products Agency (MPA) as clinical assessor of marketing authorisation applications for oncology drugs in the EU centralised procedure and providing scientific advice to industry.

Sigrid has 5 years' experience in Health Technology Assessment (HTA) as medical advisor to the Swedish Dental and Pharmaceutical Benefits Agency (TLV). This includes health economic appraisals based on cost-utility analysis, as well as EUnetHTA joint clinical assessment (JCA) of relative effectiveness. She also worked on the new EU HTA regulation and the planning of its implementation.

Sigrid has a background as a MD and PhD from Uppsala University, and as clinical Specialist in Oncology from the Karolinska University Hospital of Sweden. She applies her knowledge to successfully support companies on the clinical aspects of drug development.

Health Technology Assessment

Health Technology Assessment (HTA) is the assessment of a health intervention's value. [1] This is typically done in comparison with another relevant treatment option. The process usually starts with the evaluation of clinical relative effectiveness but may in other parts differ greatly in methodology, requirements, and outcomes. In Europe, HTA often determines the reimbursement and pricing of medical products, and thereby patient access.

The New EU Regulation

In 2021, new EU legislation was passed that mandates that the first step of the health technology assessment for most new medicines and certain types of medical devices must be performed jointly at the EU level. The Regulation on Health Technology Assessment 2021/2282 (HTAR) came into force on 11 January 2022 and will be applied to companies, referred to as Health Technology Developers (HTD)s, in a stepwise fashion beginning on 12 January 2025. [2]

The financial activities and decisions concerning reimbursement, pricing, and procurement in EU member states (MS) will still be handled at the national or more decentralised level.

The HTA regulation concerns medicinal products and medical devices, including in vitro diagnostics, and revolves around two key EU-level activities:

- Joint Clinical Assessment (JCA)
- Joint Scientific Consultation (JSC)

Implementation steps

For medicinal products, both completely new medicines, 'New active substances' from initial EU marketing authorisation procedures, and new indications from extensions of the marketing authorisation will be subject to JCA when the regulation is fully applied.

The stepwise implementation of JCA is as follows, according to HTAR, Article 7*:

- Beginning 12 January 2025, new medicinal products for the treatment of cancer, advanced therapy medicinal products (ATMP)s, and all medical devices that are in scope will be subject to Joint Clinical Assessment. At this time, only products going through their initial marketing authorisations are subject to JCA, i.e., not new indications for previously authorised medicines. JCAs are mandatory for these types of medicinal products with MAAs submitted to EMA on 12 January 2025 or later.
- On 13 January 2028, orphan designated new medicinal products will be added.
- On 13 January 2030, all remaining medicinal products in scope for JCA will start to apply, including both new medicines and new indications.

* All legal articles mentioned in the text refer to the HTAR, unless otherwise stated.

Medicinal products subject to Joint Clinical Assessment

Medicinal products for which marketing authorisation via the EU centralised procedure is mandated according to Regulation (EC) No 726/2004 [3] will through the HTAR also be required to undergo JCA.

These are:

- Biotechnologically developed products (e.g., antibodies)
- ATMPs
- Orphan medicinal products
- Products with an indication for the treatment of:
  - AIDS
  - Cancer
  - Neurodegenerative disorders
  - Diabetes
  - Autoimmune diseases and other immune dysfunctions
  - Viral diseases

Joint Clinical Assessment Relative effectiveness

The remit of JCAs is limited to the relative effectiveness compared with the appropriate health technology currently used for the same purpose or condition, the so-called 'relevant comparator'. This is identified based on country-specific conditions and may or may not be the same as the control arm in the pivotal trial used for registration of a pharmaceutical product.

While the purpose of all health technology assessment is to describe and estimate the value of a health innovation, this is explicitly out of scope for the JCA. The value judgments are left to the national level, where the financial decisions are made. Consequently, there is no health economic appraisal being performed in the JCA procedure – only clinical data is evaluated.

Formally, the HTAR therefore limits the JCA to a description of the scientific analysis of a) the relative effects of the health technology, and b) the degree of certainty of the relative effects (Article 9).

What is PICO?

The assessment scope for the joint clinical assessment is called the "PICO". This is an abbreviation where P stands for population (i.e., target population or indication); I stands for intervention (the drug, device or other health intervention); C stands for comparator and refers to the identified relevant comparator, the establishment of which is the basis for all HTA comparisons; and O stands for outcomes, meaning the appropriate study endpoints or estimands to be used for the

Assessment scope domains:

P – Population
I – Intervention
C – Comparator
O – Outcomes

condition and study type or analysis in question. The PICO thus describes the scenario(s) and type of analyses that should be provided by the company.

The dossier development and the initiation of a JCA procedure differs markedly from a marketing authorisation application (MAA). For a regulatory dossier, the drug manufacturer has the initiative and submits the data developed and selected by the company at a time of their convenience. Contrarily, for the JCA, the timing of the procedure is determined by regulation, and it is the EU HTA assessors that define the PICO, and thus the dossier contents. This is done via a scoping process whereby a survey is distributed to all members states concerning their national requirements for the PICO.[4] These requirements are then weighed together to form the PICO(s) for the JCA procedure.

The regulation requires that "the assessment scope shall be inclusive and reflect Member States' needs" (Article 8), meaning that there could be more than one PICO established for which analyses should be completed by the company in a JCA. This could for example occur if different relevant comparators are identified in different countries. It is also conceivable that more than one population for analysis might be requested, e.g., if the acceptability of the HTD's proposed indication for marketing authorisation seems questionable given the available clinical evidence; or if the drug is expected to be very expensive, to prepare for a more restrictive reimbursement population. Given that the timelines of the JCA are challenging to companies and assessors alike, in

practice, there will likely be an upper limit to the number of PICOs.

It should be noted that any information that a MS needs for their national appraisal process that has not already been submitted in the JCA, such as a certain relevant comparator not included in the JCA or health economic data for example, may be requested in procedures at the national level. Meanwhile, data already submitted in the EU JCA may not be asked for again in national procedures. (Article 13)

Timelines and processes

For medicinal products, the HTAR formally couples the JCA timelines with the EMA MAA procedure, but only parts of them are laid down in the regulation, namely the deadline for submission of the JCA dossier by the health technology developer, and the deadline for endorsement of the JCA report by the Coordination Group (CG).

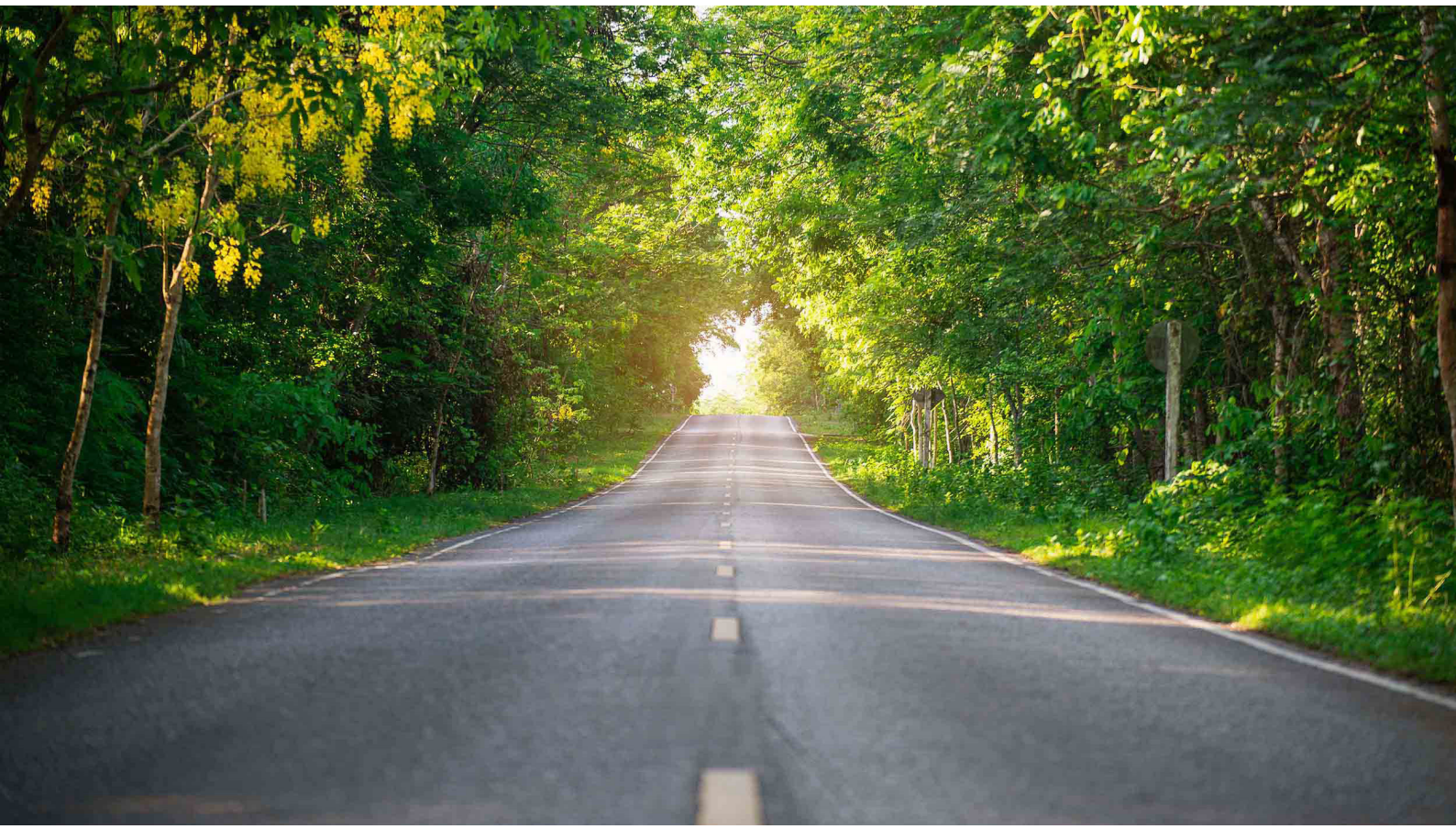
The application for marketing authorisation or a new indication to EMA is a prerequisite for a JCA. What will be the trigger to start the PICO scoping process is not mentioned in the HTAR, however, and could potentially occur before the regulatory submission. This will be established through the implementation work by EUnetHTA 21 and the European Commission (EC) in the time period before the adopted regulation starts to apply (12 January 2025, see above). The trigger point for, and length of, the PICO scoping process will determine the time available for the HTD to compile and finalise their JCA submission dossier.

The HTD will be requested to provide information on the intervention and intended use (sought indication) for the purpose of the PICO scoping. [4] When the assessors' internal scoping process is complete and the PICO(s) settled, the EC informs the company of the assessment scope and requests the submission of the dossier. The request will include the deadline for submission, the dossier template, and the requirements for the dossier as outlined in the HTAR.

The deadline for submission of the dossier concerning a medicinal product is stipulated in the regulation to occur at the latest 45 days prior to the envisaged date of the opinion (on benefit-risk and approvability) of the EMA Committee for Medicinal Products for Human Use (CHMP) (Article 10). Depending on when the request for submission from the EC is received by the HTD (see above), the timelines for producing the JCA dossier could be more or less challenging.

The other timepoint defined in the HTAR is the deadline for endorsement of the JCA report. It is stipulated as no later than 30 days after the EC decision on marketing authorisation. (Article 11) According to the current regulatory timetables (2023), this normally occurs approximately 2 months after the positive opinion from the CHMP. If this interval would be changed in the upcoming revision of the EU Pharmaceutical legislation, the JCA timelines could become even more challenging for the assessors.

For medical devices, the procedural timelines for JCA and rules for the exchange of information with the notified bodies and expert panels are not explicit in the HTAR but will be adopted by the CG and EC, respectively. (Article 3, Article 15).



Coordination and reports

The JCA process outlined below refers to HTAR Articles 8-12.

A Coordination Group composed of MS representatives from HTA authorities and bodies will be designated by the MS. The CG will in turn appoint a smaller 'designated subgroup' for JCA assessments. The designated subgroup will among themselves select institutions to perform the roles of 'assessor' and 'co-assessor'. Both assessor and co-assessor can consist of multiple individuals from the respective national or regional authorities. [5] These will collaborate on the primary assessment of the dossier and preparation of the JCA reports, with input from external experts, patient representatives, and other members of the designated subgroup. If further information from the HTD is needed, requests can be made via the Commission. In addition to the draft JCA report, a draft summary report is prepared.

The draft reports will be sent to the HTD for comments on factual or technical inaccuracies, and identification of commercially sensitive information considered by the company to be confidential. HTD comments on the results of the draft assessment are not allowed. Following the HTD input, a revised draft JCA report and summary report will be provided to the CG, who will endorse the revised draft reports by consensus. If consensus cannot be reached, divergent scientific opinions will be incorporated in the reports, which will then be endorsed.

The endorsed reports will be sent for procedural review to the EC, who can require corrective actions and re-endorsement from the CG if needed. Procedurally compliant reports will then be published on the publicly accessible webpage of the IT platform.

Procedurally non-compliant reports will instead be made available together with their procedural review to MS on the secure intranet of the IT platform.

In cases where the EC finds that the HTD dossier was not submitted in a timely manner or that it fails to meet the requirements laid down in Article 9(2-4), the EC will discontinue the JCA and make a statement regarding the reasons for discontinuation on the IT platform. The corresponding evaluation and request for documentation can then take place at the national level.

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