NDA Whitepaper

Joint Scientific Consultations – Advice for EU Health Technology Assessment

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About the author

Dr Sigrid Klaar

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. She also worked in the EMA Oncology Working Party for 9 years, drafting guidance for industry and supporting the CHMP

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.

JSC – Executive Summary

Joint Scientific Consultation (JSC) is a voluntary procedure for health technology developers (HTD)s to gain input on clinical development and evidence requirements jointly from EU HTA bodies, similar to centralised regulatory scientific advice. It is part of the new EU Regulation on Health Technology Assessment (HTAR)[1], which will apply to companies from 12 January 2025.

The purpose of JSC is to facilitate the mandatory Joint Clinical Assessment (JCA) of new medicines, new indications, and certain classes of medical devices including *in vitro* diagnostics. The JCA is a partial health technology assessment (HTA), concerned with clinical relative effectiveness and safety. It will be performed jointly between EU member states in a procedure that runs largely in parallel with the marketing authorisation procedure. The implementation of JCA is stepwise and differentiated between different product types, beginning with new oncology drugs, advanced therapy medicinal products (ATMPs) and medical devices.

The JSC will address company questions on clinical study design and other evidence generation issues from a HTA and payer perspective, in line with the PICO framework (population – intervention – comparator – outcomes). The procedure includes a discussion meeting between the company and the HTA assessors and is concluded with an outcome document with written recommendations.

The timing of the JSC request is crucial, as eligibility criteria only allow for a consultation when the clinical studies are still in the planning stage.

Requests for JSC and other communication with the HTA Coordination Group (HTACG)[2] and its subgroups will be sent via an IT platform, where the available slots for JSC will be announced. In case of too many requests, selection criteria for prioritisation outlined in the HTAR will be applied – there is no guarantee that a consultation will be granted.

Parallel EMA/HTA body (HTAb) Scientific Advice are offered in the interim period from September 2023 to the application of the HTAR on 12 January 2025.[3]

In this paper you will find further details on the JSC with references to the legal articles of the HTAR, and introductory brief backgrounds on HTA and JCA.

See also the NDA whitepaper on Joint Clinical Assessments (May 2023).[4]

Health Technology Assessment (HTA) is the determination of a health intervention's value to inform decision-making, such as reimbursement and pricing.[5] The assessment is normally performed in comparison with another relevant treatment option. It typically starts with the estimation of clinical relative effectiveness and safety but may in other parts differ greatly in methodology, requirements, and outcomes. It can include health economic evaluation, such as cost-utility analysis, or use a grading system to express the value. In Europe, HTA often determines the pricing and reimbursement of medical products, and thereby market access.

Regulation on Health Technology Assessment

The EU Regulation on Health Technology Assessment 2021/2282 (HTAR)[1] came into force in January 2022 and will take effect on 12 January 2025. It concerns medicinal products and medical devices and revolves around two key EU-level activities:

- Joint Clinical Assessment (JCA) – a mandatory partial HTA evaluation concerning clinical relative effectiveness and safety

- Joint Scientific Consultation (JSC) – a voluntary process, equivalent to regulatory scientific advice

The JCA is intended to facilitate the subsequent national HTA, pricing, and reimbursement processes throughout the 27 EU members states (MS) by reducing duplication of work and through increased alignment between MS.

In scope for JCA are medicinal products for which centralised market authorisation is required by EU law; and three classes of medical devices – class III (implantable devices), class IIb (active devices intended to administer and/or remove a medicinal product), and Class D (in vitro diagnostic medical devices for detection of transmissible agents), with some exceptions and after selection. (Article 7)*

Implementation steps

Companies with products in scope for JCA are referred to as health technology developers (HTD)s in the regulation. For these companies, the regulation will legally apply from 12 January 2025. For JCA there will be a stepwise implementation based on product type (Article 7), while JSC will be available from the start date, although with eligibility criteria that may be indirectly affected by the JCA timetable, shown below.

JCA:

- 12 January 2025: New medicinal products for the treatment of cancer, advanced therapy medicinal products (ATMP)s, and all medical devices in scope

- 13 January 2028: Orphan designated new medicinal products

- 13 January 2030: All remaining medicinal product types in scope for JCA, both new medicines and new indications

** All legal articles and paragraphs mentioned in this white paper refer to the HTA regulation.*

JSC:

- Applied under the regulation from 12 January 2025

- Interim Parallel EMA-HTA body JSC available September 2023 – January 2025

Joint Clinical Assessment and PICO

The details of the JCA are described in another whitepaper.[4] Important to know about the JCA in relation to JSC, is that a JCA is mandatory once the marketing authorisation application (MAA) has been submitted for any medicinal product encompassed by the HTA regulation (see above). The JCA is performed largely in parallel with the MAA, with the end date 30 days after the approval by the European Commission (EC). The required contents of the JCA dossier are determined by the HTA assessors and will be communicated to the HTD in a request for dossier. The analysis scope (research questions, endpoints, and analyses) required to be answered in the JCA is often referred to as "the PICO", based on the abbreviation for Population, Intervention, Comparator, and Outcomes. It has been repeatedly confirmed by HTA officials at conferences and meetings that there will often be more than one analysis case (PICO) requested for a JCA, in order to satisfy the EU member states' needs.[6]

Purpose of Joint Scientific Consultation

Joint Scientific Consultation (JSC) is a framework whereby companies can receive recommendations on their development programmes jointly from EU HTA bodies, similar to regulatory agencies' scientific advice. There is also a possibility for parallel consultations together with the European Medicines Agency (EMA) for medicines, or with an expert panel for medical devices. (Article 17)

According to the HTAR, the purpose of a JSC is to exchange information on development plans, and to facilitate evidence generation that will meet the likely evidence requirements of a subsequent joint clinical assessment for the product. (Article 16)

Eligibility and timing

The time available for compiling a JCA dossier is limited once a company receives the request from the EC, after the submission of the MAA. Having as much information as possible regarding the expected scope for JCA before the MAA submission will be an

advantage as it allows more of the work to be done in advance.

Going for a joint scientific consultation may consequently seem a good strategy. It is therefore important to note the eligibility criteria for a JSC, both of which must be fulfilled, according to HTAR Article 16:

- The health technology is likely to be the subject of joint clinical assessment
- The clinical studies and investigations are still in the planning stage

This means that timing is crucial. If your pivotal trial is already ongoing, the second criterion means that it is unlikely that you will be granted a consultation where you could get the HTA authorities' input on the scope for the upcoming JCA. In addition, the stepwise implementation of JCA might impact on eligibility. If you plan to submit your MAA before the JCA applies to that product group, you may not fulfil the first criteria for eligibility.

JSC requests and selection

The dates of request periods and the planned number of joint scientific consultations for each period will be published on an official IT platform created for communication with HTDs, where companies will also apply for JSC.

If the number of eligible requests exceeds the number of planned JSCs, selection criteria will be used, while ensuring equal treatment of requests for health technologies with similar intended indications. The following criteria for prioritisation of products for JSC will apply (Article 17):

a) Unmet medical need
b) First in class
c) Potential impact on patients, public health, or health care systems
d) Significant cross-border dimension
e) Major Union-wide added value
f) Union clinical research priorities

These criteria are similar, but not identical, to the criteria used for selection of medical devices for JCA (Article 7). While the first two criteria will be important, some of the others may be considered vague without further definitions, hampering predictions of their future application.

JSC scope

The JSC will address clinical study design and evidence generation aspects from a HTA and payer perspective, in response to company questions. According to the regulation's Article 16, the joint consultations "shall concern all relevant clinical study design aspects, or clinical investigation design aspects, including comparators, interventions, health outcomes and patient populations." i.e., all aspects of the PICO (see above).

While the regulation specifically dictates that for medicinal products, directly comparative randomised clinical studies shall be advised whenever appropriate (Article 18), it has been confirmed by HTA officials that advice on any type of (clinical) evidence generation can be given, including for example suitable approaches for indirect comparisons.[6]

It is expected that the JSC under the new regulation will maintain most of its characteristics from the previous EUnetHTA 21 JSC pilot procedures and from the interim parallel EMA/HTAb scientific advice.[6] According to these, questions on post-launch evidence generation (PLEG) are welcomed in conjunction with a discussion on the pivotal study design, but not on their own. Furthermore, some questions that are not within the scope for JCA, such as health economic issues, may still be addressed by HTA assessors in a JSC. Similarly, Quality and Non-Clinical questions, which are also not in scope for a JCA, may be posed as regulatory questions during a Parallel JSC.[3,7]

JSC procedure

According to the HTA regulation[1], the JSC procedure includes a meeting with the health technology developer and results in an outcome document with recommendations. The outcome document of the JSC does not give rise to any legal effects, e.g., in relation to a subsequent joint clinical assessment, for the EU member states, the HTA Coordination Group (HTACG)[2], or for the company. (Article 16)

The EU HTA's internal working processes for JSC and JCA are similar. The HTACG appoints a smaller designated subgroup that in turn selects an assessor and co-assessor from different member states to conduct the JSC with input from external experts, patients, and other members of the designated subgroup, as appropriate. The HTACG then approves the outcome document, which is sent by the EC to the HTD. (Articles 18-19)

The procedure as seen from a company perspective includes the following key steps, also outlined in *Figure 1* below.

Submission

After the request and acceptance of a JSC via the IT platform, the company will submit a dossier with the "information, data, analyses, and other evidence" needed for the consultation. The templates and procedural steps for this will be adopted by the EC via implementing acts after preparation by the HTACG. (Articles 3, 18, 20, 21)

The practical procedure will likely generally follow that of the EUnetHTA 21 consulations[7] and the interim parallel EMA/HTAb scientific advice[3], where an initial check of the preliminary dossier is made by HTA officers (and EMA, if a parallel procedure) in terms of "the scope, wording and clarity of the questions, whether the material provided in the briefing package is sufficient to answer the questions posed, whether all the right questions have been asked or if additional questions should be added, and to consider whether the questions are appropriately addressed to HTAbs, regulators or both".

The HTD then submits a revised final briefing document having addressed the comments and any points of clarification.[3,7]

List of Issues

To facilitate the discussion, the assessors will create a List of Issues (LoI) which is shared with the company prior to the meeting. Written responses to the LoI should be provided by the HTD in advance of the meeting (12 days in advance for HTA issues and 5 days for EMA issues according to the interim parallel procedure). If the LoI triggers major changes to the development plan compared with the final briefing dossier, the new development plan should be submitted as early as possible and by the deadline for responses to the LoI at the latest. A final presentation should also be submitted by the company two days before the meeting.[3,7]

Discussion meeting and outcome document

The discussion meeting between the HTD and the HTA will be interactive and focus on the List of Issues. For parallel JSCs with EMA, divergences between regulators' and HTA's positions on major aspects of the trial design will be discussed, aiming for potential solutions that could facilitate one trial design or at least one development plan.[3]

After the meeting, the company will receive the outcome document with the final EU HTA recommendations.

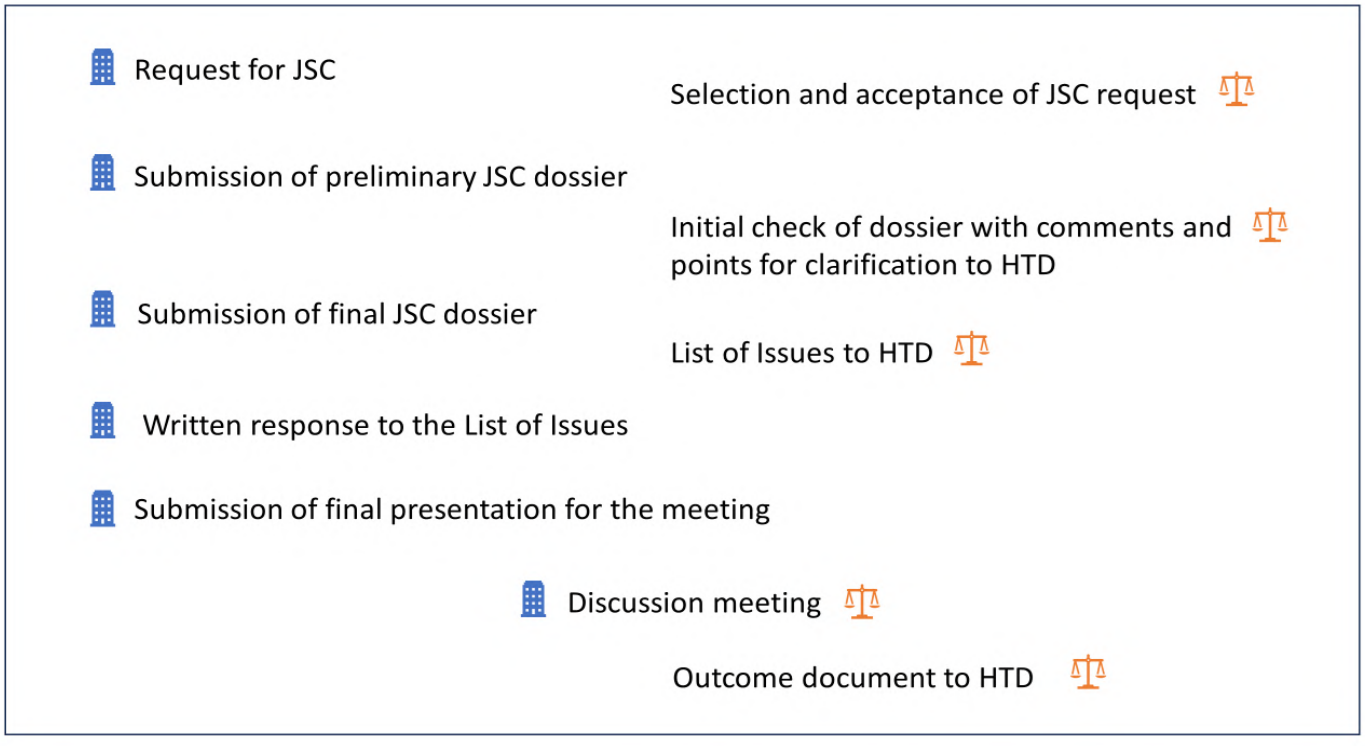

Figure 1: HTD actions are shown on the left (building symbol), EU HTA actions are shown on the right (scales symbol)

Implementing acts

Many practicalities of the HTAR, such as procedural rules, timelines, exchange of information with EMA or expert panels, templates for dossiers and JSC requests are not detailed in the regulation but will be developed by the HTACG and the EC and adopted by means of implementing acts. (JCA: Articles 15, 25-26, JSC: Articles 20-21). The use of implementing acts ensure that the same practices will be applied across the EU.[8,9] A so-called Comitology Committee[10] representing all member states, together with public consultation procedures, will also contribute to the final contents of the implementing acts. The previously contracted EUnetHTA 21 deliverables[11,12] are therefore not to be considered as the final interpretation of how the HTAR will be implemented. The public consultations are opportunities for companies and other stakeholders to provide input on the proposed legal acts. To be prepared for the new regulation, it is highly recommendable to follow the output from the EC, in terms of implementing acts, guidance and other information.

Other preparations

A JSC can be very helpful in relation to a future JCA and the subsequent national HTA procedures, especially when the treatment landscape is relatively stable and the PICOs discussed at the JSC will remain largely relevant at the time of the JCA. A health technology developer cannot rely solely on the consultations with EU HTA, however, but need to proactively consider the payer and HTA data needs, alongside those of the regulators', at all stages of clinical development. This includes horizon scanning and positioning the health innovation in relation to other technologies and unmet medical needs. Evidence generation outside the pivotal trials may be needed for many reasons and purposes. For HTA, in cases where multiple PICOs are expected for the JCA, the pivotal trial(s) may not be able to cover all scenarios and some data may need to be generated or compiled, and analysed, by other means. It is recommended to consider these issues continuously and adaptively during drug and medical device development.

Abbreviations

ATMP	Advanced Therapy Medicinal Product (EU terminology for cell and gene therapy)
CP	Centralised Procedure
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EU HTA	Government employees or processes under the HTA regulation
HTA	Health Technology Assessment
HTACG	Coordination Group on Health Technology Assessment
HTAb	HTA bodies
HTD	Health Technology Developer
HTAR	Regulation on health technology assessment (EU) 2021/2282
IVD	In vitro diagnostic medical device
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MAA	Marketing Authorisation Application
MD	Medical Device
MS	Member State
PICO	Population – Intervention – Comparator – Outcomes

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