CRA Charles River Associates

Prepared For:

EFPIA

Leopold Plaza Building

Rue du Trône 108

B-1050 Brussels (Belgium)

An industry perspective on the current EUnetHTA process for harmonised assessment – real world evidence

Final Report

Prepared By: Tim Wilsdon, Michele Pistollato and Elaine Damato

Charles River Associates

8 Finsbury Circus

London EC2M 7EA

Date: May 2020

CRA Project No. D28967-00

Executive Summary

The European Network for Health Technology Assessment (EUnetHTA) represents one of the most important HTA initiatives funded by the European Union to support high-quality collaboration between European HTA organisations. One of the central activities of EUnetHTA is the production of joint rapid relative effectiveness assessments (REAs) for pharmaceuticals technologies. The development and implementation of EUnetHTA methodology and process to produce REAs has been the result of a collaborative effort of EUnetHTA partners, which also benefitted from the input of the biopharmaceutical industry. Although considerable progress has been made since the establishment of EUnetHTA in 2005, there is still substantial work to be done to guarantee a well-functioning and fair EUnetHTA approach. Based on the feedback from the EFPIA member companies that have participated in recent EUnetHTA REAs, there are 10 high-level recommendations that could make the EUnetHTA framework the reference for joint HTA collaborations. In particular, recommendations regard: the enhancement of process for joint assessments (the need of experienced authors, the systematic involvement of Patient Organisation and clinical experts, more consistency in the approach to scoping meetings, the introduction of a review meeting); the establishment of a framework for confidentiality; the introduction of an issues resolution mechanism; and the improve of the governance (consistency in the authors' approach to the assessment, a consensual agreement to changes to the process, resource allocation and timeline prioritising high-quality joint assessments, a defined process to escalate governance issues). Continued dialogue and collaborations between all the stakeholders can help to ensure that the spirit of these recommendations is reflected in future REAs and that any new potential issues are addressed effectively and efficiently. More importantly, approach developed by EUnetHTA, as it currently stands, does not appear to be sustainable in the long term: many of the limitations noted (e.g. the lack of an issues resolution mechanism) are attributable to the fact that EUnetHTA is lacking of a legal basis – this may be resolved in a permanent system for HTA collaboration.

1. Background and approach

The European Network for Health Technology Assessment (EUnetHTA) was established in 2005 with the aim to create a sustainable European network on HTA.[1] Since its establishment, EUnetHTA has completed two joint actions (JA), JA 1 from 2010-2012 and JA 2 from 2012-2015. One of the main outputs from the first two JAs has been the development, application and implementation of an HTA Core Model for national HTA bodies to produce structured HTA information together (i.e. joint rapid relative effectiveness assessments, REAs or joint assessments), with the ultimate objective to make it applicable in national contexts. In 2016, EUnetHTA launched a third joint action (JA 3), which will run until 2021.[2] The objectives of JA 3 are to increase the use, quality and efficiency of joint

1 EUnetHTA (2018), "EUnetHTA Project (2006-2008)", available at [https://www.eunethta.eu/eunethta-project-2006-2008/]

2 EUnetHTA (2018), "EUnetHTA Project (2006-2008)", available at [https://www.eunethta.eu/eunethta-project-2006-2008/]

assessments by supporting evidence-based choices and the re-use in regional and national HTA reports and activities.[3]

The development and progress of this process have been informed by the input and collaboration from several stakeholders, including the innovative biopharmaceutical industry.[4] Since the latest industry's publications on the experience with EUnetHTA REAs in JA 3,[5,6] there have been 11 new joint assessments of pharmaceutical technologies as of January 2020.[7,8] This paper aims to share the industry experience with the most recent joint assessments and to propose some recommendations to EUnetHTA on how the process could be improved further (Table 1).

Table 1: The EUnetHTA JA 3 assessments considered in this analysis

Product assessed by EUnetHTA / EUnetHTA project ID	Status at the time of this analysis (November 2019)
Sotagliflozin [PTJA04]	**Assessment completed**
Enasidenib [PTJA05]	*Assessment ongoing* *[assessment closed on 12 December 2019 as the product was withdrawn from market authorisation]*
Polatuzumab vedotin [PTJA06]	*Assessment ongoing* *[publication occurred on 13 February 2020]*
Ustekinumab [PTJA07]	**Assessment completed**
Siponimod [PTJA08]	*Assessment ongoing* *[publication occurred on 13 February 2020*

3 EUnetHTA (2018), "JA3 (2016-2020)", available at [https://www.eunethta.eu/ja3-archive/]

4 CRA for EFPIA (2015), "An analysis of the EUnetHTA pilot assessments", available at [https://www.efpia.eu/media/25847/cra-efpia-analysis-of-rapid-rea-pilots-final-report-december-2015-stc.pdf]

5 Hebborn, A., Oberdiek, A., Birkmose, J. C., Gyldmark, M., Ducournau, P., Bahar, N., & Mowbray, K. (2018). OP163 European Network for Health Technology Assessment Joint Action 3 Relative Effectiveness Pilots: Pharma Company Experience. International Journal of Technology Assessment in Health Care, 34(S1), 59-60.

6 CRA for EFPIA (2018), "EU REA – Learnings from the first three EUnetHTA Joint Action 3 assessments", available at [https://www.efpia.eu/media/361736/cra-efpia-learnings-from-the-first-three-eunethta-joint-action-3-assessments-final-report.pdf]

.7 Given that the first JA 3 assessments [PTJA01-02-03] were assessed in a 2018 CRA report for EFPIA (CRA for EFPIA (2018), "EU REA – Learnings from the first three EUnetHTA Joint Action 3 assessments", they are not considered in this analysis. The 11th joint assessment [PTJA11] is for a product marketed by a non-EFPIA member and it is not covered in this analysis. The 13th joint assessment [PTJA13] was officially started by EUnetHTA after 29th October 2019 and no insights could be included in the analysis. The 14th joint assessment [PTJA14] started in January 2020.

8 EUnetHTA (2019), "Assessments REA (2016 – 2020)", available at [https://www.eunethta.eu/rapid-reas/]

Brolucizumab [PTJA09]	*Assessment ongoing* *[publication occurred on 12 March 2020]*
Crizanlizumab [PTJA10]	*Assessment ongoing* *[process initiated in July 2019]*
Glasdegib [PTJA12]	*Assessment ongoing* *[process initiated in October 2019]*

The experience of EFPIA member companies in recent JA 3 assessments has been collected through six structured interviews[9] with a support of Charles River Associates (CRA) under the EFPIA antitrust guidance and ethical principles. Information was gathered on five areas: (1) the process; (2) documentation; (3) confidentiality framework; (4) issues resolution; and (5) governance.[10] The industry has shared the findings from this analysis with EUnetHTA during two meetings on 15 November 2019 and 2 December 2019.

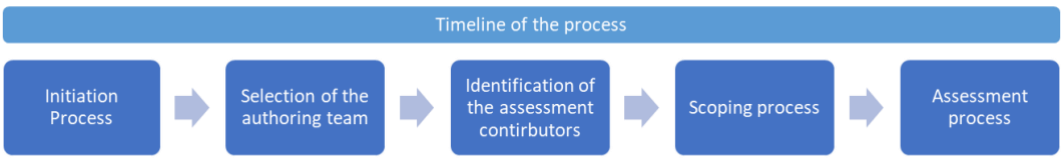
2. Learnings from recent JA 3 joint assessments

The learnings from the recent JA 3 joint assessments are grouped into the five areas discussed in the interviews.

The process

The EUnetHTA process can be analysed through five subsequent stages (initiation, selection of the authoring team, identification of the assessment contributors, scoping process and assessments process), which contribute to determine the timeline of the process (Figure 1).

Figure 1: A schematic representation of the EUnetHTA process



We examine the industry experience for each of the five stages, and their timeline, in turn.

9 This analysis covers eight EUnetHTA joint assessments: as three joint assessments regards three products from the same manufacturer, the feedback from the manufacturer about the three assessments was captured in one interview.

10 There are also other two areas that in the past have been object of the industry feedback: the methodology of the EUnetHTA joint assessments and their use in the national settings. These two areas are also of great importance for the industry and would deserve a dedicated discussion.

Initiation process

Key message: EUnetHTA Secretariat and the Joint Production Pharma Team continue to play a key role to ensure a well-functioning initiation of the EUnetHTA process.

Manufacturers' experience with the initiation of the process for joint assessments is generally positive. Prior to the submission of the Letter of Intent, which formalises the manufacturer's commitment to participate into the joint assessment,[11] the EUnetHTA Joint Production Pharma Team[12] was very responsive and efficient in providing clarifications to manufacturers' questions. Generally, communication was conducted via e-mails, phone calls and teleconference meetings. One manufacturer also had a face to face meeting at Joint Production Pharma Team 's offices in Diemen, the Netherlands. Overall, the communication was clear and helpful, and the Joint Production Pharma Team answered to all the questions in a straightforward way, being transparent about the process unknowns.

The duration of the initiation process (i.e. the timeframe between the first informal contact between the manufacturer and EUnetHTA Joint Production Pharma Team and the submission of the Letter of Intent) varied depending on manufacturers' needs: this ranged between solely two months to one year and a half. Overall, the formal initiation of the process coincided with a manufacturer's regulatory submission to EMA. This timeline is aligned with EUnetHTA guidelines, which indicate that the Letter of Intent should be submitted around Day 0 of the EMA submission.[13]

Selection of the authoring team

Key message: Criteria to select author and co-author based on their experience do not seem to be systematically prioritised across the joint assessments.[14]

Once the process initiated, the authoring team (author and co-author) was communicated to the manufacturer (between two weeks to a month from the submission of the Letter of Intent) in a timely fashion. The criteria for the selection of the assessment team have recently been published by EUnetHTA (Table 2).

Table 2: Criteria for the selection of the authoring team

How does EUnetHTA select an assessment team?
Commitment to use the EUnetHTA Assessment in the national setting. Deviations from this criterion might occur if specific skills (for example for dedicated reviewers) are required.
Expertise/knowledge of the disease area and the drug/medical device should be available within the authoring team.
Experience with and understanding of EUnetHTA procedures, tools, and methodology should be available to the authoring team.

11 EUnetHTA website: https://eunethta.eu/services/submission-guidelines/pharmaceutical-submission/

12 EUnetHTA website: https://eunethta.eu/about-eunethta/organization/the-secretariat/

13 EUnetHTA (2018), "Submission FAQs for Industry – Pharmaceuticals", available at [https://www.eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/]

14 Recommendation 1 in Section 3 could help addressing this issue.

Available skills and experience from previous Joint or Collaborative Assessments within the authoring team. Ideally, at least one agency within the authoring team should have experience with previous EUnetHTA Assessments.
Availability during suggested timelines.
No conflict of interest of participating persons (following JA3 DOI procedure).
Sufficient amount of person months in budget / willingness of agency to use local budget for production.
A geographical spread of the authoring team throughout Europe.

Source: EUnetHTA website[15]

However, at the time of the initiation of the JA 3 assessments presented in this analysis, the criteria used to select the author and co-author have not been discussed with the manufacturers. From manufacturers' experience, their choice at times mirrors EMA's choice of the rapporteur and co-rapporteur, whereas in other instances the author and co-author are from Member States which have a high prevalence of the disease (for which the asset is indicated for) or appear to be related to national HTA bodies' availability (in one instance the author was changed after the scoping meeting due to the initially selected author no longer having enough capacity to continue the assessment). In one case the selection of the author and co-author was dependent on the manufacturer's launch plan. Overall, authors and co-authors represent a variety of EUnetHTA Work Package 4 Partners (Figure 2).

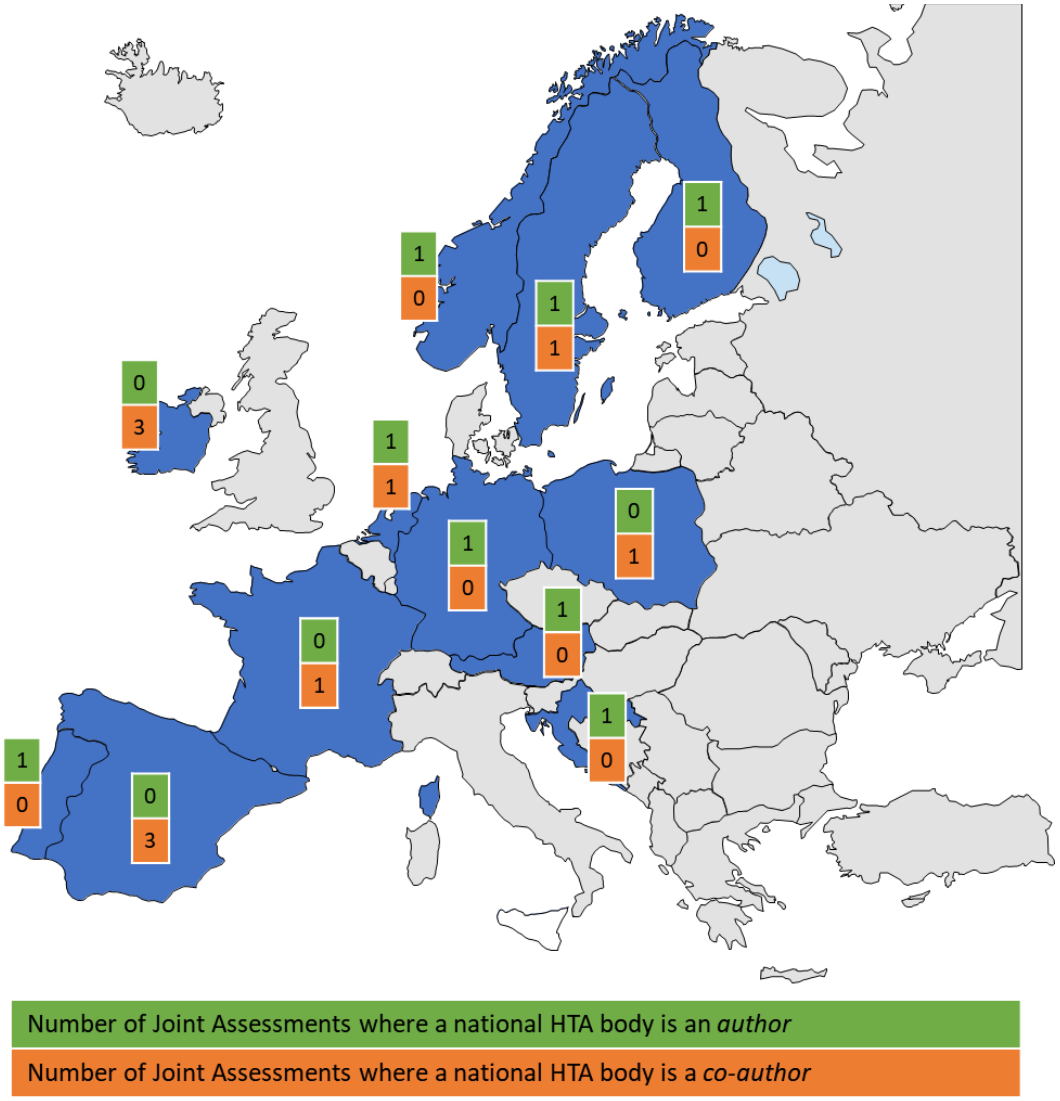
This experience seems to partly mirror the EUnetHTA criteria (as set in Table 2), however manufacturers have expressed some concerns about the "experienced author criteria"[16] not being prioritised, as this can potentially affect the quality of the assessment. In one assessment, this issue was partly rectified as a third author was added after the scoping meeting to bring more expertise to the assessment team (however, this change occurred too late in the process).

In term of clarity of the roles, EUnetHTA clearly communicates the roles of the author, co-author, dedicated reviewers and observers to the manufacturers. However, there were variabilities across the different joint assessments regarding the manufacturers' understanding of the roles and identities of the information specialists and statistical specialists involved in the assessment team. Generally, the manufacturer got to know whether information and statistical specialists were involved in their assessment from the draft Project Plan shared one or two weeks prior to the face-to-face Scoping Meeting.

15 EUnetHTA website: https://eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/

16 That is, "expertise/knowledge of the disease area and the drug/medical device should be available within the authoring team" and "experience with and understanding of EUnetHTA procedures, tools, and methodology should be available to the authoring team". Also in the EUnetHTA wording, this two criteria seem to be an ideal but not necessary requirement.

Figure 2: Authors and co-authors of the recent JA 3 joint assessments analysed in this study



Source: Authors analysis of the eight JA 3 joint assessments considered in this study

Identification of assessment contributors

Key message: Patient organisations and clinical experts do not seem to be systematically involved throughout all the joint assessments.[17]

Other project contributors are involved in the EUnetHTA joint assessments: the EUnetHTA Project Manager and Senior Scientific Officer, external expert(s),[18] Patient Organisations and a Medical Editor. Manufacturers involved in recent JA 3 joint assessments provided

17 Recommendation 2 in Section 3 could help addressing this issue.

18 The recommendations for the involvement of healthcare professionals in joint assessments have recently been published by EUnetHTA: https://eunethta.eu/wp-content/uploads/2020/04/Final_HCP-Involvement-in-EUnetHTA-assessments.pdf

their main feedback regarding the involvement of Patient Organisations and external experts.

In terms of patient organisations, these were involved in all the recent JA 3 joint assessments through an open call. In the open call, EUnetHTA "*asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment.*"[19] In almost all the circumstances, the manufacturers were asked to contribute and contact the Patient Organisations they recommended to involve.

The feedback provided by Patient Organisations is expected to feed into the Population, Intervention, Comparator and Outcome ("PICO") discussed at the scoping meeting (an example of the Patient Organisation input is illustrated in Table 3). However, throughout the process, overall the industry view is that EUnetHTA was generally not communicating in a clear manner which Patient Organisations have participated to the open call and on the type of feedback they provided. This information is instead made available when the documentation (i.e. the project plan and the assessment report) is published.

Table 3: Elements of the assessment scope of siponimod for SPMS that uses feedback provided by patient organisations[20]

Description	Assessment scope	Source
Clinical effectiveness outcomes	Confirmed Disability Progression at 6 months	Outcomes that are related to issues particularly **emphasised by Patient Organisations**
	Other measures of Disability Progression	
	Symptoms	
	Health-Related Quality of Life	
Safety	Adverse events	

For some of the joint assessments, EUnetHTA has been in contact with clinical experts to gather a deeper understanding of the diseases. However, external experts could not be systematically involved in all the assessments. Given that EUnetHTA considers clinicians which have collaborated with the manufacturer or other pharmaceutical companies as having a potential conflict of interest, the pool of clinical experts that can be selected is limited (particularly for rare disease). As a consequence, the industry participants have

19 EUnetHTA (2019), "Siponimod for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity", available at [https://eunethta.eu/wp-content/uploads/2019/11/PTJA08-siponimod-Project-Plan-Final.pdf]

20 EUnetHTA (2019), "Siponimod for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity", available at [https://eunethta.eu/wp-content/uploads/2019/11/PTJA08-siponimod-Project-Plan-Final.pdf]

concerns about the conflict of interest criteria set out by EUnetHTA[21] being too restrictive and about the risk of the most acknowledged experts in a specific disease area not being consulted.

Scoping process

Key message: Scoping is a key stage in process and there is no harmonised approach to a scoping meeting and no common understanding of what a PICO is/should be.[22]

A key stage in the EUnetHTA process is the face-to-face scoping meeting. In general, manufacturers were asked to submit the Scoping Document (highlighting their proposed PICO for the joint assessment) one month prior to the scoping meeting.[23] EUnetHTA initially attempted to share their draft Project Plan (which includes EUnetHTA's proposal for the PICO, reflecting a survey between EUnetHTA partners) two weeks in advance of the scoping meeting. In later assessments, the draft Project Plan was provided one week prior to the scoping meeting and the manufacturers found the timeline for them to prepare to be tight. However, in general, the guidance that manufacturers receive prior to the scoping meeting was reported as sufficient.

The scoping meeting happened face to face and generally was scheduled two to three months prior to the estimated date of the CHMP opinion.[24] Although the scoping meeting was expected to last about three hours and allow a meaningful discussion of the PICO and the methodology of the assessment, in certain instances the scoping meeting was not reported as sufficiently comprehensive. For instance, in one case, a new author had been added to the assessment team (but not early enough to be present at the scoping meeting): therefore, the discussion at the scoping meeting was not able to cover the technical aspects of the assessment the new author would have been responsible for, and a second scoping meeting (via teleconference) was required to onboard the new author.

According to EUnetHTA, the objective of the scoping meeting should be focused on discussing the PICO, the statistical methods for presenting the data (e.g. Network Meta-Analysis) and the information the authoring team (author and co-author) requires in the Submission Dossier.[25] In general, the PICO presented by authoring team at the scoping meeting was based on the responses to the PICO survey between EUnetHTA partners (and potentially reflect the feedback received by Patient Organisations, although this latter aspect was not always communicated clearly). There seems to be variability in the approach to discussion of the PICO between different authors. In some circumstances, there was an open discussion about the PICO and the need to adapt the approach to the scientific challenges of specific technologies. Some manufacturers reported satisfaction

21 EUnetHTA's criteria are available at: https://eunethta.eu/wp-content/uploads/2019/11/EUnetHTA-Procedure-Guidelines-DOI.pdf

22 Recommendation 3 in Section 3 could help addressing this issue.

23 Across the JA 3 assessments, there have been differences between the Scoping Documents requested to manufacturers (this point is discussed in the "Documentation" section below).

24 EUnetHTA (2018), "Submission FAQs for Industry – Pharmaceuticals", available at [https://www.eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/]

25 EUnetHTA website: https://eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/

that they were aligned with the authoring team on a scientifically strong PICO. In other circumstances, the discussion was not very informative of the submission (requiring subsequent discussions), there was limited space for discussion or some of the outcomes from the discussion were not implemented in the final assessment. In a few instances, the manufacturer also perceived that the chosen PICO lacked a strong scientific rationale (in particular, in one case it appeared that the authors did not sufficiently familiarise themselves with the Scoping Document prior the meeting and this could have limited the discussion about the PICO).

Assessment process

Key message: The lack of a review meeting can undermine the quality of the joint assessment reports.[26]

Although by the time of this analysis only a subset of products went through the assessment phase, all manufacturers agreed on some procedural aspects of the assessment process as currently designed (in particular, regarding the interaction among the manufacturers, the assessment contributors and assessment team).

During the assessment phase, the manufacturer can only communicate with the authors via e-mail (through the EUnetHTA Joint Production Pharma Team). Communication mostly regards clarification questions from the assessment team and responses from the manufacturers. In the experience of the manufacturers, e-mail communication was not suitable for addressing complex cases and more facilitated discussions between the manufacturer and the assessment team would have contributed to a more robust output from the assessment (for instance, in the EMA regulatory approval process, there is the possibility for a presentation and question-and-answer session in person between representatives of an applicant for the marketing authorisation and a EMA committee).[27]

Manufacturers also highlighted that the current EUnetHTA process lacks an official meeting to review and redact the draft assessment between the authors, the manufacturer, Patient Organisations and external experts. Such a review meeting would provide all stakeholders the opportunity to interact and provide feedback (in person), resulting in a more robust and scientifically accurate assessment.

Timeline of the process

Key message: The overall alignment with EMA is a success in JA 3 but can still be improved.[28]

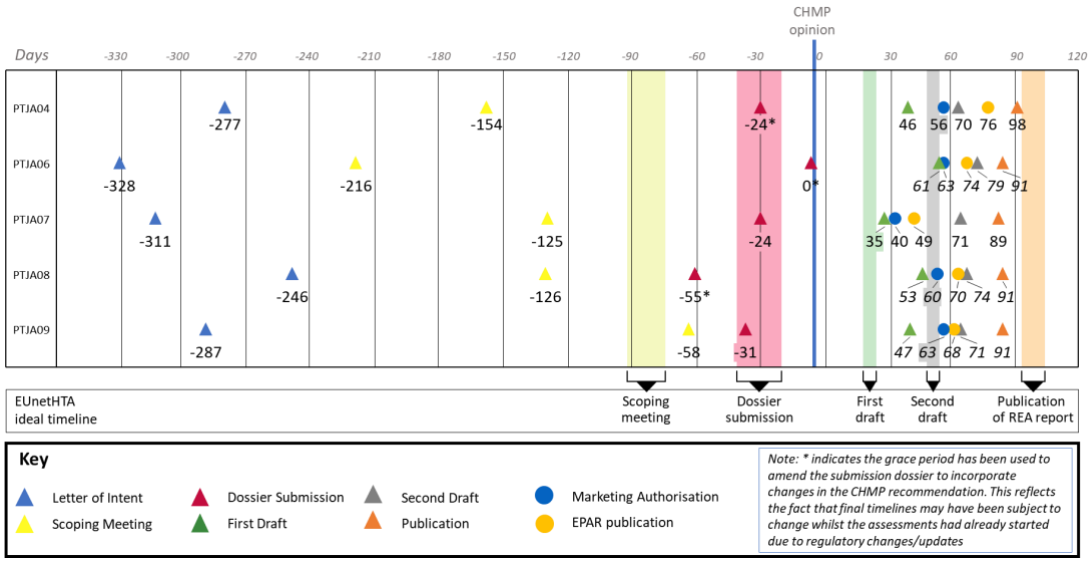
The alignment of the EUnetHTA timeline with EMA milestones was generally maintained (Figure 3).

26 Recommendation 4 in Section 3 could help addressing this issue.

27 EMA website: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance#5.1-procedure-section

28 Recommendation 9 in Section 3 could help addressing this issue.

Figure 3: Timeline of recent JA 3 joint assessments



Source: Authors' analysis of EUnetHTA's available Project Plans

The EUnetHTA process aimed to be flexible enough to adapt to accelerations or delays in the publication of the CHMP opinion and was generally able to extend the timeline if the CHMP opinion provided a change in the indication. For example, in one instance the CHMP opinion was available almost two months earlier than originally planned and EUnetHTA process adapted accordingly. Flexibility was also required for the scheduling of the scoping meeting, whose timeline varies considerably across the assessments as the exact EMA regulatory timeframe is difficult to predict.

However, this experience was not consistent across all the joint assessments. In one occasion, the EUnetHTA process was unable to adapt to accelerated EMA timelines (and the REA report was published more than one month after the EPAR publication so EUnetHTA's target of publishing REA within two weeks of the EPAR publication was not met).[29] In another instance, when managing uncertainty about the EMA timeline, the assessment team proved to be inflexible and asked the manufacturer to provide the submission dossier according to the timeline originally scheduled even though there was an expectation for the CHMP opinion to be delayed (making potentially necessary for the manufacturer to re-write and re-submit the dossier in case the CHMP recommended label would have been different from the one initially planned). In one case, the manufacturer has been asked to submit the dossier two months prior the CHMP opinion despite it was previously agreed that the dossier would be submitted closer to the CHMP opinion.

Documentation

Key message: There is a need of more transparency about documents used and clear rules around piloting new documents.[30]

29 EUnetHTA (2018), "Submission FAQs for Industry – Pharmaceuticals", available at [https://www.eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/]

30 Recommendation 8 in Section 3 could help addressing this issue.

EUnetHTA has developed (and is still developing) templates for the joint assessment process. The main templates are: the Letter of Intent, the Scoping Document and the Submission Dossier.[31] Manufacturers reported issues with the guidance provided and on the process for the development of new templates.

Overall, EUnetHTA has been flexible in dealing with manufacturers' suggestions to complement the information in the templates, especially in the submission dossier. From a manufacturer's perspective, this attitude has been positive because the possibility to include additional sections helped to improve clarity and quality of the data. For instance, in one case the manufacturer was able to include Real World Evidence even if the original submission template did not provide for this.

There has been variability and inconsistency in the guidance for the use of the documentation (especially for the Letter of Intent and the Scoping Document). For instance, in one case the Letter of Intent appeared too information demanding (and partly overlapping with the Scoping Document). In another case, the manufacturer was told that that they are not required to submit the Scoping Document if they did not have any significant new evidence to that presented in the Letter of Intent.

The templates to be used throughout the process were generally indicated prior the initiation of the process. Regarding the Submission Dossier, the indications were to use the short version of the evidence submission template also available in the EUnetHTA website. This has been a potential source of confusion, as for a period there have been two different versions of the submission template on the EUnetHTA website (however this issue has been rectified after a few weeks).[32,33] Moreover, in two cases, late in the procedure, during the scoping phase, the manufacturers were requested to use a different template than that initially shared by EUnetHTA Joint Production Pharma Team. Eventually, in all the assessments, the final submission template was based on the template available on the EUnetHTA website (as it was able to accommodate the specifics of the product).

The confidentiality framework

Key message: There is no confidentiality framework in place with the manufacturers and this could significantly reduce the information that can be shared and the quality of the assessments.[34]

Throughout the joint assessments conducted so far, there was no confidentiality framework in place between EUnetHTA and the manufacturer. Moreover, currently, there is no formal process for redacting confidential information within the EUnetHTA joint assessment report.

Up to 2018, manufacturers could include confidential information in the annexes to the Submission Dossier, and the information included there would not have been disclosed.

31 The Letter of Intent (https://eunethta.eu/wp-content/uploads/2018/11/WP4-T01_Letter_of_Intent_15_04_2018-V1-1.dotx) and the Submission Dossier (https://eunethta.eu/services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/) are available in the EUnetHTA website. The Scoping Document is currently under development and not yet publicly available.

32 EUnetHTA website: https://eunethta.eu/services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/

33 EUnetHTA website: https://eunethta.eu/services/submission-guidelines/pharmaceutical-submission/

34 Recommendation 5 in Section 3 could help addressing this issue.

However, through a process amendment introduced in December 2018, information included in the annexes can freely be quoted by the assessment team in the published REA report.[35] This rule was introduced to increase transparency and to increase the usability of the REA, however, it has implications for academic and commercial confidentiality (i.e., the public disclosure of the information could have an impact on ability of a clinical study authors to publish the results in an academic journal or undermine the commercial interests of the manufacturers). Due to this, manufacturers are hesitant on sharing any confidential material with EUnetHTA. For two joint assessments, this change occurred while the assessment process was ongoing, and manufacturers reported that they were not informed adequately, leading to subsequent issues. In one instance, the draft joint assessment report contained commercial- and academic-in-confidence information which was removed upon request of the manufacturer, who preferred to consider that information as "not provided" rather than having it disclosed. However, in the report the authors replaced the data that was removed by phrases such as "no formal assessment […] was included in the submission dossier" or "the authors are concerned that the results […] may be statistically significantly worse […] if [a] model were to be used" – which was felt to be misleading.

Issues resolution

Key message: Fact-checking is optional and there is no issues resolution mechanism.[36]

Approximately three weeks prior to publication of the joint assessment, there is a possibility for the manufacturer to do a factual accuracy check of the draft assessment, i.e. the manufacturers can make sure that the factual information in the joint assessment regarding their product is correct.[37] However, the fact-checking process appears to be optional (i.e. left to the discretion of the authoring team) while in the manufacturers' view it should systematically occur in each assessment.

Moreover, beside the fact-checking opportunity, all manufacturers expressed concern that EUnetHTA does not have an issues resolution mechanism in place. This means that if there are conflictive views on the final report, or errors or misinterpretations have not been addressed in an effective way, these issues would remain unsolved. Similar to the EMA re-

35 "To support the production and transparency of the assessment of the pharmaceutical product, the assessment teams are free to cite and transcribe information from the entire Submission Dossier, including information on methods and results of Clinical Study Reports from the attachments to the Core Submission Dossier." Pharmaceutical Joint Assessments – Submission requirements. Available at: https://eunethta.eu/wp-content/uploads/2019/09/EUnetHTA-submission-requirements-V2.pdf

36 Recommendation 6 in Section 3 could help addressing this issue.

37 EUnetHTA website: https://www.eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/

examination procedure, an issues resolution mechanism within the EUnetHTA process would provide a better guarantee for manufacturer's rights).[38,39]

However, there is recognition that, even if an issues resolution mechanism would be used in rare occasions, in these circumstances it might significantly impact the timeline EUnetHTA aim for. Therefore, its introduction should be considered carefully and result from a collaborative discussion between the EUnetHTA partners and the industry in order to implement a process that is both effective and efficient.

Governance

Key message: The current system of rules does not guarantee consistent approaches across the different assessments. Moreover, rules about transparency and implementation of changes appear to be disproportional for the manufacturers. There is also a need for EUnetHTA rules to prioritise high-quality reports. All these governance issues could be addressed by a third-party bridging EUnetHTA's and manufacturers' needs.[40]

In the vast majority of the cases, the EUnetHTA Joint Production Pharma Team was perceived to be doing its best to improve the EUnetHTA process, with the intention of achieving high-quality joint assessment reports. Many of the issues described above are seen as resulting from issues associated with governance.

The approach to transparency appeared still to be a work in progress and there appears to be disproportion between EUnetHTA's requests for transparency and EUnetHTA's disclosure of information. Good governance should promote transparency - overall, EUnetHTA is aiming to maximise the transparency of the process to non-industry stakeholders - but should recognise that there are situations where requesting transparency from manufacturers is problematic (e.g. when authors can quote confidential information from the appendices in the EUnetHTA joint assessment report) and situations where not being enough transparent to manufacturers can be detrimental to the efficiency of the process (for instance, the manufacturers will get to know the Patient Organisations that have participated in the open call and their input - or lack of input - through the draft joint assessment report late in the process: if this information is known earlier in the

38 EMA website: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-re-examination-chmp-opinions_en.pdf

39 In the EMA re-examination procedure, a manufacturer applying for the marketing authorisation can request a re-examination of the EMA CHMP's opinion within 15 days of receipt of the notification of the CHMP opinion. In that case, the applicant shall forward to EMA the detailed grounds for the request within 60 days after receipt of the opinion. The re-examination looks only at the points raised by the applicant in the grounds for appeal and is based only on the scientific data available when the CHMP committee adopted the initial opinion – in other words, the applicant cannot bring in new evidence at this stage. The applicant may request that the committee consults a scientific advisory group in connection with the re-examination. If an expert group was already consulted during the initial evaluation, different experts will be involved in the re-examination.

40 Recommendations 7, 8, 9 and 10 in Section 3 could help addressing these issues.

process, the manufacturer could try to provide further support to stimulate the participation of Patient Organisations to ensure their view is captured).[41]

The governance of how any changes to the existing process are implemented needs to be improved. In various instances there were attempts to implement unilaterally changes to the process after the assessment has been initiated. For instance, in one instance, an attempt to introduce new templates (e.g. submission dossiers for piloting) was made without discussing and agreeing this with the manufacturer who decided to participate to the joint assessment under the understanding that the existing template was being used.

The guiding principles regarding the timeline need to be articulated. It is beneficial for all that there are process rules that dictates a strict timeline for the assessment phase. It is also valuable to align with the EPAR publication, but the trade-off between a hard deadline for the EUnetHTA report and a flexibility of one or two weeks to allow the best possible standard needs to be considered. In general, flexibility in the assessment process is required for the development of high-quality reports, which would improve the report usability at national levels. A lower quality (for instance, because not all the available evidence has been captured and assessed adequately), results in a *de facto* diminished use of the EUnetHTA reports in the national context

There needs to be rules on how to escalate concerns about the process. In most cases, the EUnetHTA Joint Production Pharma Team seemed to seek negotiation with the assessment team to address issues arising from a process under development. However, no specific rules on when it is appropriate to escalate an issue and to whom to escalate the issue to.

3. Industry recommendations for future EUnetHTA JA 3 joint assessments

Based on the feedback provided by the EFPIA member companies that have participated in JA 3 joint assessments, the EUnetHTA process could be improved to ensure a robust and consistent process. In particular, the industry has developed 10 recommendations to ensure a better experience to all the participants in the EUnetHTA process and, more importantly, guarantee all the EUnetHTA reports are consistently of a high-quality standard (Table 4).

Table 4: Industry recommendations for future joint assessments

Recommendations regarding the process of joint assessments
Recommendation 1: An experienced author involved to each assessment team. To ensure a high-level quality of the joint assessments, an experienced author should be involved in each assessment. This would guarantee an appropriate level of confidence and expertise in utilising the advanced REA methodologies developed by EUnetHTA. The assessment team should consistently commit adequate resources throughout the whole process.

41 Another example is represented by the fact that the Project Plan presented to the manufacturer prior to the scoping meeting is not final and the final version is available to the manufacturer only at the time of the CHMP opinion. If changes to the draft Project Plan occurs before it is finalised (e.g. statistical experts become unavailable or are not involved), the manufacturer could provide their support to address emerging issues.

Recommendation 2: The systematic involvement of patient organisations and external clinical experts. Patient organisations and external clinical experts should systematically be involved in all the joint assessments. Their input should be considered in both the scoping and the assessment phase in order to maximise the quality of the joint assessments. There should be transparency on the criteria for their selection and on how their input is considered in all the steps of the process.
Recommendation 3: A consistent approach across scoping meetings. There should be a consistent approach to the scoping meeting, with the possibility for the manufacturers to discuss with the authors the elements of the PICO and the best methodology for the assessment. It should be responsibility of the authors to ensure that the resulting PICO is supported by strong scientific evidence and any decisions taken in the scoping phase should be taken forward throughout the assessment process. More facilitated communication between the manufacturer and the assessment team would help to expedite the process.
Recommendation 4: The introduction of a review meeting. There should be a review meeting for manufacturers, patient organisations and clinical experts to discuss the draft report with the assessment team. The factual accuracy check process should be a mandatory process step in all future assessments.
Recommendations regarding the confidentiality of joint assessments
Recommendation 5: Setting up a EUnetHTA framework for confidentiality. There should be a framework regarding confidentiality before the assessments start. This would ensure that the best and most relevant evidence is included in the final joint assessment, increasing their quality and reducing the need for subsequent integration of evidence (and, ultimately, maximising their use).
Recommendations regarding the resolution of issues in the assessment phase
Recommendation 6: The introduction of an issues resolution mechanism. The introduction of a systematic mechanism for issues resolution should be considered (as last-resort) to increase the rigour of the assessment phase and its outcome whilst demonstrating that the process is impartial and that the assessment team is accountable.
Recommendations regarding the governance
Recommendation 7: The adoption of a consistent approach across all the assessments. A consistent approach should be used for all the assessments: this should be based on an agreed European approach based on EUnetHTA methodologies capable to adapt to the scientific challenges posed by different technologies. Different national authors should be able to come to the same conclusions.
Recommendation 8: Consensual agreement to changes to the EUnetHTA process. If there is a need to adapt approaches, this should be agreed prior to starting the assessment based on discussions with the industry and agreed with the manufacturer participating to the assessment.
Recommendation 9: Resources allocation and EUnetHTA timeline prioritising high-quality joint assessment reports. The timeline and resource allocation for the joint assessments should allow for a high-quality report. The industry shares the objective to have timely publication that is aligned to the regulatory process. The process timeline should automatically adapt to changes in the timeline of the regulatory process. There should be a facilitated discussion with the assessment team about the circumstances where flexibility in the timeline could increase the quality of the report: this

would ultimately benefit the overall quality of the final assessments and support their use in national settings.
Recommendation 10: A clearly defined process for escalation of process issues. A clear set of rules to escalate and resolve process issues would be beneficial to all the stakeholders.

Finally, a key result from the EUnetHTA JA 3 is whether the joint assessments are used in a meaningful way in the national settings. Due to the timelines of this analysis (most of the JA 3 joint assessments were not completed, or were finalised only a few months earlier, at the time of this research), it was not possible to assess the use of the EUnetHTA reports from an industry perspective.[42] However, this should be the objective of subsequent analysis.

42 In November 2019, EUnetHTA published a report analysing the implementation of joint assessments from their perspective (https://eunethta.eu/wp-content/uploads/2019/12/Implementation-Report-Nov-2019_Final-27112019-for-Internet.pdf).