EUnetHTA-EFPIA Technical Meeting

Tuesday 5 December 2017 – 12.30 to 17.30 (CET)
Haute Autorité de Santé (HAS), 5 Avenue du Stade de France, 93210 Saint-Denis, France

	List of participants
Chairs	Wim Goettsch, ZIN and Ansgar Hebborn, EFPIA & Roche
Present	EUnetHTA: Michelle Mujoomdar, ZIN, Anne Willemsen, ZIN, Steve Estevao, ZIN, Marcus Guardian, ZIN, Ali Hussain, ZIN, Ingvil Sæterdal, NIPHNO, Marianne Klemp, NIPHNO, Sara Couto, INFARMED, Pilar Martin Vivaldi, NoMA, Beate Wieseler, IQWIG, Nick Crabb, NICE, Anna Nachtnebel, HVB, Tuomas Oravilahti, FIMEA, Agnese Cangini, AIFA, Anna Strömgren, TLV, Hannah Brühl, GBA, Prof. Dominique Le Guludec (President), HAS, Chantal Bélorgey, HAS, Chantal Guilhaume, HAS, François Meyer, HAS, Margaret Galbraith, HAS, Anne D'Andon, HAS, Judith Fernandez, HAS. EFPIA: Tina Taube, EFPIA, Sylvie Duclaux, Servier, Louise Timlin, Lilly, Nicole Kubitz, Johnson & Johnson, Patrick Hopkinson, BMS, Aikaterini Fameli, GSK, Milena Richter, Sanofi, Adam Parnaby, Celgene, Jan Oltvoort, NL/ Innovatieve Geneesmiddelen, Karolina Antonov, Sweden/ LIF, Thomas Borel, France/LEEM, Andrew Miniuks, ABPI, Gabriele Kapfer, Bayer, Jeremie Westerloppe, Bayer, Santiago Moreno, Novartis, Gesa Pellier, Novartis, Andre Oberdiek, Roche, Christoph Hoyle, AstraZeneca. EMA: Michael Berntgen EC: Ioana-Raluca Siska

Description	Name(s)

Welcome, introductions, and adoption of agenda
• Welcome by HAS
• Introduction of meeting Co-chairs
  ○ Wim Goettsch, EUnetHTA
  ○ Ansgar Hebborn, EFPIA
• Tour de table
	Wim Goettsch & Ansgar Hebborn

WP4 – Joint Production • Completed and proposed changes to the joint REA procedure • Feedback from companies participating in the on-going REAs • Facilitated Discussion	EUnetHTA: Ingvil Sæterdal & Anne Willemsen EFPIA: Gesa Pellier Pilot specific: Andre Oberdiek, Santiago Moreno, & Jeremie Westerloppe Tina Taube & Michelle Mujoomdar
• Anticipated use of joint REAs at a national level: examples from authoring agencies • Facilitating company participation in EUnetHTA JA3: an EFPIA perspective • Facilitated Discussion	EUnetHTA: Anne d'Andon (HAS), Pilar Martin (NoMA) & Anna Strömgren (TLV) EFPIA: Adam Parnaby Tina Taube & Michelle Mujoomdar
Break	
WP5 – Evidence Generation • Update on WP5B • Update on Early Dialogue (ED) procedure • EUnetHTA rapporteur's perspective on ED procedure • Feedback from EFPIA on experience with EDs in JA3 (Multi-HTA and Parallel Consultation) • Facilitated discussion	François Meyer François Meyer Hannah Brühl EFPIA: Gabriele Kapfer Tina Taube & Michelle Mujoomdar
EC update	Ioana Siska
Summary of decisions, actions, and closing remarks	Wim Goettsch & Ansgar Hebborn

Welcome, introductions and adoption of the agenda

This was the 2nd technical meeting between EUnetHTA and EFPIA over the course of EUnetHTA Joint Action 3.

The agenda was compiled based on input from EUnetHTA and EFPIA and has been adopted by both parties.

WP4 – Joint Production

Completed and proposed changes to the joint REA procedure

WP4 presented the objectives of WP4, which include the production of joint assessments and to refine the production processes of jointly produced assessments based on lessons learned from JA2. WP4 also aims to facilitate the uptake of joint assessments in national and local practice. To date, two Joint Assessments have been published−Midostaurin and Regorafenib and the publication of the third JA is expected in January 2018.

In the current process−and only for an initial marketing authorisation application−the EUnetHTA process is in parallel with the EMA procedure. WP4 reiterated that as per the current procedure, the assessment phase can only begin once the final submission file has been submitted by the manufacturer of the technology under assessment.

WP4 presented the feedback process, which includes a survey sent out after publication of the Joint Assessment to both, the assessment team and the manufacturer of the technology under assessment. In addition, a face-to-face meeting with authors and co-authors of the first two Joint Assessments was held during the assessment phase, to gather feedback without waiting until the end of the assessment phase. Outcomes from this were discussed at WP4 partner F2F meeting in September 2017.

WP4 highlighted the proposed changes to the Joint Assessment process. The proposed changes are based on a EUnetHTA WP4 pharma perspective and to date, do not include feedback from manufacturers. The main proposed change is the exclusion of the need to submit a draft submission file. With this change, the Letter of Intent should be more extensive. WP4 Pharma will make changes to the Letter of Intent template. In addition, in order to publish timely Joint Assessment reports, EUnetHTA will need to receive the submission file prior to the CHMP opinion. If there are unanticipated changes in the CHMP opinion, changes/updates to the EUnetHTA submission file will be permitted. The scoping phase and scoping F2F meeting will be focused on the PICO. WP4 will continue to ask authors and co-authors to prepare slides for the scoping F2F meeting describing how they plan on using the Joint Assessment report within their national HTA processes. WP4 has also started to update the assessment report template in order to enhance the readability of the final Joint Assessment report and will explore changes to the current processes of involvement of experts and patients.

WP4 presented the various tools and templates that are used throughout the Joint Assessment process and highlighted collaboration with WP6 on quality management regarding the development of SOPs WP4 confirmed that any changes to the process will be implemented when a next letter of intent is received.

Feedback from companies participating in the on-going REAs

EFPIA shared observations from the first three assessments and presenting, from their perspective, eight key improvement targets including those which EUnetHTA has met and those which haven't been met. One of the issues mentioned was the fact that it is not always clear what the role of the dedicated reviewer is with respect to their contribution and the use of the report in their national setting. In general, EFPIA would like to see a greater commitment to encourage the use of produced reports.

There is a need for a policy document describing what information is treated as confidential by EUnetHTA. This would facilitate discussions within companies and allow participating companies to share requested data/information with EUnetHTA in a timely manner. In addition, a platform or a software solution to share the information, rather than e-mail/file transfer, should be investigated. Flexibility in the procedure by EUnetHTA is welcomed; however, EUnetHTA should be more transparent regarding where in the process EUnetHTA is willing to show flexibility. Greater transparency regarding the author selection criteria would also be valuable and again, the role of dedicated reviewers could also be clarified further. Further suggestions included a structured approach to the inclusion of external experts, patients, and an increased consideration of EMA process timelines.

Some emerging or unresolved challenges include issues related to methodology and uptake/use in the national settings.

Novartis
Novartis shared from their perspective, what is going well, as well as what needs to be improved, and what will make JA3 succeed. The dialogue with the WP4 coordinator as well the rapid REA model and the REA processes are described as positive factors. Areas for improvement include the need for EUnetHTA to elaborate on their policy on handling of confidential information with a view to facilitating the provision of data to EUnetHTA by participating companies. Novartis believes the success of JA3 depends on the extent of REA adoption across Europe as well as a more active role for WP7 to encourage HTA agencies to adopt the REA reports.

Roche
Roche proposed keeping the current working style and atmosphere of EUnetHTA/WP4 coordinating team, particularly the flexibility along the process, as well as maintaining the inclusion of type II variations as REA pilots. Roche also believes that EUnetHTA needs to finalise and update the user manual and provide rationale for data citation requests.

Bayer
The overall experience from Bayer was reported. The WP4 coordinating team was found to be highly collaborative as well as being excellent at communication and provided effective coordination. Bayer also found the F2F scoping meeting very useful as it allowed the development of a shared understanding of the scope. Bayer recommended that EUnetHTA ensures that report conclusions reflect all HTA bodies involved as well as ensure stakeholder engagement from clinical experts and patient representatives is incorporated. Finally, the process could be improved if EUnetHTA permit a dialogue between pharmaceutical companies, in particular during the period in which the companies are providing feedback on the draft report.

General Discussion

WP4 thanked EFPIA and the individual companies for their feedback. It was noted that some of the input/suggestions are already being taken on board.

On the issue of confidentiality raised by EFPIA, IQWiG questions the confidentiality arrangements within EUnetHTA as in many European countries, including Germany, it is a legal requirement to publish all documents associated with a report. EFPIA clarified that the objective of such a policy would not be to limit the publication of data, but rather to facilitate provision of requested data to EUnetHTA in a timely manner.

EFPIA reiterated that the EUnetHTA guidelines should be enforced. Novartis noted that two important methods topics were missing from the list of EUnetHTA guidelines. These topics refer to the reporting of indirect treatment comparisons and how to handle single-arm studies. Novartis recommended EUnetHTA to develop its own guidelines to cover both topics or alternatively adopt published “best practice” guidelines.

The need to update the EUnetHTA guideline on indirect treatment comparisons has been recognised by WP4 and has been referred to WP6B. Regarding guidelines for handling single-arm trials, EUnetHTA responded that these kinds of trials are not adapted for a REA which includes relative effectiveness assessment and requires comparative data. EFPIA considers this as a topic for discussion as for some products it might be of relevance.

With respect to feedback regarding criteria for authors, the WP4 LP shared criteria that have been developed for author selection. WP4 stressed the importance of uptake of reports at a national level. Authoring teams need to balance this commitment to use the report in at the national level with ensuring that the reports are of high quality. IQWiG flagged that mandated uptake/use from all authoring team members (i.e., including dedicated reviewers) could be detrimental to the number of countries who could participate to joint assessments. This challenge was recognised by EFPIA, but an national uptake/use was still emphasised as being critical.

Anticipated use of joint REAs at a national level: examples from authoring agencies

HAS
The overall experience is that working on a general European level helps increase knowledge of European HTA processes and drug assessment methods across countries. Coordination by ZIN and the WP Lead and co-Lead is fundamental. Some practical difficulties are acknowledged which include overall time consumption, multiple steps/deadlines, and the need to improve the REA template to be fit for purpose for national HTABs.

HAS also stresses that implementation cannot be summarised as a simple copy and paste of the common report and that it can be done in different ways, for example from being used as additional information to the replacement of the national report with uptake of some parts of the common report, etc.
HAS reminded of the difference between an assessment and an appraisal, the former focusing on a critical analysis of the data whereas the latter means a recommendation for reimbursement and a quantification of the clinical added value voted by an independent committee as determined by the law. Rapid REAs are focused on the assessment and will not replace national appraisals. Performing common appraisals is not the aim of the common work and would require a modification to French law – which is not supported by the French Ministry of Health. Nevertheless, rapid REAs provide HAS staff with a first glimpse at the dossier. They can be a basis for national assessment and are shared with the HTA committee as an additional informative assessment report. When authoring, priority is given to the dossier so that it can be presented to the HTA committee quickly after national submission. All combined it contributes to a reduction in the time necessary for carrying out the national assessment.

In order to increase the use of rapid REAs, HAS would like to see improvement in the template so that parts of the report can be directly copied/pasted (after translation) into the national template and with the objective to have more emphasis on HTA added value.

In the future, HAS envisages asking for a lighter national submission file when HAS is involved as author/reviewer of the rapid REA to further increase national implementation of joint assessments.

NOMA
An outline of the Norwegian health care system was presented as well the role of NOMA as a HTA unit in Norway. Three criteria must be addressed in NOMAs assessment: relative efficacy with safety included, cost-effectiveness, and the severity of the disease. In June, a meeting with Novartis (MAH) was held where they were informed about the REA project. NOMA urged MAH to use the EUnetHTA joint assessment report in the submission file dossier for single technology assessment (STA). NOMA will use the Midostaurin joint assessment report in their STA in order to obtain efficiency gains

NOMA believes there is potential for further use of EUnetHTA REAs in an international setting. Pre-conditions for extensive re-use were presented and include: ensuring they are in line with the national request, are available at the appropriate time and that all involved parties are informed of the forthcoming availability of the EUnetHTA report, and that data are accessible.

Main success factors for conducting joint assessments include accepting common principles for the conduct of HTA, as well as following European project management structures and ensuring there is consistency and reproducibility in EUnetHTA reports.

TLV
TLV still requires a national application for reimbursement. A reimbursement decision is usually made within 180 days. For the Alecensa REA, TLV will use the applicable parts of HTA and add the domain on cost-effectiveness. For REAs where TLV is not part of the authoring team, TLV will find it extra useful to read discussions about alternative comparators. If relative efficacy and safety in an indirect comparison has been discussed in the REA of an alternative comparator, this could be of great value. Uncertainties in the analysis are also interesting for TLV to read.

General Discussion

Feedback at technical meetings such as this was emphasised by all parties as being important.

Facilitating company participation in EUnetHTA JA3: an EFPIA perspective

Celgene presented the interests of companies when considering participating in WP4 of JA3. From a company perspective, interests include reasonable evidence expectations, no duplication at Member State level and patient access.

A business-case led decision-making process is followed when a company reviews the decision to participate in a REA pilot. Cost is a major consideration, particularly headcount and resource considerations. Smaller companies with limited resources may not be so keen to invest heavily in pilots. Companies will also assess the benefits of the recently completed and on-going JA3 pilots and these must be distinguished from the benefits of 'EUnetHTA collaboration'.

With respect to the asset selection process, companies will undertake evaluations to consider which asset – these evaluations may be lengthy and time-consuming. Benefits to the company of participating in the pilot process must therefore be clear. Methodology was raised as a potential concern and needs to be addressed.

There was acknowledgement that much had been learned from the REAs produced to date. These positive learning experiences have allowed companies to reconsider their own internal processes.

Discussion
Industry believes it's important to the streamline process, without trading off quality.

NOMA shared that at a national level, a considerable difference is observed in the quality of the dossiers where market access and regulatory departments communicate in companies. In line with this, EUnetHTA has emphasised the importance of having both market access and regulatory representatives attend the F2F scoping meetings.

WP5 – Evidence Generation

HAS (WP5 LP) recalled the key objective of WP5 which is to help generate optimal and robust evidence for different stakeholders along the technology lifecycle. To achieve this, WP5 has two strands, Initial Evidence generation Early Dialogues (EDs), strand A, and post-launch evidence generation (PLEG), strand B.

Update on WP5B
The main activity of WP5B is to conduct PLEG pilots, that may be focused on specific products or on disease registries.

With regard to disease registries, EUnetHTA cooperates with the EMA by participating in the EMA

qualification procedure that has recently be put in place for registries. In this procedure, the applicant is not a pharmaceutical company but an academic society or a not-for-profit organisation that runs a registry. Both quality aspects and definition of the data of interest are discusses in this process and EUnetHTA brings the HTA contribution in this process. Two qualification procedures have been engaged up to now.

Product-specific pilots on PLEG will give the opportunity to EUnetHTA partners to voluntarily cooperate on selected drugs for which a cross-border effort would be worthwhile. Orphan drugs with small target populations would be good candidates for such pilots. This cooperation could minimise differences between national requests for additional data collection, and make this PLEG more robust and useful for a possible re-assessment of the product after some years on the market. The cooperation may consist in defining the common research question or the minimum data set for PLEG, as well as providing advice on methodology. The outcome of PLEG pilots give added value to national HTA bodies by proposing the 'core data set' or 'core common protocol' which allows the gathering of data from a much higher number of patients than uncoordinated national PLEGs. The final decision on a possible request for PLEG will remain at the national level.

HAS presents details of the first pilot, qualifications of registries for a rare disease, cooperation with EMA and then outlines the current status of PLEG pilots, the first product specific pilots will be decided during the WP5 annual meeting in Berlin on December 8th . The EUnetHTA-EMA work plan is also presented.

WP5A - Update on ED procedure by the WP5A Secretariat and coordinator

HAS outlines the context of Early Dialogues before starting EUnetHTA Joint Action 3 and compare it with the current situation.

The following key details on new procedure were shared:

- The Early Dialogue Working Party (EDWP) was created in order to establish and ensure robust high-quality HTA outputs. Members are HTA bodies experienced in collaborative EDs with adequate expertise, availability and budget as well as a high commitment to participate in EDs.
- Creation of the EUnetHTA ED Secretariat to facilitate streamlined logistics, improved HTA coordination
- The introduction of EDs' coordinator and rapporteur.
- The final outcome of the EUnetHTA ED procedures with a coordination of HTABs answers and an effort to reach consensus where possible.

Recommendations were made to the companies to extend dialogue/advice to discussion about post-launch evidence generation.

For further information on the ED procedure, please consult the supporting presentations.

EUnetHTA EDs rapporteur's perspective on ED procedure

GBA presents the current status of EUnetHTA EDs, highlighting that 14 requests have been received since the start of JA3. A flow chart is presented on how GBA is structured, drawing particular attention to the several points of interaction between the actors presented.

GBA has held carried out the role of rapporteur for the first EDs of JA3. From this experience, they conclude that there is strong cooperation between coordinator and rapporteur and between the EDC/SAWP coordinator. Most of the time overlap in HTAB positions has been observed which facilitates coordinator/rapporteur task to gather common position among HTAB.

Feedback from EFPIA on experience with EDs in JA3 (Multi-HTA and PC)

There is strong support for a single European parallel consultation process involving regulators and

HTA bodies, particularly because companies work on global development plans to meet multiple stakeholder needs. EFPIA also recognises that there is a role for European regulatory advice and separate national HTA advice because some regulatory questions will be less relevant to HTA bodies and national HTA bodies may have context-specific requests that may warrant different types of discussions.

Experiences so far are positive and industry supports the process as set out in the guidance document. To further improve, more consistent and predictable HTAB engagement, with dedicated resources across HTABs is needed. A more streamlined approach that consolidates HTA views and facilitates increased EMA-EUnetHTA interaction, an improvement of the timelines for sending in lists of issues and a greater involvement of patients and experts are also recommended to further improve the EUnetHTA process.

For a full list of suggested improvements, please consult the supporting presentation.

General Discussion

There is agreement that EUnetHTA must focus on production and HAS amongst other partners will be working towards increasing submissions.

EFPIA expressed concern regarding the currently eligibility for the involvement of the EDWP in that the criteria may select for certain types of products (e.g., orphans medicinal products). EFPIA's position is that no eligibility criteria be applied.

EFPIA suggests the PCI model as a way forward for vaccines, however there is concern that this model is still very new and it is too early to judge.

On the question of expected number of requests per month, EUnetHTA confirms that this is between three to four requests.

EFPIA reiterates that industry needs processes to be quick and responsive and resourcing within EUnetHTA must therefore be a key priority. HAS confirms that a decision will be made to increase capacity within the organisation, once the new financing mechanism is in place.

Whether or not scientific advice improved the HTA rating was also discussed and HAS confirmed that as the scientific advice is not validated by local scientific committees, it could be a potential intellectual conflict of interest. Additionally, HAS does not know if companies follow their scientific advice.

Concerns are also raised around the relevance of processes from country to country and there is general agreement that there is a greater need to understand these across all partners.

EC update

EC presents the timeline from 2016 to 2020 for EU cooperation on HTA. The Inception Impact Assessment was published on 15 September 2016 and an online public consultation closed in January 2017. The Impact Assessment has also been completed and received a positive response from theEC's Regulatory Scrutiny Board. EC is working on a legislative proposal to be adopted at the beginning of 2018 which should put in place a framework for EU cooperation beyond 2020. The key elements of this cooperation model system will be a member state-driven approach, a focus on clinical assessment at the time of market launch (for medicinal products) and high quality and timely output. The proposed new system will also include a mandatory uptake element, which should be understood as obligation to use the joint report at national level without any further duplication. The system must also be wholly transparent and fit for purpose.

Besides joint REA, possible areas of joint work include common tools and methodologies, horizon scanning/topic selection and joint early dialogues for multi-HTA and in parallel with regulators. Joint

REA on medicinal products will be limited to new active substances subjectto the central marketing authorisation procedure and new indications for existing substances. The new system will follow a pragmatic approach and will be subject to a controlled phase-in.

The EC presented the potential governance mechanism. This includes high-level coordination at the top including organisations responsible for HTA to be nominated by the MS, with working groups made up of MS experts carrying out joint work. A stakeholder network should provide regular input to MS experts. A secretariat is foreseen to provide MS authorities and experts with administrative, scientific/technical and IT support. The secretariat will also continue to support voluntary cooperation.

A potential timeline for the implementation procedure was presented. Prioritisation criteria will be needed as part of the phase-in approach; these could potentially be unmet medical needs, potential impact on patients/public health/healthcare systems, significant cross-border dimension, major added value and availability of resources. During the transition period, the Commission should draft additional implementing legislation based on the input (e.g. procedures, methodology) developed by EUnetHTA until 2020. The importance of the current interaction between companies and EUnetHTA in shaping the future requirements for joint work was underlined.

Summary

EFPIA and EUnetHTA felt that there have been many achievements since the last technical meeting. The process is now more reliable and predictable than before and the hope from both EFPIA and EUnetHTA is that progress continues.

Feedback from companies and a greater understanding of internal decision-making processes was found to be very useful.