30 September 2019
EMA/832382/2018

FINAL - Minutes of EMA/EUnetHTA meeting

7 December 2018

Role	Name
Co-chairs:	Hans-Georg Eichler and Giovanni Tafuri
Present:	EUnetHTA: Chantal Bélorgey - HAS , Patrice Chalon - KCE , Rudy Dupree – ZIN (via TC) , Wim Goettsch - ZIN , Marcus Guardian – ZIN (via TC) , Chantal Guilhaume - HAS , Niklas Hedberg - TLV , Krystyna Hviding - NOMA , Marit Hystad- NOMA , Vigdis Lavrak – NIPHNO (via TC) , Hannah Patrick - NICE , Juan Carlos Rejon-Parrilla - NICE , Ingvil Saeterdal – FHI (via TC) , Regina Skavron - G-BA , Giovanni Tafuri - ZIN , Tomas Tesar - UNIBA , Beate Wieseler - IQWiG , Anne Willemsen – ZIN (via TC) , Anna Zaremba – AOTMiT. EC: Flora Giorgio (via TC), Orsolya Nagy (via TC). EMA: Peter Arlett, Michael Berntgen, Laurent Brassart (via TC), Alison Cave (via TC), Hans-Georg Eichler, Harald Enzmann, Steve Estevao, Martin Huber (via TC), Kristina Larsson, Jordi Llinares Garcia, Patricia McKettigan, Jane Moseley, Alexandra Pacurariu, Elias Péan, Guido Rasi, Bruno Sepodes (via TC), Marcio Silva, Alexios Skarlatos, Violeta Stoyanova-Beninska (via TC), Enrico Tognana, Spiros Vamvakas. Payers: Menno Aarnout (AIM), Michael Ermisch (GKV-Spitzenverband)

Item	Draft agenda	Name
1.	Welcome by EMA's Executive Director	Guido Rasi
2.	Introduction to the day and adoption of the draft agenda	Hans-Georg Eichler and Giovanni Tafuri
3.	Update from DG SANTE on activities related to the EMA/EUnetHTA collaboration	Flora Giorgio
4.	Update on Joint Action 3 activities	Niklas Hedberg
5.1	Progressing the different aspects of optimising evidence generation prospectively:	• EMA: Jane Moseley, Patricia McGettigan,

Item	Draft agenda	Name
	a) Overview of early dialogues, collaboration on qualification process (EUnetHTA) b) Experience with parallel consultation (EMA)	Alexandra Pacurariu • EUnetHTA: Chantal Belorgey, Chantal Guilhaume, Hannah Patrick
5.2	Post Licensing Evidence Generation (PLEG) a) PLEG focus group progress (EMA) b) PLEG-HTA issues (EUnetHTA)	
5.3	Registries and other data sources: a) EMA Registries reflection paper and other publications o quality assurance tool ReQueST /feedback to EMA - EUnetHTA o pre-conducted comparison between tools EMA, feedback to EUnetHTA on ReQuest EMA b) (MedDRA ICH mapping – EMA) c) Real-world databases for decision-making given the potential interest of HTA and payers review - EMA	
6.	Development of guidelines – opportunities for enhanced collaboration a) Status of current plans and opportunities for mutual input b) EMA perspective on ICH updates that are important and relevant for HTAs c) EUnetHTA plans for methodological guideline updates or drafting	• EMA: Spiros Vamvakas • EUnetHTA: Patrice Chalon
7.	Optimising the exchange at time of market entry: • Planning for REAs: Information from EMA; EUnetHTA Prioritisation list; TISP recommendations • Facilitating exchange between EMA and EUnetHTA: Survey feedback; Areas for process improvement • Learnings from first products: Themes of questions; High-level analysis of EPAR vs REA	• EMA: Michael Berntgen, Elias Péan • EUnetHTA: Vigdis Lauvrak, Krystyna Hviding, Anne Willemsen, Rudy Dupree
8.	Principles for the wording of the indication • Activities so far and agreement on next steps	• EMA: Alexios Skarlatos
9.	Joint analysis on the concepts of significant benefit and relative effectiveness • Presentation of the outcome of the study • Next steps for the publication	• EMA: Kristina Larsson • EUnetHTA: Wim Goettsch
10.	Plans for review of activities from the EMA/EUnetHTA work plan 2017-2020	• EMA: Michael Berntgen • EUnetHTA: Niklas Hedberg
11.	Closing remarks	Hans-Georg Eichler and Giovanni Tafuri

This was the 16th meeting between the European Medicines Agency (EMA) and representatives from the European Network for Health Technology Assessment (EUnetHTA). The meeting was attended by the European Commission; furthermore representatives from payer organisations followed the meeting as observers.

In his introductory notes, EMA's Executive Director Guido Rasi highlighted that these bilateral meetings are by now an established event in the calendars. They are a platform to jointly progress technical topics of mutual interest, with particular focus on delivering the actions of the EMA/EUnetHTA work plan. At the heart of this joint endeavour is the facilitation of decision making for patient access to beneficial medicines. There is recognition that clinical evidence is the universal cornerstone that informs such decisions by various players within their remit. It is important to ensure that this clinical evidence is designed to substantiate the clinical benefit, or its clinical value, to deliver in the interest of the ultimate stakeholder, the patient.

The draft agenda was adopted without changes.

Update from DG SANTE on activities related to the EMA/EUnetHTA collaboration

An update on the ongoing discussions on the legal proposal for a regulation on HTA collaboration was provided. Referring to the EMA/EUnetHTA collaboration, it was highlighted that the proposal aims to provide an optimised, legally founded framework for this work as the added value is recognised also considering the synergies between HTA and regulatory issues.

During the discussion it was raised that what is presented in the legal proposal is actually lived by the participants on a day-to-day basis. It is therefore important to connect the political and the operational level. An important notion is that synergy does not mean interference, rather it means to ensure that the evidence needs are reflected in the medicines' development plan to allow decision making. The procedural practices that have been developed are considered very helpful and to ensure that there is no undue influence.

Update on Joint Action 3 activities

An overview of the achievements in the various work packages was provided. This includes starting on the preparation post 2020 and changes to the governance structures (WP1), the focus on REA identification, the TISP recommendations and the EUnetHTA Priority List (WP4), and the review of national implementation (WP7) with a report showing on average 12 uses of the REA outputs.

Progressing the different aspects of optimising evidence generation prospectively

An overview of early dialogues, and collaboration on qualification process was given by EUnetHTA, with 14 consolidated parallel advices (PCCs), 3 multi HTA only consolidated advices and 22 parallel EMA advices as several individual HTA bodies (PCIs). Parallel consultations covered a range of therapeutic areas, and included applications from SMEs, and on orphan and ATMP products, and the first parallel EMA HTA NITAG advice on a vaccine as a PCI. EUnetHTA provided feedback on areas which have been noted to preclude deeper HTA recommendations for applicants (detailed proposals on PLEG, or biomarker development, and choice of PROs). EUnetHTA suggestions for improvements were made. Experience from HTAb so far in parallel qualification advice on novel endpoints/data sources was relatively limited but thought to be an opportunity that would be of interest if clarifications and process optimisation was possible to facilitate HTA involvement, and subject to resource availability. EMA

responded to clarify outstanding questions on the process and that a timetable as per the 70 day parallel consultation could be adhered to for parallel qualification advices.

EMA presented the results of the Parallel Consultations Feedback Questionnaire (jointly designed by EMA and EUnetHTA) to applicants who had taken part in the new parallel consultation procedure. Results were based on 15 contributions received by EMA on Parallel Consultations that took place between August 2017 and August 2018. The response rate was 68% (15 out of 22), and appeared representative in terms of the breakdown between PCC and PCI as finally allocated. There was positive feedback regarding communications by EMA and EUnetHTA. The results on alignment between EMA and EUnetHTA for positions on population, comparator, endpoints for the study under the advice and whole program were consistent with previous publications. Data were also collected and presented on how expectations were met, the usefulness of the procedure, and intentions regarding implementation of regulatory and HTA advices. The feedback was positive and highlighted some areas for further process development such as communication on logistics, procedure duration, timelines, PRIME scheme involvement of HTAs, coordination regarding List of Issues, and issues pertaining to the face to face meeting. Overall, all applicants who responded said that they would repeat the procedure for other products or indications.

It was agreed to reopen the parallel consultation guidance based on the experience and feedback of the new procedure to further optimise the process. Areas to be considered for amendments include: common templates EMA-EUnetHTA for the list of issues, common guidance for F2F meeting, and a common feedback questionnaire, lead-in times and optimising the validation stages, adapting the parallel consultation opportunity for parallel consultation and PLEG proposals, including additional experts, and follow-up mechanisms (to further address differing evidence needs).

In terms of Post Licensing Evidence Generation (PLEG), EMA gave an update on the PLEG focus group progress. This is a group constituted from EMA, EUnetHTA and Industry from the EMA Platform with Industry associations on R&D support to discuss how to better progress scientific advice applications in PLEG. As a key issue is a lack of information about all aspects of this topic, a review paper has been drafted to communicate and clarify: terminology, process, and rationale for seeking scientific advice on PLEG. HTA bodies highlighted the critical issue that this should not encourage industry to invest in robust development, and that it is important to identify at the time of pivotal trial design research questions that could not be answered without PLEG. It was agreed to continue working on this stream including the paper, follow-up discussion on what the compliance with post-licensing studies and whether they are following up. In particular, EUnetHTA and EMA will continue to collaborate and clarify parallel consultation issues surrounding this topic to facilitate streamlined evidence generation post-launch and post-licensing to meet the needs of respective stakeholders.

With regard to the recent activities to ensure the quality of post-licensing evidence generation, the EMA discussion paper on registries and the ReQUEST tool by EUnetHTA are seen as complementary. This should also be subject to communication activities. The two initiatives are generally well aligned with difference of emphasis on some of the items (like the element of governance), agreement on definition and differentiation between disease registry and registry studies. It was generally noted that further alignment on terminology would be useful.

ACTIONS:

- Review of the guidance on Parallel Consultation to address recent experience, such as guidance on F2F meetings, and optimise the application form
- Finalisation of the publication on PLEG

- Technical alignment of the ReQUEST tool and the Registry paper; follow-up discussion at a future bilateral
- Report on the fulfilment of Post authorisation measures to be discussed at the next bilateral

Development of guidelines – opportunities for enhanced collaboration

EUnetHTA reported from their guideline renovation activities. Currently 15 guidelines are published, of which two are under revision (systematic reviews; indirect comparison). Two other guidelines are under development (economic evaluation, clinical evaluations). It was agreed to reflect on how to best structure collaboration with EMA on EUnetHTA guidelines. The guideline "Comparators & Comparisons: Direct and indirect comparisons" is of high interest for EMA.

EMA provided an overview of the ICH reflection on "GCP Renovation" with the modernization of ICH E8 and Subsequent Renovation of ICH E6. Data quality fundamentally depends on the quality of the study generating the data, and many aspects of study design affect the reliability of study conclusions. The goal of the renovation is to facilitate innovative approaches to clinical trials including quality-by-design processes, emphasize upfront assessment of risks specific to a study design and protocol, quality risk management, risk-based controls, focusing on critical study elements, as well as use of technological tools to ensure robust conduct, oversight, and reporting. EUnetHTA was invited to contribute to these revisions through the consultation process.

ACTION:

- EUnetHTA and EMA to explore how to collaborate in the context of methodological guidelines development and update.
- EUnetHTA to consider whether and how to contribute to the consultation on ICH guidelines

Optimising the exchange at time of market entry

The first part of the discussion covered the planning for Relative Effectiveness Assessments (REAs) on the basis of EMA information on ongoing applications, the EUnetHTA Prioritisation list, and the status of Topic Identification, Selection and Prioritisation (TISP) recommendations. Following the discussion in March 2018, a mock-up for a comprehensive report on regulatory milestones for ongoing applications has been developed by EMA. The reporting format addresses most data fields for initial MAA and all for Extension of indication / Line extension that are required by EUnetHTA. It generally provides advance information around 13-16 months before MAA Opinion. The recently published EUnetHTA Prioritisation List aims to strengthen cooperation between industry and EUnetHTA. It is expected to increase the number and diversity in topics of joint REA and should allow for better prediction on usability and implementation. Learnings and structural efforts are to be incorporated into TISP, which aims to explore the simplest possible way of identifying, selecting and prioritising new medicinal products for initial REA. A minimal data-set will be populated based on public available sources including data from EMA. In this context it was agreed to pilot the use of the EMA report with a first submission in 1Q19.

Looking at the process for facilitating an exchange between EMA and EUnetHTA on products at time of market entry, the experiences with REA-1, REA-2 and REA-3 were reviewed. Feedback from the participants of the webinars indicated that the discussions allowed getting clarity on the treatment eligible patient population and the underlying assessment. Furthermore, areas for optimising regulatory outputs were identified. Overall, participants acknowledged the value of the exchange including the mutual learning on principles of regulatory criteria vs. HTA. There is a need to continue interactions e.g. on imposed PAES studies. Areas for process improvement are the referencing of the CHMP AR in the draft REA, the timing for the webinar, and allowing an exchange on procedural progress and significant changes in the assessment.

EMA and EUnetHTA also performed a high-level review of the first three REAs versus the corresponding EPAR, focusing on identified uncertainties/limitations in the data, and post-authorisation requests to address such uncertainties. The discussion centred around the need to ensure that post-licensing/launch data addressing identified evidence gaps will be utilised for later updates of both EPARs/SmPCs and REAs. In cases where clinical studies are imposed by regulators, it is necessary to ensure that the resulting data will also inform REA updates. It was considered important to always seek opportunities to discuss the design of prospective post-licensing/launch studies by involving various decision makers.

ACTION:

- EMA to provide a report on ongoing applications (marketing authorisation/extension of indication/line extension) to support TISP activities, in 1Q19
- EMA and EUnetHTA to follow up on proposed process improvements (referencing of the CHMP AR in the draft REA; timing of the webinar; possibility for regular exchange on timelines)
- EMA and EUnetHTA to continue monitoring of outputs in terms of their similarities and differences

Principles for the wording of the indication

EMA summarised the discussions with EUnetHTA so far on experience with the wording of the therapeutic indication and its impact on HTA's definition of treatment eligible population. Regulators have been developing a guide to assessors clarifying the regulatory framework of the therapeutic indication, identifying the different elements to consider when defining the indication and focusing on justifying it in detail in the benefit - risk section of public assessment report. HTAs confirmed that the principles presented in this document will address their questions regarding the indication, and asked its systematic use to justify the indication in public assessment report. Regulators are implementing its use within the network and aim to publish it once experience is gained, also considering an ongoing revision on the guideline on subpopulation. Payers have shared HTAs' interest on this issue. Regulators welcomed receiving further feedback with practical examples from both parties which could be discussed next year during a meeting with CHMP, HTAs and Payers' representatives.

ACTION:

- EUnetHTA continue to share experience from using labelling and EPARs for their decision making
- EMA to organise a meeting with CHMP, HTAs and Payers' representatives to discuss this experience and ways moving forward

Joint analysis on the concepts of significant benefit and relative effectiveness

EMA and EUnetHTA presented an update on the ongoing joint analysis concerning significant benefit and relative effectiveness assessment for orphan medicinal products. The study aim is to assess the similarities and the differences between the SB assessment within the orphan framework assessment process as practiced by the EMA (COMP) and the REA as part of the HTA of orphan drugs as practiced by HTA institutions across Europe. Similarities and the differences are going to be assessed with regard to PICO elements, as well as the use of extrapolation and evidence other than RCTs, respectively. Five cases for in depth analysis have been identified. Whilst this work is ongoing, perspectives were invited on the initial findings.

ACTION:

- The draft report will be circulated to EMA and concerned HTAs, for comments

Plans for review of activities from the EMA/EUnetHTA work plan 2017-2020

On the basis of the priority areas in the EMA/EUnetHTA work plan 2017-2020, a review was conducted focusing on the progress with the various activities. This was to ensure that the work plan will be delivered as expected. Most activity areas are either progressing well or show at least some progress. Particular attention needs to be given to the optimisation of regulatory output documents as a result of feedback and reviews, and the guideline development. It is acknowledged that there are internal and external factors that might impact the delivery of some of the actions. The discussion identified as current priority areas exchanges on histology-independent developments and on PROs, respectively.

ACTION:

- Reflection how to further develop the discussion on PROs
- Arrangement of an exchange on perspectives and challenges with regard to histology independent developments
- Follow-up review of the work plan activities at the next EMA/EUnetHTA bilateral

Closing remarks

The next meeting will be hosted by EUnetHTA and will be scheduled for **mid-2019**.