

13 April 2018
EMA/845953/2017

Final - Minutes of EMA/EUnetHTA meeting

15 December 2017

Role	Name
Co-chairs:	Hans-Georg Eichler and Wim Goettsch
Present:	<p><u>EUnetHTA</u>: Wim Goettsch, Michelle Mujoomdar, Marcus Guardian, Anna Zawada, Beate Wieseler, Chantal Bélorgey, Cláudia Furtado, François Meyer, Giovanni Tafuri, Ingvil Sæterdal, Jacoline Bouvy, Marianne Klemp, Nick Crabb, Niklas Hedberg, Rudy Dupree, Rui Santos Ivo, Tomáš Tesař, Tuomas Oravilahti</p> <p><u>EMA</u>: Guido Rasi, Hans-Georg Eichler, Michael Berntgen, Cécile Ollivier, Corinne de Vries, Enrico Tognana Iordanis Sidiropoulos, Jane Moseley, Kristina Larsson, Laurent Brassart, Patricia McGettigan, Ralph Bax; Committee representatives: Tomas Salmonson, Harald Enzmann, Rob Hemmings, Kristina Dunder, Bruno Sepodes, Dirk Menzer</p> <p><u>EC</u>: Ioana-Raluca Siska</p>
Apologies:	Daniel O'Connor, Violeta Stoyanova-Beninska

Item	Draft agenda	Name	Time
1.	Welcome by the EMA's Executive Director	Guido Rasi	10 min
2.	Introduction to the day and adoption of the draft agenda	Hans-Georg Eichler and Wim Goettsch	10 min
3.	Update from DG SANTE on activities related to the EMA/EUnetHTA collaboration	Ioana Siska	20 min
4.	Concepts of significant benefit and relative effectiveness <ul style="list-style-type: none"> Reflections from the COMP perspective Outline of a methodology and plans for the review of the concepts 	<ul style="list-style-type: none"> EMA: Kristina Larsson, Bruno Sepodes, Daniel O'Connor, Violeta Stoyanova-Beninska, Iordanis Sidiropoulos 	45 min



Item	Draft agenda	Name	Time
		<ul style="list-style-type: none"> EUnetHTA: Wim Goettsch, Angela de Ruijter 	
5.	Update on Joint Action 3 activities	Wim Goettsch	20 min
6.	Opportunities for collaboration on horizon scanning <ul style="list-style-type: none"> Mutual understanding of scope and methodology Needs in view of WP4 topic selection Potential of future collaboration in this space 	<ul style="list-style-type: none"> EMA: Michael Berntgen EUnetHTA: Claudia Furtado 	45 min
7.	Feedback from the EMA-Payer Community meeting	Hans-Georg Eichler / Michael Berntgen	15 min
Lunch			45 min
8.	The concept of evidence transfer (also known as "extrapolation") <ul style="list-style-type: none"> Introduction to the EMA reflection paper on extrapolation Discussion of contributions also in view of the public consultation 	<ul style="list-style-type: none"> EMA: Rob Hemmings, Dirk Menzer, Cecile Ollivier EUnetHTA: Michelle Mujoomdar 	45 min
9.	Principles for the wording of the indication <ul style="list-style-type: none"> Update on the regulatory considerations regarding the labelling, including special aspects for sub-populations HTA perspective of the use of the labelling to identify the "treatment eligible population" 	<ul style="list-style-type: none"> EMA: Kristina Dunder, Laurent Brassart EUnetHTA: Beate Wieseler 	45 min
10.	Ongoing initiatives on registries and Post-licensing evidence generation (PLEG) <ul style="list-style-type: none"> Next steps for activities on qualification of registries Opportunities with EUnetHTA PLEG pilots Possible work on observational data beyond registries 	<ul style="list-style-type: none"> EMA: Jane Moseley, Patricia McGettigan EUnetHTA: Francois Meyer 	30 min
11.	Review of other activities from the EMA/EUnetHTA work plan 2017-2020	Michelle Mujoomdar and Michael Berntgen	20 min
12.	Closing remarks	Hans-Georg Eichler and Wim Goettsch	10 min

This was the 14th meeting between the European Medicines Agency (EMA) and representatives from the European Network for Health Technology Assessment (EUnetHTA). The various introductory

remarks highlighted the important role of these bilateral meetings to progress topics of mutual interest and to collectively reflect on the ways moving forward. Facilitating translation of scientific advances into innovative medicinal products that meet evidence standards to ensure patients' access to these medicines is a challenge in an ever evolving environment. In this context the collaboration is crucial to stimulate developments of innovative therapies that meet patient needs. Significant achievements in 2017 included the joint launch of the new Parallel Consultation platform in July, mutual participation in a number of events like workshops on registries or the HTAi conference, as well as the publication of a new joint work plan 2017-2020 in November. It was noted that the topics of the agenda reflect these priorities.

The draft agenda was adopted without changes.

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

The update from the European Commission focused on the upcoming publication of a legal proposal for HTA collaboration, which is scheduled for 31 January 2018. It was highlighted that any such framework should be driven by Member States with the Commission providing a support function. The focus will be on the clinical assessment since nonclinical domains are context dependent and hence to be addressed at national level. The intention is to ensure high-quality and timely outputs, to be used at national level. There will be different approaches for medicinal products and medical devices, due to specific needs. Transparency is an important element, through publication of the report and engagement with stakeholders.

From a technical perspective, the preparation through areas of joint work in EUnetHTA is important. This concerns common tools and methodologies, joint early dialogue, joint REA as well as horizon scanning for planning purposes. It is foreseen to have a phased approach for implementation that allows during a transition period to gradually increase activities and become fully operational.

For defined areas of work it is foreseen to specify collaboration with EMA: Parallel consultations; Early sharing of the CHMP adopted clinical assessment report; and Horizon scanning. In this context the current activities, including those identified in the work plan and developed by the Synergy group, will support shaping the future engagement framework. The need to have a workable cooperation framework including confidentiality aspects was noted.

Concepts of significant benefit and relative effectiveness

A joint presentation was provided by EMA and EUnetHTA describing the progress of work on the topic "Significant benefit vs. added therapeutic value for orphan medicines" as defined in the EMA-EUnetHTA work plan 2017–2020.

The presentation first focused on clarifying the concepts of orphan designation and orphan maintenance in relation to HTA assessment. A new initiative from the EMA of publishing the COMP assessment reports at time of marketing authorisation was also introduced. The publication of the orphan maintenance assessment report (OMAR) will increase transparency and ensure a consistent approach when publishing key opinion documents across the EMA. The first OMAR will be published in January 2018. There was general support from HTAs on this initiative but also an interest in learning more on what the report would actually look like in particular in relation to the EPAR. HTAs stated that it was very important to understand what data supported the conclusions by the COMP. It was also agreed to review the benefit of the OMAR for the HTAs once about 10-15 OMARs have been published.

The second part of the presentation focused on the proposal to compare significant benefit (SB) assessment done by COMP with relative effectiveness assessment (REA) done by HTAs. The draft review outline was presented and discussed by the participants. The proposal is to assess the similarities and the differences between the SB assessment within the orphan framework assessment process as practiced by the EMA and the REA as part of the HTA of orphan drugs as practiced by HTA institutions across Europe. It will be a qualitative, retrospective, descriptive and comparative analysis of secondary data, and the output is expected to be a descriptive report consisting of a limited number of case studies highlighting the similarities and differences of significant benefit and relative effectiveness assessment. It was general agreement that cases with divergent outcomes might be best to highlight differences between the two types of assessment. As there was great interest in the research proposal it was agreed to circulate the draft proposal after the meeting for comments from the participants. It is foreseen that the work will start in February 2018 to be completed in autumn 2018.

ACTION:

- EMA and EUnetHTA activity leads to circulate the draft proposal for comments and provide later updates once the analysis has been completed.

Update on Joint Action 3 activities

The overview of Joint Action 3 activities covered several areas with relevance for the collaboration with EMA. In terms of joint REA production, three products have been in scope so far. The collaboration with EMA was in relation to sharing elements of the final CHMP assessment report after adoption by the CHMP and facilitating an exchange between the CHMP rapporteurs and the HTA authors. The uptake at national level is incrementally increasing. A challenge is that the REA production requires voluntary submissions by the manufacturers and EUnetHTA will become more proactive in their outreach.

Parallel Consultation is characterised by a strong cooperation amongst all partners and a good working relationship between representatives from EMA's Scientific Advice Working Party (SAWP) and EUnetHTA's recently formed Early Dialogue Working Party (EDWP).

Within EUnetHTA future developments include increased interactions across the life-cycle (between WP4 and WP5), increased interactions with stakeholders (e.g. patients and healthcare providers), as well as developing a funding mechanism for early dialogues.

Opportunities for collaboration on horizon scanning

In a joint presentation EMA and EUnetHTA provided a perspective on opportunities to collaborate in the space of horizon scanning. The starting point is to clarify what is actually meant with horizon scanning, including objectives, scope, observation period or horizon, data sources, filtering and reporting mechanism. The drivers for collaboration between the regulators and HTAs in this space are the HTA network paper on synergies, the work plan 2017-2020 and activities in WP4 with regard to topic selection; also the upcoming legislative proposal was noted.

From EUnetHTA perspective, the expected use is in the first instance topic selection, planning and preparation of assessment. For this purpose, information from both medicines development phase and assessment phase would be useful. EMA presented the different types of information, which are already made publicly available by EMA. This includes information on marketing authorisation

applications, extensions of indications, and during development (orphan designations, PRIME eligibility). Points for reflection were the objectives of joint horizon scanning in the short/mid-term as well as the timespan.

During the discussion two distinct areas of interest became apparent: the early information about planned and ongoing submissions but also the wider horizon of major innovation that can be “disruptive” for healthcare systems. The latter would be important for member states to organise themselves. With these objectives come different challenges. It was therefore agreed to focus on the short-term needs and to be pragmatic by developing in the first instance the area of information on upcoming/ongoing submissions. Such a focus is very practical and is expected to address the current need of informing topic selection in WP4. In addition one should explore how we get to a wider framework in the mid-term; this could link up with activities from the Synergy group.

ACTION:

- As a follow-up it was agreed to jointly develop how to optimise reporting of publicly available data relevant for EUnetHTA by clarifying actual time span and products in scope in view of the WP4 current work flow. Also it was noted that the activities should be aligned with the request from healthcare payers (see below).
- Subsequently the intention is to explore in the mid-term the wider scope of horizon scanning including activities from the Synergy group

Feedback from the EMA-Payer Community meeting

EMA provided a brief report from their first meeting with the European Payer community in September 2017, based on the [published report](#). The topics of the meeting covered multi-stakeholder early and late dialogue, horizon scanning for pharmaceuticals, indication and labelling as well as definition of unmet medical need. Some of the follow-up actions overlap with the work between EMA and EUnetHTA therefore it was agreed to work together in these respective areas.

The concept of evidence transfer (also known as “extrapolation”)

EMA outlined its activities in the space of extrapolation, starting from the road map and explaining the framework that has recently been published. The initial driver came in the paediatric area, where there is the need for a regulatory framework to facilitate an informed and efficient drug development when extrapolation is used. The use of structured approaches to evidence synthesis and inference will increase in importance and quality of decision making hence a framework will facilitate an increase of predictability by using a consistent and systemic approach during the product development life cycle. The development moves the topic from expert judgement (or even practical experience) to scientific rationale.

Against this background, the extrapolation approach consists of four steps: Sources of information (adults and use of existing knowledge); Assumptions and predictions (clinical/modelling); Objectives for the paediatric development (methodological tools); Study design. The recently published Reflection paper on the use of extrapolation in the development of medicines for paediatrics describes extrapolation as extending information and conclusions available from studies in one or more subgroups of the patient population ([source population](#)), to make inferences for another subgroup of the population ([target population](#)), thus minimizing the need to generate additional information (*types of studies, design modifications, n of patients required*) to reach conclusions. At the centre are the

steps concept, plan (i.e. reduction of data requirements in accordance with predicted degree of similarities and strength of evidence) and mitigation. The concept was exemplified in the areas HIV, Gaucher disease and Pulmonary Arterial Hypertension.

ACTION:

- HTA's are invited to comment on the reflection paper in the context of the ongoing public consultation (deadline 14 January 2018)

Principles for the wording of the indication

EMA and EUnetHTA shared experience on how regulators define therapeutic indications and their impact on HTABs' activities to identify a treatment-eligible population. The therapeutic indication is a key part of the marketing authorisation which reflects in which disease and target population the benefit/risk is positive. It is used by HTA-bodies like a frame to assess the population for which the product could be prescribed and reimbursed. Furthermore, it is used to identify the relevant sub-populations to be considered in the therapeutic area and the corresponding comparator(s) to be considered in relative effectiveness assessment. The therapeutic indication is defined by EMA based on a multidimensional analysis considering the data submitted to support the claimed indication, the therapeutic context, and, the benefit risk assessment in the studied population, its subsets or the real-life population. Based on this decision-making process, the indication may be wider or more restricted compared to the studied population. When defining an indication, regulators have to balance the need for timely access to innovative medicines and the extent and timing (i.e. pre or post-authorisation) of evidence to be collected to ascertain a positive benefit risk balance. Regulators' reasoning for granting an indication is presented in public assessment report with the presentation of supportive data and their analyses. While HTABs understand that the approved indication might not be fully covered by the clinical trial program, they wish comprehensive and detailed information on available evidence in all relevant sub-populations. It was also pointed out that appropriate considerations to support the indication have to be taken early during development to generate necessary evidence and, after marketing authorisation to fill potential gaps. During the discussions, it was agreed to further share understanding on how indications are worded in SmPC and explained in EPAR, taking into account the level of evidence, considerations in subpopulation or on extrapolation, and, wording of existing alternatives. Exchange will also cover discussions on the purpose of section 5.1 of SmPC which sometimes may look a "small EPAR".

ACTION:

- As part of the EMA/EUnetHTA work plan item, further share understanding on how indications are worded in SmPC and explained in EPAR, including the purpose of section 5.1 of SmPC

Ongoing initiatives on registries and Post-licensing evidence generation (PLEG)

EUnetHTA's outline of the initiatives on registries and post-licensing evidence generation (PLEG) highlighted the objective to help to generate, all along the technology lifecycle, optimal and robust evidence for different stakeholders, bringing benefits for patient access and public health. The activities cover PLEG pilots and Standards Tool for Registries in HTA. For PLEG pilots, the objective is to prepare national decisions on PLEG by proposing a common research question or minimum data set, giving advice on methodology and once data are produced, provide an assessment of these data. The aim is to reduce differences between national requests regarding non context-specific information and

ensure, through cooperation with EMA, that PLEG is useful for regulators and HTA bodies. Regarding the Standards Tool for Registries, the objective is to adapt the existing quality standards for registries into a practical tool for use of registry data in HTA. A report on current use of registry data by HTA bodies and for the standard tools is being drafted.

For the PLEG pilots, selection/prioritization criteria are under consideration. The ongoing EMA/EUnetHTA collaboration in the qualification of a registry for a rare disease was noted, which the first time this exercise is performed. Also for the second registry qualification (starting early December) there is engagement of HTAs albeit as observer. Further products specific pilots are being considered. Whilst there is a high level of interest from EUnetHTA, there are some practical limits in that a qualification opinion would not be in the remit of EUnetHTA, and qualification advices would be preferred when products have been assessed by HTA bodies. For product specific late (peri-licensing) advice experience is lacking to date.

EMA highlighted the role of PLEG for regulators in the context of the benefit risk assessment and the product lifecycle. The expectation is for scientific questions on safety/efficacy, the right study is conducted using the most appropriate and highest quality data with results being provided in a timely fashion. PLEG is broad in scope and includes studies which are randomised and nonrandomised, and data which are real world-based and from experimental settings. Various reviews like registries and post-authorisation safety studies, have documented the types of data requested in PLEG to address remaining uncertainties that cannot be answered in pivotal data at MAA and for strengthened life cycle approach. Regulatory guidances on PLEG include scientific guidance on Post-Authorisation Efficacy Studies [PAES](#) and other guidances. There are some examples of regulatory experience in giving scientific advice (SA) on PLEG for example a rare condition, with an imposed registry for Post Authorisation Safety Study (PASS) as a Post MAA discussion, and also development discussions on pragmatic trials for a cancer indication, and for heart failure. A specific example of PLEG at MAA includes a recent product Spinraza which has imposed PAES and required registry studies.

There are opportunities for parallel consultations involving other stakeholders in planning PLEG as Parallel consultation, either product-specific or qualification advice / opinion which is not product-specific. A qualification Opinion (publicly available) considers the acceptability of a specific method (e.g. use of a biomarker, PRO) in drug development based on assessment of submitted data. For a registry, this would be an opinion on the kind of regulatory studies that could be conducted in a particular registry. However, subsequent protocol interaction with regulators is still needed for a given product. Public workshops in the frame of the patient registry initiative allow for potentially wider face to face inputs, and are complementary to the Committee qualification procedures.

Other tools relevant to PLEG for EMA/HTA interaction include the EMA patient registries [initiative](#). EMA also provided an updated on the HMA/EMA Big Data Taskforce; reports are in draft on various data classes, surveys have been carried out on pharma and NCAs. A roadmap is being developed considering the mapping and gaps identified and will be published later in 2018.

Actions:

- Exchange on the possible use of the EUnetHTA registries tool in the frame of EMA initiatives on registries
- Provision to HTA bodies of EMA papers on 'Key principles on patient registries – regulatory perspective' and 'Methodological aspects of patient registry studies - regulatory perspective', once available

- Possible evolution for the involvement of HTA bodies in EMA registries work re topic/disease selection, preparation of workshops, evolution of the procedure

Review of other activities from the EMA/EUnetHTA work plan 2017-2020

EMA and EUnetHTA presented a progress update on the various areas in the work plan, focusing on the activities that were not subject to earlier agenda items.

Action points from previous meetings

The action items from previous meetings were reviewed and follow-up activities noted.

Closing remarks

The next meeting will be hosted by EUnetHTA and will be scheduled for 2Q18.