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Final - Minutes of EMA/EUnetHTA meeting

7 December 2016 – Co-chairs: Hans-Georg Eichler (EMA) and Wim Goettsch (EUnetHTA)

Role	Name
Chairs:	Hans-Georg Eichler and Wim Goettsch
Present:	<p><u>EUnetHTA</u>: Wim Goettsch, Michelle Mujoomdar, Marcus Guardian, Antje Behring, Beate Wieseler, Chantal Bélorgey, Cláudia Furtado, François Meyer, Irina Cleemput, Marianne Klemp, Nick Crabb, Niklas Hedberg, Simona Montilla, Tuomas Oravilahti, Wojciech Wysoczanski, Zoe Garrett</p> <p><u>EMA</u>: Guido Rasi, Hans-Georg Eichler, Michael Berntgen, Alison Cave, Corinne de Vries, Enrico Tognana, Francesca Cerreta, Isabelle Moulon, Jane Moseley, Jordi Llinares Garcia, Lucia D'Apote, Manuel Haas, Spiros Vamvakas, Spyridon Drosos, Xavier Kurz; Committee representatives: Harald Enzmann, Rob Hemmings, Hans Ovelgonne</p> <p><u>EC</u>: Ioana-Raluca Siska, Helen Lee</p>
Apologies:	Christoph Künzli, Tomáš Tesař, Almath Spooner, Tomas Salmonson

Item	Preliminary draft agenda	Name
1	Welcome by the EMA's Executive Director	Guido Rasi
2.	Introduction to the day and adoption of draft agenda	Hans-Georg Eichler and Wim Goettsch
3.	Update from DG SANTE on activities related to the EMA/EUnetHTA dialogue (e.g. Joint Action 3, HTA Network, upcoming events)	Ioana-Raluca Siska
4.	Overview of the establishment of Joint Action 3: introduction to structure and partners, status of work packages relevant for the collaboration with regulators	Wim Goettsch
5.	Topics and priorities for the development of an EMA/EUnetHTA	Michael Berntgen and Wim Goettsch



Item	Preliminary draft agenda	Name
	work plan	
6.	Experiences and perspectives for multi-stakeholder scientific advice to developers: plans for the activities under work package 5a and reflection on future models	Topic leads: <ul style="list-style-type: none"> EMA: Jane Moseley, Spiros Vamvakas EUnetHTA: François Meyer (HAS) and Antje Behring (G-BA)
7.	Opportunities for advice on post-licensing data generation plans (including registries and real world evidence) and related developments under work package 5b	Topic leads: <ul style="list-style-type: none"> EMA: Xavier Kurz, Alison Cave, Jane Moseley EUnetHTA: François Meyer (HAS) and Antje Behring (G-BA)
8.	Bridge from regulatory approval to market entry: facilitating sharing the regulatory review and related information in view of joint relative effectiveness assessments under work package 4	Topic leads: <ul style="list-style-type: none"> EMA: Michael Berntgen EUnetHTA: Marianne Klemp (NIPHNO) and Michelle Mujoomdar (EUnetHTA Directorate / ZIN)
9.	Approaches for collaboration on horizon scanning to assist in joint priority setting – review of methodologies (business pipeline reviews, PRIME scheme)	Topic leads: <ul style="list-style-type: none"> EMA: Corinne de Vries, Enrico Tognana, Jordi Llinares EUnetHTA: Wim Goettsch
10.	Experience with Patient engagement in the context of regulatory and HTA activities	Topic leads: <ul style="list-style-type: none"> EMA: Isabelle Moulon EUnetHTA: Antje Behring (G-BA)
11.	Action points from previous meetings	All
12.	Closing remarks	Hans-Georg Eichler and Wim Goettsch

This was the 12th meeting between the European Medicines Agency (EMA) and representatives from the European Network for Health Technology Assessment (EUnetHTA). In the various introductory remarks reference was made to the reflection paper on “Synergies between regulatory and HTA issues on pharmaceuticals”, which was recently adopted by the HTA Network. The collaboration between the EMA and EUnetHTA, which started in 2010, contributes to the delivery of this reflection paper. As this was the first meeting since establishment of Joint Action 3 (JA3), one expected deliverable will be the establishment of a joint work programme that identifies the priorities for the cooperation. It was recognised the cooperation will need to focus on the benefit for the patient and it is in this context that

the generation of relevant evidence for decision making is necessary. Also it was noted that such collaboration of equal partners requires exchange and coordination of positions and goals.

The draft agenda was adopted without changes.

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

The European Commission referred to the reflection paper on synergies between regulatory and HTA issues to mark activities relevant to the EMA-EUnetHTA collaboration:

1) Pre-marketing phase

- Define the process of parallel early dialogue/scientific advice in order to meet the needs of both HTA and regulatory bodies
- Collaborate on the elaboration of therapeutic area-specific guidelines, non-product specific qualification advice and opinions, to generate evidence addressing both regulatory and HTA needs

2) Market entry

- Promoting initiatives that contribute to a shared understanding of how regulatory and HTA bodies develop wording for the treatment eligible population
- Identify and implement an agreement that allows for early sharing of information between regulators and HTA bodies in order to support effective, efficient, and timely HTA processes

3) Post-marketing phase

- Identify processes to appropriately involve HTA bodies in the specification of data requirements in the post-launch evidence generation phase. (e.g. post-authorisation efficacy studies/PAESs and post-authorisation safety studies/PASS)
- Promote collaboration in the specification of data to be collected in registries

Activities are linked to work in JA3 work packages 4 and 5.

As a follow-up of the adoption of the Reflection paper, the HTA Network suggested to establish a "Synergy group" to map the actions identified in the reflection paper, whether they are already on-going or planned by different fora. This is expected to facilitate contacts/interactions between the different key players represented in different fora hence contributing to the common objective of facilitating access to medicines. The representation will comprise HTA (HTA Network and EUnetHTA) and regulators (HMA, STAMP, EMA), with the Commission to facilitate.

In terms of EU cooperation on HTA beyond 2020, the Inception Impact Assessment for an initiative to strengthen EU cooperation on HTA and the Public consultation on a future initiative aiming for strengthening the EU cooperation on HTA were highlighted.

Overview of the establishment of Joint Action 3

Joint Action 3 is geared towards the development of a sustainable network on HTA in Europe. Specific objectives of JA3 are

- To increase production of high-quality joint work on HTA

- To increase uptake and implementation of joint work on HTA at the national, regional, and local level
- To support evidence-based, sustainable, and equitable choices in healthcare and health technologies

The background, establishment and structure of JA3 were reviewed. Of particular relevance for the EMA/EUnetHTA collaboration are the following work packages (WP):

- WP4 to refine the production processes of joint assessment reports based on lessons learned and experiences from JA2 and execute a phased roll-out of collaborative assessments; to develop and refine a system of horizon scanning, topic selection and prioritisation; to develop a process that facilitates the implementation of the jointly produced assessments in the national/regional practice; and to provide input to WP1 on final processes and recommendations for a sustainable model of European collaboration on joint assessments after 2020. The deliverables for year 1 include a procedure for the production of joint assessments of pharmaceuticals that more closely aligns with the timelines for market authorisation.
- WP5 on Evidence Generation with
 - Strand A on Early Dialogues (EDs), based on JA2 and SEED experience, continue and improve EDs, including parallel advice with EMA, with contribution of patients and affected stakeholders. Set up a Standing Committee gathering most experienced partners. Propose and implement a new financing system based on a fee-for-service approach.
 - Strand B on Post launch evidence generation (PLEG), based on previous work of JA2 and the PARENT JA, develop collaboration for cross-border PLEG in the form of pilots for drugs and non-drug technologies (B1); Registries: Enhance the use of high-quality registries in HTA; Defining Quality Standards for the use of registries for HTA; Conducting pilots of PLEG through high quality registries.

Furthermore, it was noted that for WP6 there should be collaborative work on guidelines. Also work of WP7 is indirectly relevant for synergies as the collaboration is expected to increase the acceptance of joint HTA reports on REA.

Topics and priorities for the development of an EMA/EUnetHTA work plan

For the development of the EMA/EUnetHTA work plan, it was agreed to be guided by the HTA Network's reflection paper on synergies and to focus on gaps that are not covered by other initiatives. Following initial reflections and subsequent discussions at the meeting, the following areas for collaboration were agreed:

1. Parallel Multi-HTA/EMA early dialogues
2. "Late dialogues" / peri-licensing advice on post-licensing data generation plans
3. Registries and real world evidence, including their application
4. Facilitating the exchange of information between regulatory outcome and HTA, including optimisation of output documents
5. Exchange on methodologies to identify and document the eligible population for a treatment

6. Mutual understanding of approaches for significant benefit vs. added therapeutic value for orphan medicines, including relevant comparator
7. Exchange on concepts including unmet need and therapeutic innovation for priority setting
8. Collaborative approaches to horizon scanning
9. Sharing of methodologies and approaches for patient and clinician engagement in the context of regulatory and HTA activities
10. Shared understanding of methodological approaches for design, analysis and interpretation of clinical trials and observational studies; avoiding inconsistencies in available guidance to industry; identifying gaps in methodology for future research
11. Population-specific or Intervention-specific areas: e.g., Paediatric medicines, vaccines, combination products/companion diagnostics

ACTION:

- Development of a detailed work plan for agreement ahead of the next EMA/EUnetHTA meeting – EMA and EUnetHTA

Experiences and perspectives for multi-stakeholder scientific advice to developers

Both EMA and EUnetHTA provided an update on the current status of the platforms for discussing development programmes involving regulators and HTA bodies. For the parallel regulatory/HTA scientific advice, the continuous improvement activities for the process along with the fine-tuning of the best practice guide were summarised. It was noted that the first regulatory HTA qualification procedure is progressing. Furthermore, the progress with the establishment of the process for early dialogue under Joint Action 3 was presented outlining the objectives, key aspects, scope, numbers and timelines of WP5 Strand A. This also included an outline of the plans for the Standing Committee to support such advice / dialogue under Joint Action 3.

During the discussion the challenge of providing adequate resources into the various procedures was noted. The high demand for such product specific discussions requires significant investment of both regulators and HTA bodies. At the same time it was agreed that for such guidance on development projects to be meaningful, there is a need to have the necessary engagement from key players. Subsequent discussions are needed to address how to best manage this challenge.

Other observations included that at present the visibility of the final advice letter to the other parties depends on the willingness of the company to share this output as well as the challenges concerning remuneration of HTA bodies e.g. through fees.

Overall it was noted that both platforms (i.e. parallel regulatory/HTA scientific advice and multi-HTA early dialogue involving regulators) can serve as learning environments that allow further developing this type of interaction with the ultimate aim of convergence into a single procedural framework. It was noted this requires the coordination amongst HTA bodies to be well established and running smoothly. In the interest of public health, it is therefore considered important to progress together in a concerted manner that allows continuous learning and fine-tuning of the frameworks whilst providing relevant guidance on product-specific developments.

ACTION:

- Follow-up discussion on resourcing parallel scientific advice / early dialogue from the perspective of HTA bodies – EC, EUnetHTA and EMA
- Collaboration on the establishment of early dialogues under Joint Action 3 – EMA and EUnetHTA

Opportunities for advice on post-licensing data generation plans (including registries and real world evidence) and related developments under work package 5b

The current initiatives to support lifecycle regulatory decision-making with regard to Real World Evidence and Registries were summarised by EMA. This included an analysis of registries imposed during 2005-2013 as an obligation at the time of authorisation for centrally approved products, where one result was that collection of HTA-related variables in registries concerning Quality of Life data and measurement of resource use accounted for 26% and 10%, respectively. EMA presented their taskforce composed of representatives of EMA Scientific committees and working parties, the European Commission, experts from national competent authorities and EMA staff, which has been overseeing a pilot phase for EMA registry activities. The objective was to serve as a platform for learning about enablers and barriers to using existing disease registries (e.g. collaborations, data sharing, additional data collaboration, transparency), establishing a new registry (e.g. core data elements, data standardisation), and sustainability. So far 18 expressions for study topics have been received (9 from pharmaceutical companies and 9 from registry managers/academia).

Under Joint Action 3 the WP5 Strand B is dedicated to post-launch (additional) evidence generation with special focus on the use of registries as data source. The objectives are to develop collaboration for cross-border PLEG in the form of pilots for drugs and non-drug technologies, enhance the use of high-quality registries in HTA through the PLEG pilots (Strand B1), and through the definition of Standards Tool for Registers in HTA, and develop a “tool” (document) to indicate the best practices for PLEG and support permanent collaboration in the field. With regard to pilots, preparatory work is ongoing to establish an inventory of existing projects/initiatives in the field, including an analysis of how they could be integrated in the project, a list of upstream and downstream stakeholders to collaborate with as well as a list of possible legal or practical barriers for data pooling and possible solutions. Round 1 pilot production is expected for mid-2017 to mid-2018. Other work in the work package concerns standard tools for registries in HTA with the objective to adapt existing quality standards for registries into a practical tool for use of registry data in HTA.

During the discussion it was highlighted that any alignment in terms of identifying the needs by HTA bodies and regulators in the context of the request for registry data would be advantageous. From an HTA perspective, cross-border pilots on post-licensing evidence generation would be most useful for rare diseases and for innovative technologies. The current EMA pilot on registries includes advanced topic proposals and for these, collaboration with WP5 could be envisaged. It would be worth exploring what discussions can occur earlier in the development (e.g. through scientific advice) and which discussion might be best held closer to the time of decision making around market entry. Furthermore, to avoid duplication it would be relevant to enhance discussions in the context of methodologies. Here it was noticed that learnings from other relevant initiatives (like PARENT, Get Real, ENCePP) should be taken into account.

ACTION:

- Foster engagement in the context of ongoing pilots from the EMA as well as pilots identified by WP5B – EMA and EUnetHTA
- Explore the concept of “late dialogue” to facilitate product-specific discussions around Opinion phase – EMA
- Close collaboration in the area of methodologies for registries – EMA and EUnetHTA

Bridge from regulatory approval to market entry: facilitating sharing the regulatory review and related information in view of joint relative effectiveness assessments under work package 4

A working group from EUnetHTA and EMA presented the status of an initiative to facilitate that the final assessment by the EMA's CHMP is made available to the HTA bodies early enough for inclusion in the process of rapid relative effectiveness assessment (rapid REA) of pharmaceuticals. The objective is to develop a clearly defined process for collaboration between the EMA and EUnetHTA in the context of joint production under JA3 WP4, with identified roles and responsibilities, to make available to HTA reviewers the outcome of the regulatory assessment after CHMP opinion under the terms of a confidentiality arrangement and to facilitate mutual understanding of the outcomes of each decision making. Key concepts for the process and its operation were presented.

The importance of this initiative was recognised and it was agreed that a step-wise approach should be taken to ensure all parties are comfortable with the engagement and learnings can be embedded. Direct interactions between assessors from regulators and HTA bodies were deemed relevant to enhance mutual understanding whilst respecting the individual remits. Oversight and capturing the experience are therefore necessary during the piloting and respective closing meetings should be organised. Furthermore, it was noted that national update of joint production will be an important success factor; WP7 will track such national update.

It was highlighted that transparency of this engagement is necessary and that the procedural guidance should be made available on the websites of both EMA and EUnetHTA. Also there are opportunities for provision of information about the pilot by EMA to prospective applicants in the context of pre-submission meetings and pipeline discussions.

ACTION:

- The working group of EMA and WP4 will continue the preparation of the process, in collaboration with the EC.

Approaches for collaboration on horizon scanning to assist in joint priority setting – review of methodologies (business pipeline reviews, PRIME scheme)

In the context of preparedness and planning, EMA presented its activities around business pipeline analysis and forecasting, as well as the Innovation task force and the EU Innovation Network. With information from about 50 large pharmaceutical companies about their business pipeline as well as engagement with small innovators at very early stages, there are opportunities to plan upcoming product evaluations as well as to support identification of products addressing unmet medical need. Furthermore, an outline of the experience with the PRIME initiative was provided. Given that the final goal is to ensure patient timely access to priority medicines, the question was raised on how to best engage with HTA bodies in the context of awareness and information sharing, and how to facilitate HTA

participation in PRIME (e.g. with regard to identification of unmet medical need, post authorisation data generation, and participation in scientific advice).

From EUnetHTA perspective, horizon scanning is relevant for activities in WP4 on relative effectiveness assessments in order to facilitate the product selection and the identification of HTA authors for the joint production. Also it was noted that some countries have their own processes and that others collaborate on a national basis. The insight into the planning process at EMA is therefore relevant, particularly with regard to business analysis and forecasting. Visibility of early innovation appears less of relevance for HTA bodies for their planning. On the other hand, it was noted that, whilst the follow-up on perspectives for unmet medical need is scientifically interesting for HTA bodies, there are challenges how to resource and finance such additional work. Initiatives by the BeNeLuxA cooperation with regard to identification of unmet medical need were noted.

ACTION:

- Explore needs amongst HTA bodies regarding medicinal products in the pipeline that could be addressed with information routinely available through the EMA activities – EUnetHTA. Following on from this, identify the opportunities for making relevant information available to HTA bodies – EMA
- Engage in the discussions about the concept of unmet medical need as part of the joint work programme – EMA, EUnetHTA and EC.

Experience with Patient engagement in the context of regulatory and HTA activities

EMA presented the experience with patient engagement with a view to facilitate participation in benefit/risk evaluation and related activities throughout the life cycle of medicines to capture values and preferences and obtain information on the use of medicines from early development through evaluation and post-marketing surveillance. This included a review of the opportunities for involvement throughout medicines' lifecycle; distinctions were made for patients representing *patients'* organisations, patients representing *their* organisations, and patients as *individual* experts. Methodologies include participation in scientific committee meetings (e.g. oral explanations), in working party meetings (e.g. Scientific Advice Working Party), in Scientific Advisory Group meetings (SAGs) or Ad-Hoc Expert group meetings, in dedicated meeting on medicine or disease-specific issues, in written consultation (product /disease related), and in online survey / questionnaire (non-product related). Other methodologies include eliciting patients' values and preferences, e.g. Multi Criteria Decision Analysis (MDCA).

On the example of G-BA experience it was displayed how patients can best contribute to the HTA and the decision process. Patient representatives are present in all meetings of the G-BA (working groups, sub-committees, oral hearings, and plenum). They take part in discussions, but have no right to vote.

It was noted the EC recently presented on "EU cooperation on HTA" at the EMA meeting with all eligible patients' and consumers' organisations and that the participants suggested to set up a specific PCWP topic group on HTA to support the involvement of patients/consumers. This could be one way to facilitate that EUnetHTA get in contact with patient organisations which may so far not be part of the engagement.

ACTION:

- Follow-up on the proposal to establish a specific PCWP topic group on HTA to support the involvement of patients/consumers – EMA

Action points from previous meetings

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

ACTION:

- Updated listing to be circulated to participants.

Closing remarks

The next meeting will be hosted by EUnetHTA and will be scheduled for 2Q17.