EMA / EUnetHTA meeting – Summary Report

10 December 2013, 10:30 – 17:00 CET

Local host: Institute for Quality and Efficiency in Health Care (IQWiG)
Im Mediapark 8; Room Munchen BC
D-50670 Cologne, Germany

AGENDA

Co-chairs: Finn Børlum Kristensen and Hans-Georg Eichler

Coffee – light refreshment	*10.00 – 10.30*
Welcome by the IQWIG's Executive Director(Jürgen Windeler)	10:30
Adoption of draft agenda and review of the action points from the last meeting (co-chairs)	
Update on the HTA Network development (DG SANCO representative)	10:40
Benefit-risk methodologies for regulators and assessment methodologies for HTA bodies including update on EMA's effects table (EMA, EUnetHTA (IQWIG))	10:50
Coffee break	*11:30*
Update and open discussion on the role of regulators ("adaptive licensing"), HTA entities, and payers along the life cycle of technologies; including how drug/technology development process could be re-engineered in the companies to better meet the requirements (EMA, EUnetHTA (CVZ)	11:45
Lunch break	*13.00 - 14.00*
Update on public access to full study reports (EMA)	14:00
Path towards increased efficiency in early dialogue (EMA, EUnetHTA (HAS)	14:30
Coffee break	*15:00*
Improving the quality of the SmPC ("Summary of Product characteristics") document – update (EMA, EUnetHTA (HVB)	15:15
EMA's input and participation in the programme of the EUnetHTA Conference October 30-31, 2014 "HTA 2.0 Europe – teaming up for value" (EUnetHTA (Secretariat)	15:45
Identifying and agreeing on specific activities to implement the 3-year work plan (co-chairs)	16:15
Any other business and closing remarks	16:45

This was the seventh meeting between the European Medicines Agency (EMA) and representatives from the European network for Health Technology Assessment (EUnetHTA), led by Co-chairs Finn Børlum Kristensen (EUnetHTA) and Hans-Georg Eichler (EMA).

Participants were welcomed by the IQWiG's Executive Director, Jürgen Windeler, who emphasized German support for dialogue between European regulators and HTA bodies through the EMA-EUnetHTA collaboration. He further explained the position of IQWiG in the German health care system, importance of IQWiG health technology assessments during the last 10 years, and the GBA appraisal process and current regulatory framework (AMNOG).

Hans-Georg Eichler welcomed all participants on behalf of co-chairs, and after tour de table the draft agenda was adopted with the exception that the agenda point on improving the quality of the Summary of Product characteristics would not be addressed in this meeting.

Update on the HTA Network development

The representative of the European Commission summarised the recent developments of the European cooperation on HTA as per Article 15 of Directive 2011/24/EU. The EU cooperation on HTA is now organized in two levels, a strategy level (the HTA Network (HTAN), with the 1st meeting held on 16 10 2013 and adoption of the Rules of Procedure and the Work Plan 2014-2015) and a scientific and technical cooperation level (EUnetHTA), to work in synergy and complementarity, with involvement of stakeholders in both strategic and scientific level. EMA is included as third party in the HTA network (as per the Rules of Procedure).
The representative informed that on the strategy level, a HTAN working group has been formed to start the work on the long term strategy (the 1st meeting was held on 09 12 2013) formulating a clear long term vision for EU cooperation on HTA, (so-called HTAN Position Paper). The HTAN will also produce a reflection paper on conditions to facilitate re-use of HTA information at national level (2014, 2015) and a reflection paper on synergies between HTA and the regulatory process (2nd half 2015). Other relevant developments that were mentioned as attracting attention of the HTAN were collaboration on pharmacovigilance, Joint Action on pharmacovigilance, post authorization efficacy studies (PAES), Network of competent authorities for pricing and reimbursement, EC funded tender SEED, the clinical trials directive, and regulation for medical devices.
It was concluded in the HTAN meeting that proof of return on investment is needed for future EU funding for HTA collaboration and that the life-cycle approach should play a key role in finding further value (increase synergies/defragmentation up- and downstream from the point of marketing approval).
It was noted by the HTAN that it varies per country whether the strategy and scientific levels involve different organisations from that country.
It was also noted that the discussions on the strategic level were constructive but that there is variance in how far countries want or are able to engage in collaboration due to, e.g., legal issues.
After the presentation there was a discussion on the strong expectation from the HTA organisations on the regulation on medical devices and there was reluctance whether the current regulations will meet these expectations (one of the major concerns being transparency (of the work and results of the Notified Bodies)).

Action point:

- No specific action points determined.

Benefit-risk methodologies for regulators and assessment methodologies for HTA bodies including update on EMA's effects table

EMA presented the current status of the benefit-risk project (through five WPs) at EMA. The main aim of the project is to improve transparency, communication and consistency of benefit-risk assessments. Based on this research, for which reports are available on the EMA

website, an Effect table is proposed (qualitative method) that summarises the key issues that should be discussed for the benefit risk decision. A quantitative method (MCDA) has been explored and is positioned as a tool for making more explicit value judgments. The Effects table is being piloted with the CHMP, that gave an overall positive feedback. There will be a second pilot phase to test the table in more detail, to be able to finalise ET guidance. It was noted by HTA organisations that it would be helpful to have information on the precision of effect estimates in the table.
IQWIG presented their methodology on the assessment of the extent of added benefit of new drugs. The methodology is based on requirements from German law which specifies the types of endpoints to be included in the assessment and the categories of benefit to be used. A drug can have added benefit, no added benefit or less benefit compared to a defined comparator intervention. Added benefit has to be categorised into major, considerable, minor or not quantifiable added benefit. The qualitative uncertainty of the evidence will be categorised into three levels: proof, indication or hint. The categorisation of benefit considers the relevance or impact of the endpoint and the effect size. IQWIG's methodology defines thresholds to be used for adjusted hypotheses describing the different extents of added benefit. IQWIG also uses effects tables to present the extent of added benefit on an endpoint level before combining all results to a summary statement. One table includes relative risk estimates with 95% confidence intervals as well as absolute risks, and information on the (qualitative) uncertainty of the evidence per outcome. A further table provides the (semi-) quantified comparison of positive and negative effects along with the corresponding qualitative uncertainty.
CVZ presented the current methodology that is used in Work Package 5 of EUnetHTA for rapid relative effectiveness assessments. The summary of the rapid assessments synthesises information from the first four domains of the HTA Core Model. Research has led to the conclusion that there is no state of the art method to quantify the benefit/harm balance. Therefore data are also presented in an effects table that includes information on intervention vs comparator, the effect size of the mean outcomes and uncertainty of the evidence.
It was pointed out that a difference between regulators and HTA bodies is that regulators assess the quality of individual studies whereas HTA bodies assess the overall evidence, often using GRADE methodology. It was concluded that the idea behind the tables is similar but the content varies. Further collaboration in this area was considered fruitful for all parties to exchange knowledge and experience and to align the content of the tables.

Action points:

- EMA will invite EUnetHTA to identify HTA organisations to the next working group meetings on benefit-risk methodology

Update and open discussion on the role of regulators ("adaptive licensing"), HTA entities, and payers along the life cycle of technologies

EMA explained that the thinking behind a drug regulation approach with updating a license along with the maturity of the evidence available. It was noted by EMA that the regulatory tools like CMA are already available; also tools like the PAES framework are under development. Involvement of payers and HTA in the design of data collection after the initial market authorisation is paramount, and also in situations when early access is granted but there is no reimbursement. Unless the idea of revising decisions along the path of development is shared by different decision makers it will be difficult to move forward. This also involves wider inclusion of stakeholders (such as patients). There are considerations for a safe environment for volunteering companies to embark into pilots.
It was noted by the HTA bodies that this approach might not be viable for all pharmaceuticals (e.g. large patient populations or high probability of off-label use) but more suitable for e.g. new compounds or in case of no alternatives, high unmet need, severe disease, small populations, among others). In addition, it was added that the current experience from

gathering data after decision making (coverage with evidence development) are not very promising. Moreover, other aspects such as political willingness to revise decisions is for example a real-life hurdle. The HTA bodies also supported the idea that more uncertainty in the data could lead to a lower price and vice versa. It was also pointed out that payers might be very reluctant to pay at all for a product with increased uncertainty. It was also questioned if adaptive licensing should lead to earlier licensing.
It was emphasised that participation in EMA pilots is at the discretion of individual HTA bodies and is not an EUnetHTA decision.

Action point:

- EMA will inform EUnetHTA and send invitations to HTA bodies to participate in pilots, once identified

Update on public access to full study reports

EMA explained the current status of public access to full study reports. EMA is working toward full access of study reports for all pharmaceuticals that received market authorization. There are some setbacks in achieving this. A final position from EMA will be published in 2014.

It was indicated by CVZ that it is difficult to receive information produced by EMA as input for the early phase of the pilots in work package 5. It was emphasised by EMA that it is up to companies to share this information. There is no need to ask EMA for permission. It was noted by EMA that this has been discussed before and EMA asked whether the problem is that companies are not aware of the situations.
In addition, a request was made whether it is possible to have more insight in the CHMP agenda for timing purposes. EMA responded that the CHMP agenda will become publicly available. This may help the HTA organisations to have a quicker insight on the timing of final opinions of the CHMP.
There was a request from HTA bodies to the European Commission whether HTA bodies can have access to CHMP information between CHMP opinion and EC decision. The HTA bodies indicated that it would help the HTA organisations also to start joint pilots in situations where the companies are not willing to be involved in a pilot. The EC responded that it is not likely that the current practice will be changed and it is probably easier to approach pharmaceutical companies directly.

Action point:

- Letter from CVZ on behalf of EUnetHTA asking for early access to scientific advice from CHMP so EMA can respond that companies can share the information if they want to. Additionally, EMA indicated that they could inform companies that it is possible to inform HTA agencies during the CHMP process if they want to.

Path towards increased efficiency in early dialogue

There was an introduction by EMA based on the press release on early dialogue between regulators and health technology assessment bodies. The press release focuses on parallel early dialogue performed by EMA and not HTA dialogues. EMA explained that there is need from stakeholders to have publicly available information on the current process for parallel early dialogues. Therefore EMA is investing in a procedure that will be subject to consultation mid 2014 (guidance for EMA-HTA parallel scientific advice).
HAS explained the work done in EUnetHTA on early dialogues by HTA bodies in the last years. A total of 10 early dialogues pilots have been done and the process will now move into the SEED tender phase which will include 7 early dialogues on pharmaceuticals and 3 on medical devices. THE SEED consortium will base its work on EUnetHTA's work and all HTA

partners SEED are partners in EUnetHTA. Three EMA-SEED dialogues are planned in 2014. These three dialogues will test three scenarios with different levels of aligned processes between regulators and payers. The SEED should come up with recommendation to the European Commission for a permanent structure for early dialogues from HTA bodies after having consulted EUnetHTA.
It was clarified that in the EUnetHTA pilots all HTA bodies draft answers to the questions from the company. These are discussed between the countries. If different opinions remain, different countries explain different positions to company.

Action point:

- EMA, EUnetHTA and individual HTA bodies will try to align their position on permanent infrastructure for parallel early dialogues.

Improving the quality of the SmPC ("Summary of Product characteristics") document – update

This point was removed from the agenda

EMA's input and participation in the programme of the EUnetHTA Conference October 30-31, 2014 "HTA 2.0 Europe – teaming up for value"

The details about the conference were presented by the EUnetHTA secretariat. Key points to be addressed in the conference are practice of HTA production in the context of interaction among the current developments in HTA, regulation, health policy/decision-making_ putting methods into practice and teaming up with other players. The conference will host about 600-800 people and will be organised with plenaries as one of the few formats of interaction. The HTA network will meet the day before Day 1 of the conference. EUnetHTA would welcome eg, a plenary session with EMA. EMA confirmed their interest to participate in the EUnetHTA conference. Session on medical devices will be welcomed.

Action point:

- An EMA-EUnetHTA plenary session will be organised at the EUnetHTA conference in 2014
- EUnetHTA will propose a format and content for a EMA-EUnetHTA plenary session. Based on the proposal EMA and EUnetHTA will develop specific proposal for EMA's inclusion in the conference programme.

Review of the action points from the last meeting (Appendix 1).

- EMA confirmed that an observer status in their scientific advice activities can be extended to the EUnetHTA representative(s). EUnetHTA is to clarify internally which organisation(s) are to act as EUnetHTA representatives in the EMA scientific advice exercises.
- Post-authorisation collection for the ENCePP HTA working group the main focus is on capacity building. Only two additional core members from EUnetHTA in the ENCEPP HTA WG can be accommodated. Thus, EUnetHTA will need to reduce the list of proposed partners to join the group. For parallel advice on post-authorisation data collection, this will be developed in 2014 and may be included in the new guidance
- Scientific guideline development: 1) EUnetHTA does indeed receive EMA's list of draft guidelines for consultation. This service is appreciated by EUnetHTA. It was mentioned by EMA that it is also possible to involve HTA bodies in the drafting of guidelines if this would be preferred. 2) EMA would like to have information about EUnetHTA's work on disease specific guidelines. It was confirmed that EMA should be involved in time.
- Orphan medicines products: will be discussed in next meeting

Action points:

- EMA continues to send the list of consultations on guidelines to EUnetHTA secretariat on a regular basis.
- EUnetHTA to inform its members on a possibility to be directly involved in the drafting of the guidelines.
- EUnetHTA will involve EMA in the work on disease specific guidelines – details of involvement (mode and timing) will be clarified by the EUnetHTA WP7 LP
- Orphan medicines will be listed as agenda item for the next meeting

Identifying and agreeing on specific activities to implement the 3-year work plan

There was a discussion whether all topics that had been addressed at the meeting could be grouped in the bullet list in the 3-year work plan. This was confirmed. It was mentioned that the benefit risk group meetings can be considered cooperation in pilot projects. Further it was discussed whether personalised medicine including companion diagnostics should become a discussion item.

Action points:

- No specific action point identified.

Any other business and closing remarks

- Minutes of this meeting will be published on public websites.
- Next meeting will be called by EMA in London, most probably in May.

PARTICIPANTS LIST

EMA / CHMP representatives

Attendee	Organisation
Peter Arlett	**EMA**
Michael Berntgen	**EMA**
Hans-Georg Eichler	**EMA**
Harald Enzmann	**EMA /CHMP**
Tomas Salmonson	**EMA /CHMP**
Spiros Vamvakas	**EMA**

EUnetHTA

Eva Zebedin-Brandl	**HVB, Hauptverband der Österreichichen Sozialversicherungsträger**	Austria
Frank Hulstaert	**KCE, Belgian Health Care Knowledge Center**	Belgium
Mirjana Huic	**AAZ, Agency for Quality and Accreditation in Health Care and Social Welfare**	Croatia
Finn Børlum Kristensen	**DHMA, Danish Health and Medicines Authority (EUnetHTA Secretariat)**	Denmark
Francois Meyer	**HAS, Haute Autorité de Santé**	France
Antje Behring	**G-BA, Gemeinsamer Bundesausschuss**	Germany

Jürgen Windeler **Stefan Lange** **Ruth Schwarzer** **Alric Rüther** **Beate Wieseler**	**IQWIG, Institute for Quality and Efficiency in Health Care**	Germany
Agnese Cangini **Simona Montilla** **Paolo Siviero**	**AIFA, Agenzia Italiana Del Farmaco**	Italy
Luciana Ballini	**ASSR, Regional Agency for health and social care – Emilia Romagna**	Italy
Sarah Kleijnen **Wim Goettsch**	**CVZ,** **Health Care Insurance Board**	Netherlands
Marianne Klemp	**NOKC, Norwegian Knowledge Centre for the Health Services**	Norway
Anna Zawada	**AHTAPol, Agency for HTA in Poland**	Poland
Leonor Varela	**AVALIA-t, Galician Agency for HTA Assessment**	Spain
Auxiliadora Castillo	**AETSA, Andalusian HTA Agency**	Spain
Elisabeth George	**NICE, National Institute for Health and Care Excellence**	United Kingdom

European Commission

Name	Organisation
Flora Giorgio	**European Commission, DG Sanco**
Jerome Boehm	**European Commission, DG Sanco**