Minutes of the EMA-EUnetHTA meeting

22 February 2012 – chaired by Mira Pavlovic (HAS)

Participants

Institution	Name	Surname	Country
European commission	TYSSE	Anders-Lamark	Belgium
EMA	EICHLER	Hans-Georg	UK
EMA	ARLETT	Peter	UK
EMA	BERNTGEN	Michael	UK
EMA	VAMVAKAS	Spiros	UK
EMA/CHMP	ABADIE	Eric	UK
EMA/CHMP	ENZMANN	Harald	UK
EMA/CHMP	IRS	Alar	UK
EUnetHTA/HBV	BUCSICS	Anna	Austria
EUnetHTA/IQWIG	WIESELER	Beate	Germany
EUnetHTA/NICE	LONGSON	Carol	UK
EUnetHTA/NICE	GEORGE	Elisabeth	UK
EUnetHTA	BORLUM KRISTENSEN	Finn	Denmark
EUnetHTA/AIFA	FOLINO	Pietro	Italy
EUnetHTA/CVZ	GOETTSCH	Wim	The Netherlands
EUnetHTA/CVZ	KLEIJNEN	Sarah	The Netherlands
EUnetHTA/NOKC	KLEMP	Marianne	Norway
EUnetHTA/HAS	MEYER	François	France
EUnetHTA/HAS	PAVLOVIC	Mira	France
EUnetHTA/HAS	GUZINA	Irena	France
EUnetHTA/HAS	GOURVIL	Anne	France

Agenda

HAS Welcome Speech: *Jean-Luc Harousseau (F. Meyer)* **Introduction to EMA-EUnetHTA meeting:** *Finn Børlum Kristensen , Hans-Georg Eichler*	10.30 - 11.00
1. Progress of relevant work packages in EUnetHTA - **Pilot:** *Wim Goettsch* - **Guidelines:** *Mira Pavlovic*	11.00 – 11.45
Anne Gourvil (EUnetHTA) and Michael Berntgen (EMA) **2. Evaluation of the new EPARs**	11.45 – 13.15
Lunch break	13.15 - 14.15
Mira Pavlovic (EUnetHTA) and Spiros Vamvakas (EMA) **3. Scientific advice** - **EMA/HTA parallel advice (Pharmaceuticals)** - **EUnetHTA scientific advice (other HT)**	14.15 – 15.45
Coffee break	15.45 – 16.15
Peter Arlett (EMA)and Irena Guzina (EUnetHTA) **4. Databases for post-licensing studies** – **Follow-up from previous discussions**	16.15 – 17.00
Conclusion to EMA-EUnetHTA meeting: *Finn Børlum Kristensen, Hans-Georg Eichler, M. Pavlovic*	17.00 - 17.30

Summary of discussion

The main objective of this meeting was to follow on previous discussions between EMA and HTA bodies on how the EPAR could make a better contribution to the assessment of relative effectiveness by HTA bodies and to initiate a discussion on HTA scientific advice (EMA-HTA joint scientific advice and early dialogues of HTA bodies).

It was acknowledged that this EMA-EUnetHTA collaboration is supported by all participants of the meeting.

1- Update of EUnetHTA workpackage 5:

Rapid model, pilot and future developments:

The ongoing pilot (Pazopanib for the treatment of advanced or metastatic renal cell cancer) to test the draft model for rapid relative effectiveness assessment will be released for the Stakeholder Advisory Group (SAG) consultation in March 2012 and for public consultation in May 2012. A second pilot is planned before October 2012 and 14 other pilot rapid assessments are anticipated for Joint action 2 between October 2012 and October 2015. They will concern 10 pharmaceuticals (coordinated by CVZ) and 4 other health technologies (coordinated by LBI-HTA).

The second pilot will be organised differently than for pazopanib that involved 3 authors per domain. Two organisations will perform the assessment of the 4 domains (one institution being author and the other co-author or thorough reviewer) and a pool of dedicated HTA organisations will critically review the report. The selection of the product for the 2nd pilot is ongoing.

There was a discussion on how the information produced by EMA/CHMP could be made available to the HTA bodies early enough to be used for drafting the pilots:
The EPAR of a newly approved product is published only after the issuing of the Commission Decision, around 3 months after the positive opinion is adopted by the CHMP. The EPAR is the CHMP assessment report (AR) supporting the positive opinion and has only commercially confidential information deleted. Commercial information mainly concerns the manufacturing process (clinical information is not considered by the EMA as commercial confidential information). The CHMP AR supporting the positive opinion is adopted together with the Opinion at the same CHMP meeting. EUnetHTA could request this document from the company; alternatively EMA could explore whether the CHMP AR may be provided directly by EMA to EUnetHTA if the company agrees. In the future, as part of the pilot submission file, EunetHTA may also ask the company to submit the clinical part (CTD sections 2.5, 2.7.3, 2.7.4) of the marketing authorisation application as an appendix to the HTA submission file. Furthermore, access to full study reports according to ICH E3 is helpful (Section 5.3.5 of the CTD). These reports could also be added as appendices to the HTA submission file. Alternatively, since EMA is discussing to make the full study reports publicly available in the future, the full study reports could be linked to the EPAR on the EMA website.

It was also discussed how EMA/CHMP could help EUnetHTA in their selection process for the pilots. It has been announced that, starting beginning of March, EMA will publish on its website a list of products under review (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000349.jsp&mid=WC0b01ac05805083eb).

CVZ will soon identify 4 to 5 candidates for the 2nd pilot - preferably to treat a disease where comparators are available but not necessarily - either from the list of products included in the assessment pipeline of CVZ or from the EMA published list of drugs that is under review.

Methodological guidelines:

9 draft methodological guidelines (GL) are currently available: criteria for choice of most appropriate comparator(s), direct and indirect comparisons, clinical endpoints, surrogate endpoints, composite endpoints, health-related quality of life, safety, internal validity and external validity (applicability). These GL are EUnetHTA products (with the acknowledgement of the main contributors). Their primary objective is to help assessors performing REA of pharmaceuticals and give pragmatic and practical recommendations. However, these GL will be read by industry and it is expected that companies will take these recommendations into account when deciding on the development plans and the preparation of the submission dossiers.

The main comments received after the first WP5 consultation were about the scope and the terminology of the GL, the structure of the documents, the consistency across the GL and most importantly, about giving clear and useful recommendations to HTA assessors and pilot authors (These GLs were to be used as a basis for the assessment of pazopanib pilot with the core model).

The 2nd drafts of all guidelines were received in June 2011. The 3rd drafts should be prepared, taking into account the comments from pazopanib pilot authors and comments agreed during the recent meeting of WP5 (Vienna, 9-10 February 2012):

- The GLs needing only editorial changes (first batch) should be ready for March 5th: Clinical endpoints, Composite endpoints, Choice of comparator, Direct and indirect comparisons and Surrogate endpoints
- The GLs needing more important changes (second batch) should be ready by April 5th: Health-related quality of life, Safety, Internal validity and Applicability.
- WP5 and SAG consultation:
  - First batch: March 8 – April 13, 2012
  - Second batch: April 16 – May 25, 2012
- EMA and public consultation:
  - First batch: May 14 – July 14, 2012
  - Second batch: June 29 – September 3, 2012

There was a discussion on how the EMA/CHMP and EUnetHTA could mutually contribute to their respective guideline production during the consultation phase:

- Concerning the EUnetHTA GLs, the timelines proposed for the EMA's consultation (2 months) were endorsed. The expectations in terms of comments from the EMA are mainly to check the consistency with the EMA guidelines and to provide scientific input.
  The primary objective of these GLs is to help rapid assessment of pharmaceuticals. To make this objective straightforward before the consultation phase, it was decided that a general statement on the objective would be mentioned at the beginning of each GL.
- For the GLs produced by the EMA/CHMP and with relevance for HTA organisations (clinical and methodological), the EMA will establish a process to provide EUnetHTA (Finn Børlum Kristensen) with a list of guidelines under public consultation on a regular basis.

2- EPAR improvement project – critical review of first experiences

The background of the EPAR review is the result of discussions between EMA and EUnetHTA at 3 previous meetings in 2010 (EMA, London) and 2011 (CVZ, Diemen) where it was decided to adapt the EPAR template in line with the comments from MEDEV/EUnetHTA. The assessment report templates and EPARs were revised by EMA and used for Opinions since November 2010.

A questionnaire to monitor the implementation of new EPARs was developed by EMA based on the action items previously agreed by HTA and EMA. The review of 10 new EPARs was carried out in parallel by both EUnetHTA and EMA using the same questionnaire (36 questions targeting the identified areas for improvement i.e. the format, the scientific content and the support for SmPC of the EPARs) and methodology (the mean values in terms of compliance rate across all ten EPARs and all reviewers for each question were calculated).

The outcome of the review by EMA and EUnetHTA was presented and compared. Mainly, there was a high compliance of the EPARs regarding the jointly developed summary table of main efficacy data and the presentation of patient flow. However, there is still space for improvement in the critical discussion of the key elements of the clinical study design i.e. patient population (including sub-population and special populations), comparators, duration of the study, endpoints and/or composite endpoint use (some of these aspects are present in the clinical efficacy discussion but not enough visible or not enough discussed). Shortcomings of efficacy data would deserve more discussion and additional analysis requested by the CHMP should be better identified and elaborated in the EPAR. The substantiation of the SmPC was variable with some sections requiring additional attention (mainly "contra-indication", "warnings/precautions", "interactions" and "dose recommendations" (particularly deviations from standard dose)).

Suggestions for improvements were proposed and discussed, mainly increasing the granularity in the structure of the report template to address main aspects of the clinical efficacy discussion and make the information more visible, elaborating more on shortcomings/uncertainties and reasons for requesting additional analysis from the company. However, no formal agreement was reached on these proposals during the meeting. It was agreed that EUnetHTA would make a consolidated proposal for further improvements of the EPAR, highlighting their expectations and a new face-to face meeting to solve the remaining issues could be envisaged. Also the review will be presented to the CHMP together with any additional suggestions for improvement.

It was concluded that this parallel EPAR review work is of high interest given that it responds to the initial recommendations from the HLPF, and should be published after data refinement and results fine tuning.

3- Scientific advice

Parallel HTA-EMA pilot scientific advice

So far, 11 parallel HTA-EMA scientific advice procedures have been organised (9 finalised and 2 ongoing). 6 procedures happened through Tapestry network and 5 procedures were requested by individual companies. HTAs and payers from Sweden, UK, France, Italy, Netherlands, Spain, and Germany were invited by the companies to participate to the exercise. Further 4 parallel HTA-EMA SA requests are announced for 2012.

The main therapeutic areas concerned by those requests included diabetes, heart failure, Alzheimer's, lung cancer, breast cancer, melanoma, asthma, rheumatoid arthritis, multi-resistant infections, food allergies. The products all had new mechanisms of action in the respective area (new monoclonal antibodies, new chemicals or tumour vaccines).

Some of these products were at a very early stage of the development with non-clinical proof of concept and no clinical data. In this case, the responses given at the discussion meeting were general but the companies could benefit from orientation of what would be needed (pharmacological concept and general study design). Other products were at a later stage with available exploratory clinical data. The responses given at the discussion meeting were in that case more precise i.e. on which end-points, duration, comparators, size of the trial and statistical plans are important.

Some companies kept the request at a very "high level" and short, considering the variable background of the stakeholders. However, all stakeholders were of the view that comprehensive submission of the scientific facts is beneficial for the discussion. It is understood that there is a

higher degree of assumptions in the context of HTAs after Marketing Authorisation than with the regular CHMP scientific advice procedure. It is therefore recommended to keep a balance between assumptions and facts in a submission.

Early dialogues between developers and HTA bodies

This is one of the priorities for European Commission, in line with Pharmaceutical Forum recommendations, and part of EUnetHTA Joint Action 2 WP7: "improvement of evidence generation" (led by HAS and co-led by IQWIG, starting November 2012 until 2015). Pilot early dialogues with several HTA bodies are planned for 2 or 3 pilots (drug, non-drug) before the beginning of JA2 and will be coordinated by the HAS. This is a learning exercise to explore the feasibility of such pilots. These HTA early dialogue pilots aim at gaining experience on thinking prospectively of evidence requirements based on concrete examples and on working across HTA organisations in a specific field, having better input in parallel EMA – HTA advices and preparing JA 2, especially for non-drug technologies.

The procedure will be somewhat similar to the EMA SA procedure, i.e. a briefing document submitted by the company containing questions and company's position on comparators, comparisons, outcomes, cost-effectiveness, face-to-face meeting with a company and detailed minutes or written answers to questions, reviewed by all HTA bodies participating in the exercise.

There was a discussion on how the parallel HTA-EMA pilot scientific advice is going to further evolve in the near future. This European collaboration is important to foster innovative drug development for unmet medical needs. However, from the European Commission (EC) perspective, the EMA and HTA should be viewed as separate entities; it is therefore recommended to call the EMA-HTA SA "parallel" and not "joint". In addition, companies expect a streamlined position on their advice which may be different from a harmonised position.

Presently, the parallel HTA-EMA pilot scientific advice involves a limited participation of HTA bodies at time of the discussion meeting only (corresponding to D60 of the EMA SA procedure). Some are active participants and some others are "observers"; this is considered acceptable and part of the learning process of this exercise. In addition, HTA bodies do not issue written answers to the company (and the CHMP final advice remains confidential to HTA bodies). They only comment on the minutes of the discussion meeting. Providing written answer would require additional and empowered resources (3 times more than an oral input) and fees to afford it; at the moment, the HTA participation is generally free of charge for the company.

As a conclusion on this topic, it was decided to carry on building experience with the parallel HTA-EMA scientific advice for drugs with the existing EMA procedure. EUnetHTA (HAS [lead], NICE, AIFA) together with EMA (Spiros Vamvakas) will elaborate a list of topics to be discussed/improved in this common exercise such as defining the level of participation of HTA representatives (active participants or observers), issuing written responses or not, improving the current procedure, etc. The early dialogue pilots on drugs between developers and HTA bodies will be performed to prepare JA2. A procedure will be drafted soon by the HAS and released for comments beginning of March to HTA bodies which will participate to the pilots (6 HTA organisations). The first pilot meeting is planned beginning of May and a 2nd one beginning of June. With the experience from the 2 pilots, the draft procedure is intended to be improved and refined and the final procedure will be elaborated during JA2.

4- Databases for post-licensing studies

EUnetHTA WP7 EVIDENT: its main goal is to facilitate collaboration on generation of further evidence in order to promote collection of a coherent critical mass of data and to enable global analysis of consistent results. It will include information on:
- Additional studies or any kind of Additional Data Collection (ADC) requested by HTA bodies: minimum information necessary for establishing collaboration (PICO), protocols, results of studies, etc.

- The related technology: assessment status, evidence gaps, research questions, required additional studies, coverage decision status, etc.

All types of technologies are concerned (drugs, devices, procedures). In order to promote collaboration, information on the possible request for a study should be entered at the earliest possible stage by HTA bodies.

The public consultation on EVIDENT is now finalized and the next step is the IT development. Database's launch is planned for September 2012.

ENCePP is available to the general public and offers information on the available sources of expertise and research experience across Europe. It is fully searchable and allows the identification of Research Centres, Research Networks and data sources. It is adapted for both study sponsors and researchers seeking to identify collaborations for the conduct of specific pharmacoepidemiology and pharmacovigilance studies in Europe. It is linked to ENCePP e-register of studies, a free and publicly accessible resource for the registration of post-authorisation studies (currently, focus on post authorisation safety studies). Its aim is to increase transparency, reduce publication bias, promote information exchange and facilitate collaborations within the scientific community.

An update of the new EU pharmacovigilance legislation and its implications was presented by the EMA and the opportunities for further collaboration between medicines regulatory and HTA institutions in the context of post-licensing were also discussed. The following areas of collaboration were identified and proposed:

- Linking ENCePP studies database and EUnetHTA WP7 EVIDENT and creating common searches
- JA WP4 - Core HTA:
  - "Safety" domain definition and practical application
  - An HTA to include an assessment of the adverse events resulting from the use of a health technology both to benefit individual patients and to inform policy makers.
  - Definitions and terminology of safety used in HTA may need standardisation
  - Access to ADR data
- Comments on EMA/CHMP and EUnetHTA guidance (refer to previous discussion under point 1)
- Product specific discussions (focus in 2013?): possibilities to be explored through a pilot collaboration on Risk Management Planning:
  - Objectives / Design of post-authorisation safety studies
  - Objectives / Design of post-authorisation efficacy studies
  - Objectives for measuring the effectiveness of risk minimisation

Conclusion

A wrap-up of the day was done by the Chair of the meeting to summarise the main items that were discussed/decided at the meeting:

- **Rapid model, pilot and future developments**
  - Possibility for EUnetHTA to request the CHMP assessment report supporting the positive opinion from the company if the EPAR is not yet available. Alternatively EMA could explore whether the CHMP AR may be provided directly by EMA to EUnetHTA if the company agrees.
  - As of March 1st 2012, the EMA will publish in their website the list of drugs which are under review by the CHMP.
  - CVZ will identify 4 to 5 candidates for the 2nd pilot - preferably, but not necessarily, to treat a condition for which comparators are available - either from the list of products included in the assessment pipeline of CVZ or from the EMA published list of drugs that are under review.

- **EUnetHTA Methodological guidelines:**
  - The timelines proposed for the EMA's consultation (2 months) were endorsed (First batch: May 14 – July 14, 2012 and second batch: June 29 – September 3, 2012).
  - A general statement aiming at clarifying the objective of EUnetHTA guidelines (i.e. to support rapid assessment of pharmaceuticals) will be added to each guideline before the start of the consultation.
  - The EMA will establish a process to provide EUnetHTA (Finn Børlum Kristensen) on a regular basis with a list of guidelines produced by the EMA/CHMP and with relevance for HTA organisations (clinical and methodological).

- **EPAR improvement project – critical review of first experiences**
  - EUnetHTA (coordinated by HAS) will make a consolidated proposal for further improvements of the EPAR, highlighting their expectations and a new face-to face meeting to solve the remaining issues could be envisaged.
  - The EMA-EUnetHTA parallel EPAR review should be presented to the CHMP and published after data refinement and results fine tuning.

- **Scientific advice**
  - It was decided to carry on building experience with the parallel HTA-EMA scientific advice for drugs with the existing EMA procedure.
  - EUnetHTA (HAS [lead], NICE, AIFA) together with EMA (Spiros Vamvakas) will elaborate a list of topics to be discussed/improved in this common exercise such as defining the level of participation of HTA representatives (active participants or observers), issuing written responses or not, improving the current procedure, etc.
  - Pilots on early dialogue between developers of drugs and HTA bodies will be performed in 2012, before JA2. A procedure will be drafted by HAS and released for comments (early March) to HTA bodies which will participate to the pilots (6 HTA organisations). The first pilot meeting is planned beginning of May and a 2nd one beginning of June.

- **Databases for post-licensing studies**
  - The possibility to link ENCePP studies and EUnetHTA WP7 EVIDENT databases and to allow common searches will be explored
  - Establishing bridge between pre-marketing and post-licensing activities in the context of safety and RMP.

Next meeting

The next meeting will be held in **November 2012** (date TBD) either in Copenhagen (to be confirmed by Finn Børlum Kristensen by the end of March) or in London (EMA)