WP1

Appendix 4

EUnetHTA-EMA f-t-f meeting summary, February 11, 2010, London, UK

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 March 2010
EMA/96943/2010

Minutes of the Workshop on High Level Pharmaceutical Forum Recommendations on EPARS' contribution to Relative Effectiveness Assessment

11 February 2010 – chaired by Hans-Georg Eichler

Role	Name
Chair/Vice-chair	Hans-Georg Eichler (EMA)
Present:	Patrick Le Courtois (EMA), Xavier Luria (EMA), Francesco Pignatti(EMA), Michael Berntgen (EMA), Agnès Saint Raymond (EMA), Jordi Llinares (EMA), Laurent Brassart (EMA), Antionio Cherchi (EMA), Frida Rivère (EMA), Spiros Vamvakas (EMA), Eric Abadie (CHMP), Harald Enzmann (CHMP), Anders Lamark Tysse (EC), Wim Goettsch (EUnetHTA), Finn Børlum Kristensen (EUnetHTA), Francois Meyer (EUnetHTA), Anna Bucsisc (EUnetHTA), Sarah Kleijnen (EUnetHTA), Anne Dandon (EUnetHTA)
Teleconference:	Alar Irs (CHMP), Patrick Salmon (CHMP/COMP), Kerstin Westermark (COMP)

The European Medicines Agency (EMA) and representatives from the European network for Health Technology Assessment (EUnetHTA) Joint Action initiated a new collaboration, in which the EMA and EUnetHTA will be considering how the European Public Assessment Report (EPAR) could make a better contribution to the assessment of relative effectiveness of pharmaceuticals by health technology assessment bodies in the EU Member States.

1. Introduction

The Chair introduced the meeting summarising the background of this initiative. The collaboration between the EMA and EUnetHTA was initiated to address one of the recommendations made by the High Level Pharmaceutical Forum to improve the availability and best use of data relevant to relative effectiveness assessment. It was agreed that this new collaboration should be explored in a step-wise approach starting from the politically agreed mandate to consider how EPARs can further contribute to the relative effectiveness assessment of pharmaceuticals. Any further topics will be jointly reflected upon by the EMA and EUnetHTA. The primary objective of this meeting was therefore to allow for an

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initial discussion about the role of EPARs in activities of HTA bodies and to agree on next steps to explore future topics.

Introductory presentations were given on the following topics:

- European network for Health Technology Assessment - Finn Børlum Kristensen
- European Medicines Agency - Patrick Le Courtois
- Joint Action Work Packages 5 and 7 - Wim Goettsch, Francois Meyer

The presentations are provided for reference.

2. Discussion on EPARs

Focus of the collaboration will be the EPARs, which reflect the scientific conclusions reached by the EMA's Committee for Medicinal Products for Human Use (CHMP) at the end of the evaluation process, after deletion of commercially confidential information. An overview of the EPAR structure and workflow was provided by Francesco Pignatti. A broader initiative at the EMA was noted aimed at facilitating access to EPAR information by stakeholders; recent revisions were introduced in the assessment report templates and the CHMP continues to look at new ways to improve the transparency of the scientific assessment.

In 2009, MEDEV provided comments on the usefulness of the EPARs and Summary of Product Characteristics (SmPCs) in the context of relative effectiveness assessment of pharmaceuticals. The domains quality, structure and content were covered by these comments. A summary of these comments together with some examples was provided by Anna Bucsics.

It was agreed that the EMA should draft guidance for improved data presentation that would address the usability for HTA bodies. The MEDEV comments should be the starting point for this exercise. This draft guidance would then be subject to a wider consultation within the EUnetHTA network as part of the Work Package 5.

3. Next Steps

EMA will draft guidance for improved data presentation in the EPAR based on the MEDEV comments by **25 March 2010**. EUnetHTA will perform a consultation on this draft and provide comments by **7 May 2010**. Contacts for this exercise are Francesco Pignatti (EMA) and Wim Goettsch (EUnetHTA).

A meeting to discuss these comments will be arranged in **June 2010**. The aim is to have a joint document agreed by **July / August 2010** to allow for implementation with the next revision of CHMP assessment report templates scheduled for **October 2010**.

Separate from this initiative, a road map to explore other areas of possible collaboration or exchange of information in future will be developed. Contacts for this exercise are Hans-Georg Eichler (EMA) and Finn Børlum Kristensen (EUnetHTA).

Brief minutes of the meeting will be prepared by EMA for review by EUnetHTA.

A joint press release of the two organisations will be published. A draft will be prepared by EMA for review by EUnetHTA

Next meeting:

The next meeting will be held in June 2010 (date/time tbd).

WP1

Appendix 5

EUnetHTA-EMA f-t-f meeting summary, June 3, 2010, London, UK

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 August 2010
EMA/364003/2010

Minutes of the Second Workshop on High Level Pharmaceutical Forum Recommendations on EPARS' contribution to Relative Effectiveness Assessment

3 June 2010 – chaired by Hans-Georg Eichler

Role	Name
Chair/Vice-chair	Hans-Georg Eichler (EMA)
Present:	Patrick Le Courtois (EMA), Xavier Luria (EMA), Francesco Pignatti(EMA), Michael Berntgen (EMA), Agnès Saint Raymond (EMA), Laurent Brassart (EMA), Antionio Cherchi (EMA), Spiros Vamvakas (EMA), Eric Abadie (CHMP), Harald Enzmann (CHMP), Patrick Salmon (CHMP/COMP).Kerstin Westermark (COMP), Jerome Boehm (EC), Wim Goettsch (EUnetHTA), Finn Børlum Kristensen (EUnetHTA), Francois Meyer (EUnetHTA), Anna Bucsisc (EUnetHTA), Sarah Kleijnen (EUnetHTA), Anne Dandon (EUnetHTA), Marianne Klemp (EUnetHTA), Carole Longson (EUnetHTA), Pietro Folino Gallo (EUnetHTA)

This was the second meeting between the European Medicines Agency (EMA) and representatives from the European network for Health Technology Assessment (EUnetHTA) in the context of a collaboration with the objective to explore how the European Public Assessment Report (EPAR) can make better contribution to the assessment of relative effectiveness of pharmaceuticals by health technology assessment (HTA) bodies in the EU Member States.

1. Introduction and Updates

The Chair introduced the objectives of the meeting. The agenda as well as the minutes of the previous meeting were adopted without changes.

Brief updates on topics of interest for the participants were provided by the European Commission, EUnetHTA as well as the EMA. It was noted that EUnetHTA is currently developing guidance documents on comparators/comparisons, outcomes and level of evidence, respectively; these topics could become areas for future exchange. From the EMA update the initiatives about publication of reports on the

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maintenance of orphan criteria at time of marketing authorisation as well as the review of conflict of interest rules were identified for discussion at future meetings.

2. Discussion on EPAR Improvements

The following documents circulated prior to the meeting:

- Preliminary Analysis of EPAR Improvements in view of Contribution to Health Technology Assessments

Analysis - EPAR contribution t...

- EUnetHTA response to the preliminary analysis

Response netHTA on EMA draf

- Action Plan for EPAR Improvements – Draft 1

Action Plan for EPAR Improveme...

The discussion was based on the draft action plan. Agreed items for implementation with the next template update (section 1) as well as items for monitoring as part of current templates (section 3) were briefly summarised. Regarding the presentation of data in tabular format (section 5) the comments were discussed and additional input will be received by EUnetHTA by the end of the month, after which EMA will produce an updated version. The main discussion was held on the items for further reflection (section 2); here the outcome of the discussion was either implementation with the next template update (Structural characteristics for biologicals; inclusion of references), follow-up discussion at the next meeting (Conflict of interest) or internal review by EMA (Dedicated section related to "Product Information"; Enhanced QC review procedures; Version control of printed labelling documents; Fulfilment of commitments). With regard to the additional items raised by EUnetHTA (section 4), these were discussed and no actions other than the ones already agreed need to be taken.

An updated action plan (draft 2) as a result from these discussions will be produced and distributed to participants.

3. Next Steps

EUnetHTA will provide additional comments on the presentation of data in tabular format by **end of June**. Based on this input EMA will produce a revised template table together with an updated action list by **mid July**. Any additional comments on these documents should be provided by **10 September** given that documents would need to be finalised and circulated for formal adoption by the CHMP in **October**. It is planned to issue a dedicated press release once these changes to the template are finally adopted and about to be implemented.

Regarding the implementation of the template, it was agreed that this should occur with Opinions on initial marketing authorisations after adoption in October 2010 acknowledging that EPARs will only be published after adoption of the Commission Decision, i.e. the first EPARs with this information could be expected in 1Q10. Both EMA and EUnetHTA intend to monitor the implementation of the improvement. A joint meeting to exchange the first experience is planned after around 10 EPARs have been published, which would be envisaged by July 2011.

Brief minutes of the meeting will be prepared by EMA for review by EUnetHTA.

4. Next meeting

The next meeting will be held end of 2010 / beginning of 2011. The following topics are envisaged for this meeting:

- Assessment of potential Conflict of Interest by EMA;
- Experience exchange on reports about the maintenance of orphan criteria at time of marketing authorisation;
- Information on EUnetHTA guidelines (Work Package 5) regarding comparators/comparisons, outcomes and level of evidence, respectively.

WP1

Appendix 6

EUnetHTA-EMA f-t-f meeting summary, March 7, 2011, Diemen, Netherlands

Third EUnetHTA - EMA meeting

March 7, 2011, CVZ, Diemen
10.30-17.00

Role	Name
Chair	Wim Goettsch (EUnetHTA)
Present:	Ad Schuurman (CVZ/MEDEV), Finn Børlum Kristensen (EUnetHTA), Francois Meyer (EUnetHTA), Mira Pavlovic (EUnetHTA), Anna Bucsisc (EUnetHTA), Sarah Kleijnen (EUnetHTA), Elisabeth George (EUnetHTA), Marianne Klemp (EUnetHTA), Beate Wieseler (EUnetHTA), Alric Ruther (EUnetHTA), Anders Lamark Tysse (EC DG Sanco), Hans-Georg Eichler (EMA), Patrick Le Courtois (EMA), Michael Berntgen (EMA), Peter Arlett (EMA), Alar Irs (CHMP), Harald Enzmann (CHMP) Sandra Kruger (CBG)

Background

In 2010 The European Medicines Agency (EMA) and representatives from the European network for Health Technology Assessment (EUnetHTA) Joint Action initiated a collaboration, in which the EMA and EUnetHTA are considering how the European Public Assessment Report (EPAR) could make a better contribution to the assessment of relative effectiveness of pharmaceuticals by health technology assessment bodies in the EU Member States. The current meeting was planned to discuss the follow-up of the changes that have been implemented and other shared topics.

Introduction

The meeting was opened by Bert Boer, member of the Board of the Dutch Health Care Insurance Board (CVZ) with a description of the tasks of CVZ

Follow-up on EPAR

Michael Berntgen presented an update on the implementation (process) of the new EPAR template. From November 2010 onwards the updated assessment report templates have been implemented for CHMP opinion meetings. In addition a questionnaire is currently being developed with specific focus on the changed items in the EPAR. This questionnaire will be used to evaluate the implementation of the changes by EMA.

It was discussed that there also is a need to evaluate the implementation by HTA agencies functioning as external customers. This evaluation should preferably be one joint response through EUnetHTA including also comments from MEDEV. The HTA agencies will discuss the approach of the evaluation in the coming period. It was indicated that during the summer 5-10 EPAR with the implemented changes will be available which will be a decent number for an evaluation. For this review it was considered beneficial if this EMA questionnaire was not only used by EMA but also by the EUnetHTA partners as a part of their evaluation.

Short update on WP5 and WP7 of EUnetHTA

Finn Kristensen briefly provided an update on the EUnetHTA network. A proposal is being drafted for a Joint Action 2 which should start in 2012 and will focus on the production of assessment reports.

Presentations were provided by Wim Goettsch (WP5) and Mira Pavlovic (WP7) on the progress of the projects. The presentations are provided for reference.

For WP5 a public consultation will soon start on a background review. In addition EMA will be consulted in the near future for the selection of a specific topic (pharmaceutical) for a pilot assessment based on the model that is under development within this work package.

WP7 focuses on new technologies. Opportunities for collaboration will be discussed during the agenda item on 'Cooperation in post marketing data collection'.

Guidelines

Mira Pavlovic provided a presentation on the guidelines that are under development by WP5 on methodological issues. The presentation is provided for reference.

A consultation of EMA is planned in April 2011 for all these draft guidelines. It was indicated by EMA that the consultation period of 1 month will be a challenge for them. WP5 will reconsider the consultation period and moment of consultation. HAS will send EMA a list with the subjects of the guidelines and dates for the consultation.

Post-meeting note: EUnetHTA indicated to EMA after the meeting that the consultation on draft guidelines was re-scheduled for later in 2011 or 2012.

EMA Reflection paper on 'Active Controls'

The content of the reflection paper was presented by Hans-Georg Eichler. The paper proposes that there are 2 situations in which 3-armed studies should be a requirement. The paper is currently open for public consultation with a deadline for 31 March 2011. The HTA agencies will either provide a joint response if this can be arranged in time, otherwise agencies will respond individually. It was indicated by EMA that a week delay in response would be possible but should preferable be indicated in time. MEDEV will respond but maybe a week late.

Cooperation in post marketing data collection

A presentation was provided by Peter Arlett on the changes to the post authorisation data collection and the ENCePP database. The presentation is provided for reference.

Is was discussed that it would be helpful to identify a minimum dataset that would be useful for postmarketing studies as well as studies for additional evidence generation (EIFFEL database). In addition it might be explored if information on studies on pharmaceuticals that are collected in the EIFFEL database should maybe be transferred to the ENCePP database. The lead of WP7 will join the ENCePP meeting in June and a discussion will be started on possible collaboration.

Scientific Advice

Mira Pavlovic provided a presentation on the experience of scientific advise in the Tapestry network. The presentation is provided for reference.

EMA indicated that a joint or parallel advise of regulators/ reimbursement agencies should be pursued. The HTA agencies indicated that the agencies first need to sort out how they can combine input for several reimbursement agencies before further collaboration with EMA. On scientific advice EUnetHTA can facilitate with knowledge, but not be an official partner as the official partners are the reimbursement agencies.

Next meeting:

The next meeting will be held in the second half of 2011 (date/time tbd) in Paris.

WP1

Appendix 7

EUnetHTA-EMA f-t-f meeting summary, February 22, 2012, Paris, France

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)

WP1

Appendix 8

EUnetHTA-EMA f-t-f meeting summary, November 20, 2012, Copenhagen, Denmark

EMA-EUnetHTA meeting

November 20, 2012
Copenhagen

10h30-17h30

***Local host**:* Danish Health and Medicines Authority, *DHMA*
Address of the meeting venue:
Islands Brygge 67, meeting room 501
2300 Copenhagen S

Contact:
*Julia Chamova, **juch@sst.dk**, Tel.: +45 4062 9357*

Summary report

Agenda

Coffee – light refreshment	10.0 – 10.30
1.Welcome to Danish Health and Medicines Authority (DHMA): *Director General and Chief Medical Officer Else Smith* Introduction to the EMA-EUnetHTA meeting: *Finn Børlum Kristensen*	10.30 –10.50
2. EPAR improvement project – reporting of first experiences, additional proposals from EUnetHTA in light of the reviews of recent EPARS (HAS, EMA)	10:50 – 11:30
3. Databases for post-licensing studies (HAS) Update on the new EU PhV Legislation and opportunities for bridging to HTA (EMA) The FP7 IMI Protect Project (DHMA)	11:30 – 12:30
Lunch break	12.30 - 13.30
4. Rapid model for REA, pilot and future developments; i.e. possibilities to streamline the timelines of rapid pilots with EMA assessments (CVZ)	13:30 – 14:15
5. Early scientific advice; EMA-HTA scientific advice, and multi-HTA scientific advice (NICE, HAS, EMA)	14:15 – 15:15
Coffee	15.15 – 15.45
6. EUnetHTA Methodological guidelines for REA (HAS)	15.45 – 16.30
7. Significant benefit for orphan medicinal products: concept and experience (EMA)	16:30 – 17:00
8. Conclusion of EMA-EUnetHTA meeting and next steps: *Hans-Georg Eichler, Finn Børlum Kristensen*	17.00 - 17.30

1. Opening remarks and welcome

Ms Else Smith, the Director General and Chief Medical Officer at the Danish Health and Medicines Authority (DHMA), welcomed the participants to the meeting and to the DHMA. She expressed DHMA's continuous commitment to EUnetHTA coordination since 2005 and wished the participants a fruitful meeting underlining the importance of the corporation between EUnetHTA and EMA.

Finn Børlum Kristensen, EUnetHTA Secretariat, chaired the meeting and also welcomed everybody. He introduced EUnetHTA and stressed the importance of the Directive 2011/24 EU on Cross-border healthcare and the work of reaching a sustainable and permanent HTA network in Europe. As a follow up on previous meeting between EUnetHTA and EMA he emphasised the importance of the continuity in the collaboration between the Agency and the Network.

2. EPAR improvement project – reporting of first experiences, additional proposals from EUnetHTA in light of the reviews of recent EPARS (EMA, HAS)

Michael Berntgen (EMA) presented the progress of the EPAR Project (*Presentation no. 2*). Since the last meeting between EMA and EUnetHTA, all agreed items for implementation and monitoring had been delivered. Currently work is going on in the areas of: Implementation of new Pharmacovigilance Legislation, Pilots for an Executive Summary, Guidance regarding data in geriatric patients, further strengthening of internal review and a continuous reflection on the best approach for templates.

Anne Gourvil (HAS) presented EUnetHTA's observations after review of 10 EPARs (*Presentation no. 3*) and the key discussion points on the content of EPAR and post-authorisation measures were summarized as follows:

- Results of the progress and current development in the collaboration between EUnetHTA and EMA should be presented to the CHMP and in parallel a manuscript should be developed to be published in a relevant journal should be made. Action point: EMA and HAS to follow up.

- In general EMA expressed the continuous improvement initiatives hence a readiness to take in suggestions from outside. Regarding the recent EPAR revisions (e.g. executive summary) EMA welcomed comments from EUnetHTA. Also on new and future templates (e.g. template for extensions of indications; new RMP summary document) EUnetHTA comments are welcome Action point: EUnetHTA will follow up.

- On the issue of EMA's draft quality review of Summary of Product Characteristics (SmPC) – Anne Bucsics (HVB) should send a letter of request and EMA will reply accordingly. Action point: Anne Bucsics to send a letter and EMA to reply.

3. Databases for post-licensing studies (HAS); Update on the new EU PhV Legislation and opportunities for bridging to HTA (EMA) and The FP7 IMI Protect Project (DHMA)

Irena Guzina (HAS) presented the EVIDENT database which was launched in November 2012 (*Presentation no. 4*). The goal of the EVIDENT database on new technologies is to promote generation of further evidence and facilitate European collaboration in conducting requested additional data collection. The scope of the database is studies requested by European HTA bodies after HTA that are in initial stage of development and is addressing all health technologies (i.e. drugs, devices, procedures). The content of the database is information on additional studies or any kind of additional collection (ADC) and information on related health technology (i.e. assessment status, evidence gaps, research questions, required additional studies, coverage decision status).

Ana Hidalgo-Simon (EMA) updated the meeting participants on the implementation of the new Pharmacovigilance Legislation and the newly created ENCePP working group on HTA (*Presentation no. 5*). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) is a collaborative scientific network coordinated by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The ENCePP Database of Research Resources and the E-Register of Studies for the registration of pharmacoepidemiological and pharmacovigilance studies are both publicly available.

Steffen Thirstrup (DHMA) presented the EU FP7 IMI funded project 'Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT)'. The goal of the project is to strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods to enhance early detection and assessment of adverse drug reactions from different data sources and to enable the integration and presentation of date on benefits and risks. Both methods will be tested in real-life situations (*Presentation no. 6*).

The key discussion points on the three presentations were summarized as follows:

- The EVIDENT database has just been launched. There is a need to clarify how parts of the EVIDENT database can be made publicly available without compromising the confidentiality of some of the information. Action point: EUnetHTA to follow up.

- The ENCePP working group on Health Technology Assessment can help in exploring methodologies and initiatives to link ENCePP and EUnetHTA. The key element could be for EUnetHTA and EMA to develop and agree on a methodology for observational studies to identify and collect information to fill knowledge gaps in the post licensing phase. Francois Meyer (HAS) participated in the ENCePP's working group on HTA's first meeting, and has been named EUnetHTA liaison with the working group. EMA is happy to consider additional EUnetHTA members and stronger presence of EUnetHTA on the working group. Action point: EMA and EUnetHTA Secretariat will follow up on this.

- In relation to post-authorisation safety and efficacy studies (PASS/PAES) Anders Tysse encouraged EUnetHTA to send concrete suggestions to his Unit, Risk Assessment, Head: Tapani Piha, in DG Sanco (i.e. to Jerome Boehm). Action point: EUnetHTA to follow up.

4. Rapid model for REA, pilot and future developments; i.e. possibilities to streamline the timelines of rapid pilots with EMA assessments (CVZ)

Wim Goettsch (CVZ) presented the model for Rapid REA of Pharmaceuticals and shared the planned work on pilot REAs in EUnetHTA Joint Action 2 (*Presentation no. 7*). Potential collaboration with EMA and the possibilities to streamline the timelines of rapid pilots with EMA assessments was discussed and the key discussion points were summarized as follows:

- It is possible for HTA bodies to get CHMP assessment reports soon after a positive opinion of CHMP from the applicant; it is difficult to get an indication on a possible decision before the final CHMP discussion and this depends on the applicants to provide the information; Information from the CHMP assessment report should not be included in a REA document for public consultation before Commission Decision; the time between the CHMP opinion and the final availability of the EPAR for specific products is about 80-90 days (around 70 days are for the Commission's Decision Making Process). As a way forward EUnetHTA should explore and encourage the companies to share the assessment information – EUnetHTA could ask EFPIA to facilitate this. EMA cannot share this information with EUnetHTA at any stage. Action point: EUnetHTA to follow up.

5. Early scientific advice; EMA-HTA scientific advice, and multi-HTA scientific advice (NICE, HAS, EMA)

Spiros Vamvakas (EMA) provided a presentation on HTA-EMA Scientific Advice and shared EMAs experience and examples of HTA discussions. Scientific advice is an important activity for EMA and advice is given by the CHMP on recommendations of the Scientific Advice working Party (*Presentation no. 8).*

Carol Longson (NICE) gave a short presentation NICE's early scientific advice service and provided insight into NICE's experiences with scientific Advice Projects in collaboration with EMA (*Presentation no. 9*). Work is in progress to develop an efficient and acceptable procedure for the provision of 'parallel' written advise and there is a need to explore how best to involve both regulatory and HTA experts in the advice meetings.

Mira Pavlovic (HAS) presented the EUnetHTA initiative on early dialogues - multi-HTA scientific advice and the first experience gained (*Presentation no. 10*). Several EUnetHTA partners have participated and the experiences have been rather successful. However, cooperation between EMA and EUnetHTA should be considered for a better process and result.

The key discussion points on the three presentations were summarised as follows:

- The Commission hopes this exploratory phase of early scientific advice will lead to a new framework and a new basis, and there is a push from the Commission on two areas: 1. is it possible to have shared ground in terms of Early Scientific Advice and to some extend aligning practices? 2. Could EUnetHTA involve smaller HTA organizations as participants in early scientific advice pilots? Action point: EUnetHTA to follow up.

- EUnetHTA should keep EMA informed and there will be a formal invitation to participate as observer at the meeting on the 18th of December in Paris and all dates for meetings in 2013. Spiro Vamvakas from EMA has green light for participating as observer but cannot give EMA advice in evaluation process but give personal comments and inputs. Action point: EUnetHTA to send invitation and EMA to follow up.

- Every agency that participates will be required to share the basis for their advice in writing. There should be time for reflection on the procedure and process after each EUnetHTA pilot. Action point: EUnetHTA.

- The expert involvement in the EMA early scientific advice and the EUnetHTA early scientific advice pilots should be a topic for discussion in the coming EMA-EUnetHTA meetings. Action point: EMA and EUnetHTA.

6. EUnetHTA Methodological guidelines for REA (EMA, HAS)

Michael Berntgen (EMA) and Mira Pavlovic (HAS) both presented an overview and current status of the mutual commenting on Guidelines (*Presentation no. 12 and 13*) and the processes for the exchange was discussed. The key discussion points were summarized as follows:

- There is a need to elaborate on the processes of how EUnetHTA will be commenting on EMA draft guidelines and concept papers – not many members have contributed with comments so far. EMA welcomes and encourages EUnetHTA to continuously in the future comment on both draft guidelines and concept papers and specifically disease specific guidelines in the framework of early dialogue. Information should be sent to the Secretariat for posting (current procedure), but the task of deciding who should comment will be handled by the Lead Partners in WP5 - CVZ (Wim) and HAS (Francois). Next year, this process should be evaluated. Action point: EUnetHTA.

- The EMA disease specific guidelines will be a starting point for EUnetHTA's JA2 work on disease specific guidelines for HTA. Action point: EUnetHTA.

7. Significant benefit of orphan medicinal products: concept and experience (EMA)

Jordi Llinares (EMA) presented EMA's experience with significant benefit of orphan medicinal products (*Presentation no.13*). The concept of orphan medicinal products and their marketing authorisation were discussed. The key discussion points for the way forward were summarized as follows:

- As the topic is very complicated it should be discussed further during next meetings. Action point: EUnetHTA and EMA.
- The possibility to develop a confidentially agreement or memorandum of understanding to facilitate information exchange between EMA and EUnetHTA similar to the agreement that was made between EMA and FDA, has legal implications and it should be explored with the European Commission. Action point: EUnetHTA (and EMA).

8. Conclusion of EMA-EUnetHTA meeting and next steps

Finn Børlum Kristensen (EUnetHTA Secretariat, DHMA) and Hans-Georg Eichler (EMA) thanked the participants for a good meeting. The key discussion points for way forward were summarized as follows:

- Should a memorandum of understanding be drafted between EMA and EUnetHTA in order to be able to share confidential information?
- The development of a 3-year work plan was suggested. Action point: EUnetHTA to come up with a draft.
- The communication and cooperation between EMA and the EUnetHTA should be made public at a relevant stage. Action point: EUnetHTA Secretariat, EMA.
- The next meeting will be around April 2013 in EMA. Action point: EMA to follow up.

The meeting was adjourned at 17.30.

Participants List

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