

# Report on the implementation of the EMA-EUnetHTA three-year work plan 2012-2015

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## 1. List of abbreviations

<a href="#">ADAPT-SMART</a>	Accelerated Development of Appropriate Patient Therapies a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
ADR	Adverse Drug Reaction
<a href="#">ASSR</a>	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care), Emilia Romagna, Italy
BPG	Best Practice Guidelines
<a href="#">CHMP</a>	Committee for Medicinal Products for Human Use
<a href="#">COMP</a>	Committee for Orphan Medicinal Products
<a href="#">DIA</a>	Drug Information Association
<a href="#">EC</a>	European Commission
ED	Early Dialogue
EIFFEL	EUnetHTA Interface to Facilitate Furthering of Evidence Level
<a href="#">EMA</a>	European Medicines Agency
<a href="#">ENCePP</a>	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
EPAR	European Public Assessment Report
<a href="#">EUnetHTA</a>	European network for Health Technology Assessment
<a href="#">EVIDENT</a>	Evidence database on new technologies
<a href="#">HAS</a>	Haute Autorité de Santé (French National Authority for Health), France
HTA	Health Technology Assessment
<a href="#">IMI ADVANCE</a>	Innovative Medicines Initiative: Accelerated development of vaccine benefit-risk collaboration in Europe
<a href="#">IMI Get Real</a>	Innovative Medicines Initiative Incorporating real-life clinical data into drug development
<a href="#">IMI Protect</a>	Innovative Medicines Initiative: Pharmacoepidemiological research on outcomes of therapeutics by a European consortium
<a href="#">IMI WEBRADR</a>	Innovative Medicines Initiative: Recognising Adverse Drug Reactions
<a href="#">IQWiG</a>	Institute for Quality and Efficiency in Health Care, Germany
<a href="#">ISPOR</a>	International Society for Pharmacoeconomics and Outcomes Research
JA2	Joint Action 2
MAA	Marketing Authorisation Application
MCDCA	Multiple Criteria Decision Analysis
MEDEV	Medicines Evaluation Committee
<a href="#">NICE</a>	National Institute for Health and Care Excellence, United Kingdom
PAES	Post-authorisation Efficacy Studies
<a href="#">PARENT</a>	PAtient REgistries iNiTiative
PASS	Post-authorisation Safety Studies
<a href="#">PRAC</a>	Pharmacovigilance Risk Assessment Committee
Q&A	Questions and Answers
REA	Relative Effectiveness Assessment
RMP	Risk Management Plan
<a href="#">SEED</a>	Shaping European Early Dialogues
SmPC	Summary of Product Characteristics
STAMP	Safe and Timely Access to Medicines for Patient expert group
ToU	Terms of Use
WP	Work Package

## 2. Introduction

In 2010 the European Medicines Agency (EMA) and the European network for Health Technology Assessment (EUnetHTA) initiated a collaboration based on a mandate of the High-Level Pharmaceutical Forum 2008. After an initial work on improving the way information on the benefits and risks of a medicine contained in European public assessment reports (EPAR) could be better presented to address the needs of HTA bodies, the collaboration covered additional areas of interaction.

The objective of the EMA-EUnetHTA collaboration is to identify and undertake specific steps to improve the efficiency of the processes and conditions for patients' timely access to an effective medicine. During the years 2013-2015 the following areas of collaboration were identified and included in the 3 year work plan as a part of the activities within the framework of the EUnetHTA Joint Action 2 (JA2).

- Scientific advice/early dialogue involving regulators and HTAs
- Scientific and methodological guideline development
- Post-licensing (post-authorisation) data generation
- Availability of clinical study data
- Orphan medicinal products
- Cooperation in pilot projects
- Cooperation in specific pilot projects of EUnetHTA JA2
- Conferences, workshops and seminars/meetings

As a result of a regular review and update, a few issues were added to the items planned initially, i.e.:

- Exchange on the use of Effects Tables to describe the benefits and the risks of a medicine
- Sharing experience with patient interactions (eliciting patient values, preferences)
- Collaboration on initiatives such as Adaptive Pathways as well as support programmes to the development of innovative medicines
- Better understanding of principles for Product information

## 3. Organisation of regular meetings of EMA and EUnetHTA representatives

Between February 2010 and November 2015 a total of 11 meetings were organised. They were hosted interchangeably by EMA and the EUnetHTA partner organisations.

The first four meetings took place between February 2010 and February 2012 and were largely driven as workshops on the EPAR improvement project. During the period from 2012 to 2015, seven biannual meetings of EUnetHTA with EMA were the platform for the joint work plan delivery providing updates on developments in areas of common interest.

All meetings were attended by representatives from the EUnetHTA Secretariat and EUnetHTA member organisations, from EMA and its scientific committees as well as the European Commission. The last meeting in EUnetHTA JA2 was hosted by the EUnetHTA Secretariat, at the Danish Health Authority in Copenhagen, Denmark in November 2015.

Summary reports from the meetings were made publicly available through the websites of both EUnetHTA and EMA.

No.	Date	Host/ place	Summary reports
1.	11 Feb 2010	EMA/ London	Summary reports from the meetings are regularly published on the <a href="#">EMA website</a> , and on the <a href="#">EUnetHTA website</a> .
2.	3 June 2010	EMA/ London	
3.	7 March 2011	CVZ/ Diemen	
4.	22 Feb 2012	HAS/ France	
5.	20 Nov 2012	DHMA/ Copenhagen	
6.	14 May 2013	EMA/ London	
7.	10 Dec 2013	IQWIG/ Cologne	
8.	15 May 2014	EMA/ London	
9.	9 Dec 2014	ZIN/ Diemen	
10.	8 May 2015	EMA/ London	
11.	23 Nov 2015	DHMA/ Copenhagen	

## 4. Creating synergies, avoiding duplications

### 4.1. Exchange and advice on product-specific development programmes

#### ***Multi-HTA early dialogues***

EUnetHTA's Early Dialogue (ED) pilots tested a mechanism for HTA bodies in Europe and companies developing health technologies, seeking marketing and reimbursement access in European markets, to exchange their views on scientific issues during the development phase of new medicinal products and non-drug technologies. An overall aim of the EDs is to improve the quality and adequacy of initial evidence generation in order to facilitate the HTA process and support coverage decisions.

Pilot early dialogues have been among the prioritised activities to be supported by the European Commission. The initiative was started by EUnetHTA in 2012 and coordinated by Haute Autorité de Santé (HAS), France, during JA2. Regular updates on this multi-HTA scientific advice initiative early dialogues were provided by HAS representatives at the consecutive EMA-EUnetHTA meetings. The early dialogue activities started with two initial pilots to explore feasibility before the official start of the JA2. The entire activity was planned to gain more experience in prospective requirements of evidence by HTA organisations. Concrete examples of compounds and medical technologies were included in this project with participation of multiple HTA organisations. In total eleven HTA organisations from nine countries participated in these pilots providing preparatory input to the ED meetings.

In the end of 2012 an invitation was sent to EMA to participate in the meetings. An EMA representative was present in a few meetings organised within EUnetHTA from

December 2012 onwards, acting as an observer. In total, 22 EDs (11 EUnetHTA and 11 SEED) were produced during the three year period of JA2.

### ***Regulatory HTA scientific advice activities***

Parallel regulatory HTA Scientific Advice was initiated by EMA in 2010. Apart from involvement of stakeholders and regulatory National Competent Authority delegates from EMA, it also includes representatives of voluntary HTA institutions suggested by the sponsoring drug developer.

In 2011 EUnetHTA was officially invited by EMA as an observer in the programme, providing facilitation and access to knowledge of its partners.

After EUnetHTA completed 10 pilot Early Dialogues, starting from 2013, additional pilot EDs were scheduled within the SEED consortium. Financed by EC, this consortium of HTA bodies was closely linked to EUnetHTA, and coordinated and led by HAS after a tendering phase. Four of the pharmaceutical EDs were performed in 2014/5 with an aim to test various timings of interactions between EMA/regulatory and EUnetHTA participants. EMA and the SEED coordinator collaborated together on defining these timings.

By the end of December 2015, the overall number of completed procedures for the regulatory-HTA scientific advice is 63. Of the overall 63 procedures, 4 were conducted under the framework of the Shaping European Early dialogue (SEED) Consortium, 6 were very first multi stakeholder consultations with third party facilitation, while the remainder were under the best practice guide (BPG) procedure. Four BPG procedures followed on from Adaptive Pathways discussions.

In December 2013, following a request from stakeholders to publish information on the process, EMA together with delegates from National Competent Authorities and HTA bodies started to develop a procedure and guidance for EMA regulatory-HTA parallel scientific advice. A *draft* [Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice](#) procedures was published for a 3 month public consultation in May 2014. A review of contributions submitted in response to the public consultation on the draft Best Practice Guide (BPG) for the parallel regulatory-HTA scientific advice pilot indicated a high level of support for the concept and provided constructive suggestions for changes in the medium and longer term. The final guidance is expected to be published in 2016.

The best practice guide has been agreed between regulators and participating HTA Bodies. Publication of the best practice guide will ensure that all stakeholders can have up-to-date guidance on the procedure, and should help applicants' access parallel advice. The guidance is based on the experiences of more than 50 procedures under Best Practice Guide, 4 parallel regulatory SEED procedures, and the public consultation of the draft best practice guide. It is considered that a final sustainable model of parallel scientific advice is needed whereby the regulatory-HTAs interactions through parallel advice can be developed beyond what can be achieved in the current framework.

### ***Conceptual exchanges on early dialogues/scientific advice at EMA/EUnetHTA meetings***

Regular discussions on early dialogues/scientific advice were held at each of the EMA-EUnetHTA meetings. Issues discussed as a result of the mutual updates included:

- possibility of shared ground in terms of Early Scientific Advice and alignment of practices;
- involvement of smaller HTA organisations in the process
- expert involvement

It was concluded that the aim of the initiatives is to help companies to understand the evidence needs of stakeholders such as regulators and HTA bodies in order to facilitate efficient data collection. It is understood that different frameworks drive the data needs for regulators and HTA bodies. It is important that such interactions happen early in a medicine's development while trial plans can still be amended as needed to ensure the development plans provide the data needed for each stakeholder, thus avoiding as far as possible the need for two different -development programmes for a new product. Alignment between EU Regulators and the HTA bodies and among HTA bodies themselves is not in itself a primary goal of the early dialogues/scientific advice initiatives though some degree of alignment was foreseen as a likely result of the collaboration.

The discussions towards an alignment of requirements were continued. They included:

- novel clinical endpoints (i.e. multiple measurement scales to ascertain the impact of clinical outcome);
- surrogate endpoints

An aim of the initiative is in accelerating patients' access to innovative therapies which have added value for patients and which are affordable to the EU Member States' health systems. Therefore this area of collaboration between EMA and EUnetHTA should be included in future work plans. Efficient procedures for providing scientific advice to the companies that are realistic and acceptable by all stakeholders should be further explored. At this moment, due to the specific nature and role of HTA in Europe resulting from different health care systems and the voluntary nature of the European network for HTA, scientific advice given by HTA, often reflects the view of the individual HTA organisations participating in parallel advice programme.

Nevertheless, with regard to further development of parallel scientific advice, it is foreseen that an optimised Model of multi-stakeholder parallel scientific advice would fully respect national competence in delivery of health care and decision making regarding pricing and reimbursement but recognise that evidence generation is global. The aim is to build on synergies between regulators and HTA bodies, have broader HTA body involvement, reduce duplication and provide an optimum multi-stakeholder advice output that can facilitate efficient drug development that answers the needs of HTA bodies and regulators, and potentially facilitate timely access to new medicines for EU patients. HTA bodies and regulatory participants should be equal partners in such parallel advice.

## 4.2. Initiatives on additional (post-authorisation) data collection

Collaboration between EMA and EUnetHTA on post-authorisation data collection began in March 2011. The aim was to explore whether post marketing studies and other post marketing sources of evidence that could be useful from the perspectives of both the regulatory and HTA bodies. The discussions started from collaboration on two projects: ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, under leadership of EMA, and the EVIDENT database (former EUnetHTA JA1 EIFFEL database): the database containing evidence information on new technologies (work on the EVIDENT database was organised by EUnetHTA JA2 WP7). The collaboration with ENCePP was notable in particular for the work on methods for studies of joint interest that was included in the ENCePP methods guide ([http://www.encepp.eu/standards\\_and\\_guidances/methodologicalGuide.shtml](http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml)), and for the work on capacity for conduct of such studies within the EU ([http://www.encepp.eu/publications/documents/ENCEPP\\_HTA\\_Poster\\_ICPE2014.pdf](http://www.encepp.eu/publications/documents/ENCEPP_HTA_Poster_ICPE2014.pdf)). In 2015 an EMA lead initiative on registries, leveraging the outputs of the PARENT Joint Action, was launched with EUnetHTA representation. The objective is to facilitate the establishment of patient registries that can serve regulatory and HTA needs. During the bi-annual meetings more initiatives have been identified that hold promise for collaboration and for delivering on the objective of studies with outcomes for both regulation and HTA. These opportunities were documented as a list of all initiatives to facilitate data collection. In the most recent paper, additional projects have been added as potential future collaboration opportunities: EMA Scientific Advice for post-authorisation studies and risk minimisation (including input from the EMA Pharmacovigilance and Risk Management Committee – PRAC), enhanced PRAC consideration of the need for non-industry generated data (from real-world 'best' evidence), EU Network Training Centre, EMA framework contracts on procurement of studies, as well as EU funded projects IMI ADAPT-SMART, IMI Get Real, IMI ADVANCE, IMI WEBRADR, further enhancement of the initiative on registries. These initiatives build on a number of complementary tools and activities available to regulators that are enshrined in EU law, including:

- Routine pharmacovigilance (reporting of suspected adverse reactions and periodic safety update reports from industry)
- Formal assessments of safety and benefit-risk (EU 'referrals')
- Legally imposed Post-authorisation Safety Studies (PASS)
- Legally imposed Post-authorisation Efficacy Studies (PAES)
- Legally imposed Risk Management Plans
- Scientific Advice/parallel advice on post-authorisation data collection.

New opportunities for collaboration are foreseen within the next years, although streamlining of new and the existing activities will be needed for the EMA-EUnetHTA collaboration to increase its benefit. Such collaboration should also contribute to bridge the gap between HTA and regulators' requirements with regard to requests for additional evidence generation. An important focus area of the additional evidence generation is the methodological challenges in studies which could meet both the needs of regulators and HTA.

### 4.3.Improvements in publicly available regulatory assessment reports

The European Public Assessment Report (EPAR) reflects the scientific conclusions reached by EMA's Committee for Medicinal Products for Human Use (CHMP) at the end of the evaluation process, after deletion of commercially confidential information. Presentation of data and information in the EPARs was a focus of the collaboration between EMA and EUnetHTA in the years 2010-2012. This includes the four first workshops in February 2010, June 2010, March 2011 and February 2012. The initiative was the response to the recommendations from the High Level Pharmaceutical Forum, with an objective to improve the contribution of EPARs to the assessments of relative effectiveness of pharmaceuticals by the HTA bodies.

In line with comments of EUnetHTA and MEDEV, and following the agreed action plan, EPARs were reviewed and the EPAR template was adapted. Changes concerned the formal data presentation as well as information to be provided through the discussion, without impacting the actual decision criteria. In terms of the discussion on clinical effects, important aspects highlighted by EUnetHTA included:

- key elements of the clinical study design
- 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

As part of the project a new summary table of main efficacy data were developed jointly by EMA and EUnetHTA. Furthermore, more guidance was provided concerning the substantiation of SmPC statements, including elements like contra-indications, warnings/precautions, interactions and dose recommendations (particularly deviations from standard dose).

EPAR templates revised on the basis of EUnetHTA input have been used for CHMP Opinions since November 2010. In order to monitor implementation of the new format of data presentation in EPARs, a questionnaire was developed by EMA and used both by EMA and EUnetHTA representatives. The questionnaire was composed of 36 questions related to areas for improvement of the EPAR and methodology as identified by EMA. The result of this analysis gave an overall positive feedback. EMA and EUnetHTA developed jointly a [manuscript](#) on this project and published in a relevant journal.

In the context of data presentation in the EPAR, an exchange was held on the use of effects tables by regulators and HTA bodies. The EMA's effects table was developed as part of the project on benefit-risk methodologies as a structured display of key effects; this project also explored quantitative methods (e.g. MCDA) as a tool for making value judgment more transparent. From HTA perspective, methodology of the assessment of benefit-risk and added benefit of new drugs was presented by IQWiG and the WP5 Lead Partner of EUnetHTA JA2. The discussion after these presentations led to the conclusion that there is currently no single generally agreed method that allows quantification of the benefit/harm balance that is suitable for regulators/HTA. It was agreed that further follow-up discussions would be useful based on future



experience with different approaches. Therefore it is recommended that this fruitful experience should be continued during the JA3 of EUnetHTA taking into account a number of existing examples.

Furthermore, discussions are envisaged whether and how EPARs can support the health technology assessment by providing additional information like detailed reporting of results of health-related quality of life studies submitted in drug applications. These discussions will also consider alternative sources like the future publication of underlying study reports from the regulatory submission dossier (see 6.1).

#### **4.4.Facilitating EUnetHTA's pilot projects on rapid Relative Effectiveness Assessment of pharmaceuticals**

In February 2012 a discussion was started on how the final assessment report produced by EMA's CHMP could be made available to the HTA bodies early enough to be included in the process of rapid Relative Effectiveness Assessment (REA) of pharmaceuticals. The time between the CHMP opinion and the final availability of the EPAR for specific products is about 80-90 days. To be useful for REA, an assessment report of the Committee would need to be shared before final decision of the European Commission is publicly available. Making this document available to the HTA bodies earlier is important due to several reasons:

- to prevent too strong dependency of the REA process on the cooperation by the pharmaceutical industry
- to decrease the probability of assessing only products which carry the lowest risk for the companies when entered into a REA
- to secure usefulness by timely production of assessments for national implementation and reporting
- to decrease duplication of work across Europe
- to accelerate access of patients to effective and safe pharmaceuticals by making timely decisions based on the REAs produced jointly by EUnetHTA members and adapted nationally or locally by HTA bodies.

EUnetHTA identified the parts of the EPARs that are relevant for REAs: introduction, clinical aspects and the benefit-risk section. It was noted that these sections usually do not contain any commercially confidential information. A conceptual framework of sharing such regulatory assessment reports under confidentiality with HTA bodies has been developed by EMA. This includes:

- determining the most relevant timelines for the EMA information to be shared
- facilitating uptake by informing companies with MAA procedures ongoing about REA pilots and possibility for participation in order to accelerate evidence collection spread across Europe
- requesting HTA bodies to treat all information received from EMA as confidential.

The legal framework proposed by EMA is under review by the European Commission.

An information initiative has been discussed between EMA and EUnetHTA with the aim to increase awareness and accelerate involvement of the pharmaceutical industry in the joint REAs. This is an ongoing process that included development of leaflet by the

WP5 Lead Partner in JA2 and criteria for selection of potential candidates among manufacturers who would receive such a leaflet at early meetings with EMA.

## **5. Sharing experiences**

### **5.1. EUnetHTA partners' input to EMA's guidelines under public consultation**

Discussions on how EMA and EUnetHTA could mutually contribute to their respective guidelines production began at the meeting in February 2012. Starting from the meeting in November 2012 overviews and status of this activity were provided regularly.

EMA continues to send the list of consultations on guidelines to the EUnetHTA Secretariat on a regular basis, which informs its members on a possibility to comment on the drafts, as well as to be directly involved in the drafting of both disease specific and methodological guidelines. On top of the immediate publication of the announcement of lists of guidelines by the Secretariat on the EUnetHTA intranet, WP5 and WP7 Lead Partners also contacted its members directly in selected cases in order to encourage participation of the EUnetHTA members in the public consultations.

During the course of 2012-2015 a total of 16 sets of guidelines under public consultation have been provided by EMA to EUnetHTA. This included 33 guidelines on the clinical investigation of medicinal products, 5 methodological guidance documents and 7 pharmacovigilance-related guidance documents. Comments received from individual HTA organisations (e.g. NICE, IQWiG, HAS) have been considered along with all other comments received during the public consultation and made public in Overview of comments documents.

Some drawbacks in the process are reflected in lack of practical possibility to provide formal consolidated comments from EUnetHTA and in a relative low response rate from EUnetHTA partners. Whereas the first is difficult to obtain due to the voluntary character of the EU network for HTA, the other could possibly be countered, e.g. by providing the opportunity to contribute by the HTA organisations earlier in the guidelines development process. This could improve the engagement among EUnetHTA partners.

There have also been considerations to collaborate on the joint drafting of guidelines. This would allow an earlier interaction thereby ensuring that guidance documents for public consultation already contain the regulatory and the HTA perspective. Of particular relevance is this for disease specific guidelines. Such initiative should be considered for the future Joint Action 3.

### **5.2. Wording of the therapeutic indication**

The relevance of the approved wording of the therapeutic indication for relative effectiveness assessments was highlighted by EUnetHTA. This was initially raised in the context of medicinal products to treat hepatitis C virus (HCV) infection as well as medicinal products for treatment of type 2 diabetes. For the latter a reflection paper was issued in 2014 containing suggestions for a simplified therapeutic indication wording than the approach employed previously. EMA invited EUnetHTA partners to

provide feedback and consolidated comments from three EUnetHTA partners (ASSR, IQWiG and NICE) were presented at the meeting in December 2014 and in May 2015. Aspects of defining the patient population that are crucial from a regulatory perspective are of major relevance for HTA assessments. An explanation on how regulators come to a certain decision regarding an approved indication (in a situation where the patient population covered by the approved indication is broader or narrower compared to the population in the pivotal trials) was requested by HTA organisations to be included in the EPAR.

As a result of these discussions EMA will share with EUnetHTA draft principles for indication wording, for EUnetHTA partners' further comments and discussions in the next meetings.

### **5.3. Specific aspects of orphan medicinal products**

Issues specific to orphan medicinal products were considered important for the discussions and collaboration between EMA and EUnetHTA from the beginning. One of such issues was evaluation of the "significant benefit" as a criterion for orphan designation of the pharmaceuticals. The criterion is understood differently by EMA and HTA bodies, as a criterion of major contribution to patient care such as "ease of use" is sufficient for the Committee for Orphan Medicinal Products (COMP) to, among other criteria, support significant benefit and designate orphan status of the drug, and maintain it at time of marketing authorisation. In turn, HTA organisations expressed expectation of improved effectiveness as a result of the "ease of use".

This topic was discussed with a view to improve the mutual understanding of the respective assessment approaches relevant to regulatory decision making and HTA recommendations, respectively. To further explore this topic it was agreed to perform a scientific comparison of orphan drug assessments by EMA and EUnetHTA, based on real-world examples, which is planned to be presented at the one of the future meetings.

Closer collaboration of EMA and EUnetHTA on aspects concerning orphan drugs seems to be needed as one of the areas where more consolidated response to unmet needs could be provided.

### **5.4. Experience from the pilot projects of rapid and full HTAs on medicinal products**

Experience from the pilot assessments of pharmaceuticals were regularly shared by EUnetHTA with EMA representatives at the meetings starting from February 2012. Pilot rapid assessments are done in order to test the capacity of national HTA bodies to produce structured core HTA information (full core/rapid HTAs) together and apply it in national context (by including local data on e.g. patient population and costs) and to test the overall efficiency of the production within the network. The overarching aim of this work is to show the capacity to cooperate for increased efficiency of the production of HTA across Europe (one of the objectives of the EUnetHTA JA2).

The process of pilot assessments (including timelines), methodology as well as the HTA Core Model for rapid REA were regularly presented at the meetings. At the meeting in November 2015, considerations on use of the HTA Core Model domains

outside REA at the local level were added to the discussions. It was stressed by the EUnetHTA participants that many countries need to include economic, social or organisational aspects in their analyses, and therefore it would be advisable to have the possibility of including them in the future assessments.

Other potential issues and areas for further collaboration identified but not yet discussed thoroughly were the "Safety" domain definition, terminology and practical application as well as access to ADR data. Furthermore, involvement of patients in decision making deserves more exchange of experience and good practices.

## **6. Increase of transparency**

### **6.1. Publication of the clinical data for medicinal products and other related information**

Discussion on transparency of the clinical data for medicinal product started at the first workshop of EMA and EUnetHTA in March 2010, together with discussions on EPARs. It was EMA's initiative followed by request from stakeholders to facilitate access to EPAR information and improve transparency of the scientific assessment.

The relevance of the study reports for HTA was confirmed in a review done by IQWiG on the completeness of information for study outcomes in clinical study reports, registry reports and journal publications. The results of [the review](#) were presented at the EMA-EUnetHTA meeting in May 2013.

The policy on publication of clinical data for medicinal products for human use was adopted by the Management Board of EMA in October 2014. The date for coming into effect of the policy was set for 1 January 2015, meaning that it will apply to new applications submitted after that date. Because data will start to be accessible after the final decision by the EC (about 18 months from the submission of the application), the first publicly available study reports can be expected from September 2016.

With regard to the newly developed Terms of Use and the "Policy on publication of clinical data for medicinal products for human use", EUnetHTA enquired if the ToU allow pharmaceutical companies to use clinical (study) reports of competitor companies for the preparation of dossiers for HTA bodies. It was explained by EMA that the use of the data for scientifically sound relative effectiveness comparisons (produced by either HTA bodies or pharmaceutical companies) is in the interest of public health, and as such would not be reasonably deemed per se an unfair commercial use. An appropriate clarification of this explanation of EMA was included in the relevant [Q&A document from 8 June 2015](#).

Other EMA transparency initiatives noted by EUnetHTA included:

- List of marketing authorisation applications under review
- Publication of the CHMP agenda was made publicly available, which gives HTA bodies quicker insight into timing of final opinions of CHMP.

- EUnetHTA also noted that EMA makes summaries of observational studies available via the EU PAS Register ([http://www.encepp.eu/encepp\\_studies/indexRegister.shtml](http://www.encepp.eu/encepp_studies/indexRegister.shtml)) and that reports of suspected adverse drug reactions are made public via the [adrreports.eu](http://www.adrreports.eu) website (<http://www.adrreports.eu>).

## **6.2. Transparency proposals for orphan medicinal products**

The transparency proposals for orphan medicinal products were identified as an important issue at the EMA-EUnetHTA meetings. First information was shared by EMA in May 2013 by providing an overview of the publicly available summary of the position of the Committee for Orphan Medicinal Products (COMP) at time of authorisation, which includes information on prevalence, seriousness, significant benefit and link to EPAR. Currently information is published in the minutes of the COMP but that is not regarded as comprehensive enough nor is it linked to the specific product on the EMA website and as such not easily accessible for anyone looking at the information about a specific product. EMA is considering further advances in making information on the significant benefit assessment available to the public.

## **6.3. Optimisation of the presentation of information in regulatory documents for later use in HTAs**

To improve the availability and best use of data relevant for HTA was one of the most important objectives of the cooperation between EMA and EUnetHTA, emphasised by the Pharmaceutical Forum in its recommendations from October 2008.

The dialogue on the usefulness of the EPAR and SmPC for the relative assessments of pharmaceuticals, built upon early comments provided by MEDEV in 2009. Further workshops and rounds of consultations resulted in optimisation of assessment reports of the CHMP in terms of usefulness for relative effectiveness assessments. Lessons learned from this initiative have been published (see 4.3).

## **6.4. Publication of the summary reports from the EMA/EUnetHTA meetings**

Following a [joint press release](#) in 2013 an initiative to publish all final meeting minutes of the EMA-EUnetHTA meetings on the websites of EMA and EUnetHTA was taken. This also included summary reports from the previous meetings and preliminary workshops.

## **7. Discussion**

A six years' experience of regular meetings between EMA and EUnetHTA was an implementation of the recommendation of the High Level Pharmaceutical Forum from 2008. After the first positive experiences in collaboration through the workshops organised in years 2010-2012, the decision to continue the cooperation was taken with the aim of improving exchange of data and information, including scientific assessment and guidance between European regulators and HTAs. The areas of common interest were identified and included in the EMA-EUnetHTA three-year work plan.

The delivery of the work plan was followed up through regular bilateral meetings. Furthermore, numerous external conferences and workshops took place where topics have been progressed, like the EUnetHTA Conference in Rome (Oct 2014), the [Workshop](#) on parallel scientific advice in drug development organised by EMA (Nov 2013), and various sessions at DIA and ISPOR meetings.

Thanks to exchange of information and fruitful discussions, areas for possible synergies were identified. Improvement was also achieved in mutual understanding of differences between procedures for approval of pharmaceuticals to enter the European market and procedures designed for informing decisions on reimbursement and coverage or inclusion into national or local treatment schemes and packages.

Apart from the fruitful collaboration on the EPARs which had started before this three year work plan were developed and which is carried forward up to date, there were a few other interactions on the EMA newly developed Policies and guidelines, where EUnetHTA's input resulted in achieving consensus and improvements on information relevant to HTA. This includes, for instance:

- The Question and Answer document on the Policy on publication of clinical data for medicinal products for human use, where an intended use of those data were clarified by EMA for further use for production of relative effectiveness comparisons produced both by HTA organisations or pharmaceutical companies).
- Continuous collaboration on possible criteria and on general aspects of indication wording in the SmPC and on adding justification in the EPAR in cases where the therapeutic indication(s) are broader or narrower than the pivotal trial population

One of the specificities of the cooperation (not only EMA-EUnetHTA cooperation but also within EUnetHTA) is the voluntary nature of participation by the European HTA organisations in the European cooperation on HTA bringing along different legal bases, organisational structures and roles in the health-care systems of the Member States. This in some cases prevented EUnetHTA from taking a consolidated singular position regarding issues discussed during the meetings. Nonetheless, the level of engagement and participation in the EMA initiatives on the individual basis by EUnetHTA partner organisations has increased in the past 3 years. This includes:

- development of the pilot procedure for Parallel Scientific advice, with an aim of accelerating patients' access to efficient pharmaceuticals, by providing early scientific advice to the pharmaceutical companies;
- commenting on the draft guidelines during the public consultation;
- participation in the IMI2 Consortium on Enabling platform on medicines adaptive pathway to patients (ADAPT-SMART);
- contribution by different HTA institutions to the initiatives on Adaptive Pathways / MAPPs.

A few areas of cooperation which has already been extensively discussed could be accelerated and brought to the next level of collaboration between EMA and EUnetHTA

in Joint Action 3, especially by more intensive involvement of the European Commission (EC) and by securing a legal framework for collaboration:

- to further clarify together with the EC a legal basis for and enable timely sharing of the CHMP assessment reports so that it is useful for early development of the REAs of pharmaceuticals, which could then be timely adapted by the national or local HTA organisations and used for local decision making related to patients' access to effective treatments;
- To further develop an information package and criteria for applicants who would be informed during the EMA's pre-submission meetings about the opportunity to participate in EUnetHTA joint REAs.
- To directly collaborate in the drafting of scientific guidelines on the design of clinical development programmes.

New opportunities for collaboration in the initiatives related to additional evidence development should be carefully considered and planned after taking into account limited resources available to the HTA organisations and payers, in order to secure their representation in relevant projects.

There were also a number of topics which were introduced during the meetings and an interest for continuation, and further development of the collaboration in these was expressed by both EMA and EUnetHTA partners:

- to develop further understanding of the similarities and differences between the regulatory significant benefit used in the assessments of orphan drugs by EMA and the joint REAs by EUnetHTA in terms of objective and content;
- further discussions and sharing of experience on the engagements with patients to be included in the process of REA in JA3.
- joint development of terminology and definitions, e.g. in the field of Safety and Registries.

In conclusion, it is worthwhile to notice that collaboration of EMA and EUnetHTA through the life-cycle of development and management of pharmaceuticals already brings added value in terms of finding concrete synergies in the processes. In the future this can have positive consequences in terms of avoiding duplications of work and optimisation of timing and planning of the separate phases of pharmaceutical products' development, assessment and management.

Such initiatives need to carefully take into consideration the different roles and remits of regulators and HTA bodies, respectively. Respecting these principles is necessary to ensure that the collaboration between EMA and EUnetHTA can meet the expectation in its significant potential to improve efficiency of processes and activities as well as quality by way of improving procedures, exchanging experience, using mutual networks and supporting partnership initiatives.