EMA/EUnetHTA Meeting Minutes
5 July 2018 - 11:00-16:30 CET
Meeting venue: Hyatt Place Amsterdam, Netherlands

Role	Name
Chairs	Hans-Georg Eichler, EMA Giovanni Tafuri, AIFA
Present EUnetHTA:	Chantal Belorgey, HAS | France (via TC) Susanne Brück, GBA | Germany Jadwiga Czeczot, AOTMIT | Poland Angela de Ruijter, ZIN | The Netherlands Steve Estevao, ZIN | The Netherlands Claudia Furtado, INFARMED | Portugal Wim Goettsch, ZIN | The Netherlands Marcus Guardian, ZIN | The Netherlands Ali Hussain, ZIN | The Netherlands Marianne Klemp, NIPHNO | Norway Francois Meyer, HAS | France Tuomas Oravilahti, FIMEA | Finland Pauline Pasman, ZIN | The Netherlands Juan Carlos Rejon-Parrilla, NICE | United Kingdom Ingvil Saeterdal, NIPHNO | Norway Regina Skavron, GBA | Germany Giovanni Tafuri, AIFA | Italy Tomas Tesar, UNIBA | Slovakia Rick Vreman, ZIN | The Netherlands Beate Wieseler, IQWiG | Germany Anne Willemsen, ZIN | The Netherlands
European Commission:	Flora Giorgio, DG SANTE
EMA and CHMP:	Michael Berntgen Laurent Brassart (via TC) Kristina Dunder (via TC) Falk Ehmann (via TC) Hans-Georg Eichler Harald Enzmann Lise Flaunoe (via TC) Ana Hidalgo-Simon (via TC) Xavier Kurz (via TC) Kristina Larsson (via TC) Jordi Llinares Garcia (via TC) Peter Mol Jane Moseley Iordanis Sidiropoulos (via TC) Alexios Skarlatos (via TC) Spiros Vamvakas (via TC)

Agenda:

Item	Description	Name
1	Welcome, introduction to the day and adoption of the agenda	Marcus Guardian, ZIN Giovanni Tafuri, AIFA Hans-Georg Eichler, EMA
2	Update from DG SANTE on activities related to EMA/EUnetHTA collaboration	Flora Giorgio, DG SANTE
3	Update on Joint Action 3 activities	Marcus Guardian, ZIN
4	The landscape of Advanced Therapy Medicinal Products – what is coming into the market and how can we work together in this space	Chantal Belorgey, HAS Ana Hidalgo-Simon, EMA
5	Indication wording – exchange on principles and review of examples	Regina Skavron, GBA Susanne Brück, GBA Laurent Brassart, EMA Alexios Skarlatos, EMA Jordi Llinares Garcia, EMA Kristina Dunder, EMA
6	Update on the ongoing study on the comparison between significant benefit (COMP, EMA) and REA (HTA) for orphan drugs	Angela de Ruijter, ZIN Wim Goettsch, ZIN Rick Vreman, ZIN Kristina Larsson, EMA Iordanis Sidiropoulos, EMA Bruno Sepodes, EMA
7	Collaboration on patient registries – experience so far and future opportunities	Francois Meyer, HAS Xavier Kurz, EMA Jane Moseley, EMA Peter Mol, EMA
8	Update on other activities	Francois Meyer, HAS Claudia Furtado, INFARMED Juan Carlos, NICE Anne Willemsen, ZIN Jane Moseley, EMA Michael Berntgen, EMA Falk Ehmann, EMA
9	Closing remarks	Hans-Georg Eichler, EMA Giovanni Tafuri, AIFA

1. Welcome, introduction to the day and adoption of the agenda

The Chairs and the EUnetHTA Secretariat welcome participants to the meeting and thank them for their participation.

Conclusions:

The draft agenda was adopted without changes.

2. Update from DG SANTE on activities related to the EMA-EUnetHTA interaction

DG SANTE confirms that the debate on the proposal for regulation on HTA in Europe is ongoing. In the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO), it emerged clearly that there is a political willingness to discuss technical solutions to issues.

The aim is to ensure sustainability of the ongoing collaboration, while recognising the concerns of some member states. The EC recalled that the proposal was preceded by an impact assessment based on an open call for consultation; a regulation was deemed as the most feasible instrument based on feedback.

Amongst the many areas of discussion, Article 8 (uptake) is identified as requiring further discussions. Discussions in the Council Working Party and voting on amendments within committees in the European Parliament will happen within the next few weeks and further meetings are due to take place.

Interaction between HTA and the regulatory side is an important topic and discussions are also taking place on how this synergy will continue post-2020.

Discussions on the scope of medical devices to be included as part of the proposal are also ongoing in the European Parliament. The EC is working with industry to acknowledge their concerns, however discussions on future inclusion continue.

The Austrian presidency has invited all member states to provide written comments on the proposal of the Commission before 20 July 2018. They will compile comments and create a compromise text before the end of August as a basis for further talks. The presiding committee on the matter, the ENVI (Environment) Committee will hold a vote on their opinion in early September, followed by the plenary vote in October.

Conclusions:

DG SANTE agreed to keep EUnetHTA and EMA informed as discussions within political institutions on the future of the HTA proposal continue.

3. Update on Joint Action 3 activities

ZIN (Secretariat) provides an update on current JA3 activities.

It is noted that the focus continues to be to develop a sustainable model for joint HTA work. This includes increasing the use, quality and efficiency of HTA. Part of this means increasing collaboration (sharing knowledge), production (aligning processes) and usage (implementation). Furthermore, the Secretariat will continue their work on engaging stakeholders and defining processes to move from a project structure to a sustainable network.

The core focus is split into two areas; network products and project management. Network products infers aligning all seven working packages to ensure they serve the areas of Joint Assessments, SA/EDs, Horizon Scanning and Registries. The focus on individual project management means continuing to engage Heads of HTA agencies, the Executive Board and members and partners. The EUnetHTA-EMA collaboration platform is an essential tenet of this work.

ZIN presents the achievements of the EMA-EUnetHTA work plan 2017-2020 which includes the new platform for parallel consultations and the registry qualification exercise following the EMA procedure for the Qualification of novel methodologies for drug development.

Conclusions:

As the project continues, there is a consensus that further collaboration with regulatory bodies is positive and must be maintained as a platform for information sharing.

4. The landscape of Advanced Therapy Medicinal Products – what is coming into the market and how can we work together in this space

HAS presents a brief overview of when exchanges have taken place between interested EUnetHTA partners and the EMA. The group have so far cooperated on; general information sharing, common lists of forthcoming ATMPs, encouraging developers to bring ATMPs to parallel scientific advice and building on experiences from CAR-T cells.

A list of ATMPs is to be launched within the next five years and this will be populated by HAS. This will be a compilation of published data (namely from Clin.gov, the Innovation Observatory, the Advanced Therapy Conference and PRIME). This would then help anticipate and plan future EUnetHTA cooperation.

279 SA procedures have begun with CAT involved (routinely) in all SAs for ATMPs (as of March 2018). There has been an increase in SAs for ATMPs between 2012-2017, the majority of which is for GTMP.

HAS presents a graph outlining the numbers of scientific advice and parallel SAs for all products versus ATMPs in 2017 and the first half of 2018.

An update is presented on EUnetHTA/HTA involvement in EMA activities related to PLEG for CAR-T cells.

This involvement is channelled via observatory participation in the Qualification of cellular therapy module of the EBMT registry and the participation of individual HTABs in the CAR-T cell therapy registries workshop.

HAS notes a willingness to build on experiences from CAR-T cells by exchanging information in a range of areas from the results of assessments to PLEG requests as well as hosting a EMA-EUnetHTA workshop. This workshop has been planned in 2019 as per the EMA-EUnetHTA work plan.

A discussion on how collaboration in this area could be advanced was held among participants.

Conclusions:

There was consensus about the importance of early dialogues and information sharing in the field of ATMPs.

Action items	Responsible
Sharing of learnings from recent ATMP evaluations (regulatory and HTA) with the perspective to engage with developers about the value of prospective discussions on evidence generation plans for future products	EUnetHTA-EMA
Develop methods to further collaborate on creating registries for qualification	EUnetHTA-EMA
Consider as part of the ongoing collaborative work on horizon scanning how relevant information on upcoming ATMPs can be highlighted	EUnetHTA-EMA
Identify common issues on the collection of data (beyond CAR-T cells) and highlight methods to advice developers at an earlier stage	EUnetHTA-EMA

5. Indication wording – exchange on principles and review of examples

EMA begins by presenting an overview of the CHMP-internal reflection paper on the wording of therapeutic indication. The paper aimed to improve clarity of indications in SmPC and EPAR for all stakeholders and support a consistent approach in the process of defining the therapeutic indication. The content focused primarily on clarifying the regulatory framework of the therapeutic indication and identifying the different elements to consider when assessing the indication (of CAP).

Ultimately, it was stressed that the wording of the indication should be explained in the benefit/risk section of EPAR and the therapeutic indication should reflect in which disease and target population the benefit/risk balance is positive. EMA presents the components to consider when defining the indication. This includes elements such as target disease/condition, target population and place of therapy.

EMA thanks G-BA, IQWiG, AOTMiT, FIMEA and NICE for their feedback on the reflection paper.

EUnetHTA representatives begin by posing the question, “where and when is the indication important in HTA procedure?” The wording of indication is noted as having implications at different points in time in HTA assessments and is particularly important for products in the same/similar indication. The problem at the moment is the discrepancies between evidence (pivotal studies) and wording of indication.

Following up on the statement that “the scientific basis for and the reasoning behind the final wording of the indication should be clearly documented in the benefit/risk section of the CHMP AR,” examples are presented on how, in some cases, marketing authorisation/indication is broader than evidence from trials. A wording template is proposed in an effort to reduce discrepancies and harmonise definitions. EUnetHTA representatives conclude with the priorities from HTAB perspective; distinct definitions, harmonisation of wordings and transparent documentation of underlying evidence, decision-making process and resulting wording of indication.

Presentations conclude with a consensus that the reflection paper has been helpful in providing greater clarity. It was agreed that the target population should be well-defined and any broadening or restricting of the approved use beyond the use for which data is available (and shows a positive benefit/risk) should be justified in the AR. If there are several products for the same or similar indication, the wording should be harmonised if possible.

Finally, EMA outlines a few requests for further explanation which are discussed as well as some suggestions to improve the reflection paper.

Conclusions:

The review of the reflection paper was a useful exercise and exchanges following the presentation would be considered when conducting studies in the future.

Action items	**Responsible**
Create opportunities to provide feedback from HTA bodies to CHMP (Rapporteurs and assessors) on the principles described in the reflection paper (e.g. training webinar, plenary discussion)	EUnetHTA-EMA
Highlight to CHMP the importance of clarity and completeness of the rationale for the indication wording in the EPAR (including specific considerations for subpopulations covered by the label) to better inform subsequent decision making	EMA
Discuss with the CHMP the possibility to publish the reflection paper, in addition to the monitoring of implementation	EMA

6. Update on the ongoing study on the comparison between significant benefit (COMP, EMA) and REA (HTA) for orphan drugs

The context of the study as well as its aim and objectives are recapped. The team is currently selecting cases and beginning to write a report and a journal article containing five case studies. The goal of this analysis of secondary data is to define drugs which exemplify differences. Based on the criteria set out, 75 drugs (per indication) were found in the EMA database fulfilling the first two criteria and 22 of these were assessed by at least four HTA bodies.

Data from reports were extracted in six domains corresponding to the study objectives and drugs were categorised based on whether they would allow the assessment of similarities and differences between SB and REA in these domains. Following the case studies, five drugs were selected. The results have so far been disseminated in the ISPOR abstract submission.

Following this activity, a draft report will be finalised in August and circulated for feedback. An article will then be produced for publication in a peer reviewed journal. Active participation and feedback is welcomed.

Conclusions:

The group agreed on the importance of the study and welcomed the opportunity to provide feedback within the coming months.

Action items	Responsible
Finalisation of the analysis and publication of the report, including involvement of HTA bodies responsible for the reports subject to the review	EUnetHTA-EMA
Lessons learned from this research on the basis of the selected cases in terms of the application of the two concepts, including potential follow-up through a quantitative study	EUnetHTA-EMA

7. Collaboration on patient registries – experience so far and future opportunities

Current EUnetHTA results

Joint Action 3, WP5, objectives, main activities and general aspects are recapped. These activities are split into Strand A: Early Dialogues and Strand B: Post-launch evidence generation (PLEG) and registries.

In terms of product specific pilots arising from HTA, two pilots are ongoing. This is on an orphan drug, led by AIFA and which began in April 2018. The other is on breast cancer, led by TLV and which began in May 2018. Both are expected to end mid-2019. A medical device, led by Avalia-T, is upcoming. On disease/registry specific collaborative pilots, two pilots have been carried out as well as a registry qualification exercise following the EMA procedure for the qualification of novel methodologies for drug development. For EUnetHTA, this resulted in qualification advice on topics discussed.

The selection and prioritisation criteria for PLEG pilots is also recapped.

The second activity led by WP5B is on registry quality standards. The objectives of this are to adapt existing quality standards for registries into a practical tool for use in registry HTA data and build upon the work of the PARENT Joint Action (Parent Registries Initiative). This activity has led to a report being produced on the current use of registry data by HTA bodies, the upgrade of the Registry Quality Standards Tool and the testing of it by three EUnetHTA partners. Next steps will include undertaking an external consultation on the latest version of the tool and producing a final version in September 2019.

Lessons from the EMA Patient Registry Initiative

EMA outlines the current problems with registries which support new drug applications. Amongst many reasons why problems have been encountered, it is highlighted that the approach to registries is often suboptimal in scientific and research terms. This is because, existing registries are not exploited (causing a duplication of efforts and inefficiencies) and there is a discrepancy between data collected by registries and data requested by regulators. The fact that existing patient (disease) registries were not set up for regulatory purposes adds to the issue as it is challenging to use them for regulatory studies.

This has led to the EMA Patient Registry Initiative. Launched in September 2015 as a cross-committee task force, it aims to facilitate use of patient (disease) registries by introducing and

supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines. The key components of this initiative are outlined as being to promote dialogue between regulators, companies and registry holders, and to understand barriers and opportunities of using disease registries.

Lessons and challenges from a series of workshops are presented followed by a list of recommendations on how regulators can support the use of disease registries. The presenters concluded that although there are some concerns about data quality of existing disease registries and the gap between the amount/type of data collected in disease registries, there is also recognition that the EU regulatory network develops tools to support use of disease registries and the qualification process through EMA scientific advice may provide confidence in registry data.

Conclusions:

The discussion resulted in several actions that pave the way for further collaboration in this area.

Action items	**Responsible**
Continuous mutual engagement in the context of the development of guidance and standards for patient registries	EUnetHTA-EMA
Seeking opportunities for prospective product-specific or broad discussions on registries	EUnetHTA-EMA

8. Update on other activities

Post-licensing evidence generation

Regulatory perspective on registries' Qualifications

EMA recaps the role of RWE for regulators and presents information on the toolbox for collaboration (in planning evidence generation). The first parallel review was completed for the European Cystic Fibrosis Society Patient Registry (ECFSPR). The opinion gives a defined range of studies and circumstances, caveats and recommendations based on a better understanding of the data strengths and limitations. Another qualification process was completed for the European Society for Blood & Marrow Transplantation (EBMT) Registry; the draft opinion following this is presented.

When reflecting on qualifications, of the many observations, it is noted that regulators see improved data quality, better understanding of quality, governance, study feasibility and trust in data. To progress, RWE discussions on specific proposals are needed and there should be a focus on talks including decision makers and representatives.

Horizon scanning activities

A trilateral meeting was held a few months ago between regulators, EUnetHTA and payers. The outcome of this meeting categorises any collaboration on horizon scanning in three different areas.

The first encapsulates products under regulatory assessment. This is important to keep the development of EUnetHTA Joint Assessments in line with the progress of the regulatory assessment. It was communicated that although the information is publicly available, it is not

easy to find. An agreement was made here to provide improved reporting on regulatory milestones.

The second interpretation refers to products, which are about to be submitted to EMA. It is important to explore possibilities to collate (public) information at the time of the pre-submission to EMA.

The third interpretation refers to the wider horizon. This means what is coming up over the next five to ten years. This was discussed as an area for concrete collaboration with work to be done across stakeholder groups on how the information can be compiled.

Combination products/companion diagnostics work stream

Some background is provided and the objective of the group is recapped; the EMA-EUnetHTA three-year work plan highlights the need for both parties to share practices and experiences with combination products/companion diagnostics. Within the national plan for NGS in France the work group will be supporting HAS in developing guidance on how to assess NGS. Furthermore, another priority area is related to the evaluation of Genetic Signature Tests. The group also agreed to consider potential funding sources for a literature review on the assessment of algorithms used to target treatments based on NGS, leading potentially to highly personalised treatment regimes. On the area of operational issues around patient access to companion diagnostic tests, the group will consider issues such as CE marked in-house tests and their relative costs, quality and quality assurance provisions.

As part of easing the exchange of strategically important information and articulating consensual views on relevant strategic topics, there was an agreed joint NICE/HAS/IQWiG written response to the EMA consultation on a specific concept paper. The group also shares any (non-confidential) information that could be useful to day-to-day activities.

Information exchange between regulators and HTA bodies at the time of market entry

The joint presenters recap REA submissions in 2017 and present feedback on the preparation and discussion of the reports.

Conclusions:

Updates will continue to be provided on these areas at follow up meetings.

Action items	**Responsible**
Continue to explore opportunities to engage optimising HTA awareness of regulatory steps and timelines	EUnetHTA-EMA
Address operational aspects from first pilots on collaboration at time of market access (reference to CHMP AR in the draft REA; timing of webinars)	EUnetHTA-EMA

9. Closing remarks

The meeting restated the need for active and continued collaboration between HTA and regulatory bodies. Both Chairs thanked participants for their attendance and wished everyone a safe journey home.

Conclusions:

The next meeting will be hosted by EMA and is scheduled for Q4 2018.

Key:*

EUnetHTA	European Network of Health Technology Assessment
JA3	Joint Action 3
WP	Work package
EMA	European Medicines Agency
HTA	Health Technology Assessment
DG SANTE	Director General Health and Food Safety
TISP	Topic Identification, Selection and Prioritisation
CHMP	Committee for Medicinal Products for Human Use
SA	Scientific Advice
ED	Early Dialogues
EBMT	European Society for Blood & Marrow Transplantation
HTAb	Health Technology Assessment bodies
SmPC	Summary of product characteristics
ECFSPR	European Cystic Fibrosis Society Patient Registry
EPAR	European Public Assessment Report
NGS	Next generation sequencing
REA	Relative Effectiveness Assessment
CAP	Centrally authorised products
CAT	Committee for Advanced Therapies
AR	Assessment report
ATMPs	Advanced Therapy Medicinal Products
PLEG	Post Launch Evidence Generation

*Organisation abbreviations have not been included