EMA/265469/2021

Report on the implementation of the EMA-EUnetHTA work plan 2017 - 2021

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 in the work plan 2013-2015. During EUnetHTA Joint Action 3, the EMA-EUnetHTA collaboration continued in the work plan 2017-2021 and the following areas of collaboration were identified:

- Early Dialogue / Scientific Advice
- Late dialogues / peri- licensing advice
- Information exchange between regulators and HTA bodies
- Methodologies to identify the treatment eligible population
- Significant benefit vs. added therapeutic value for orphan medicines
- Unmet medical need and therapeutic innovation for priority setting
- Patient and clinician engagement
- Shared understanding of methodological approaches for design, analysis and interpretation of clinical trials and observational studies
- Population-specific or Intervention-specific areas

This report presents the achievements and reflections of the EMA-EUnetHTA 2017-2021 work plan.

Organisation of regular meetings of EMA and EUnetHTA representatives

Under Joint Action 3, between May 2016 and June 2021, a total of 10 meetings were organised and were hosted alternately by EMA and the EUnetHTA Secretariat ZIN.

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

Table **Fout! Geen tekst met de opgegeven stijl in het document.**-1: List of bilaterals

Date	Location
7 December, 2016	London, UK
8 June, 2017	Diemen, The Netherlands
15 December, 2017	London, UK
5 July, 2018	Amsterdam, The Netherlands
7 December, 2018	London, UK
4 July, 2019	Diemen, The Netherlands
21 November, 2019	Diemen, The Netherlands
13 July, 2020	Online
16 December, 2020	Online
28 April, 2021	Online

Action by topic area

Activity	Achievements	Reflections
Early Dialogue / Scientific Advice		
Design and implement a single, common, European procedure for Parallel Consultation (previously known as parallel scientific advice/early dialogue)	In July 2017 a revised **single process for Parallel Consultation** (joint scientific consultation involving EMA and HTA bodies) was **launched** (Consolidated Parallel Consultations/ PCC). This initiative replaced the former parallel scientific advice procedure (Individual Parallel Consultations/ PCI) by EMA and HTA bodies, whereby medicine developers had to contact Member State HTA bodies individually. **Guidance for the** Parallel Consultation procedure **was published and regularly improved** (last in Summer 2020); **multiple communication to stakeholders**. Overview of procedures: • 31 completed PCCs • 28 completed PCIs to date • 2 Parallel consultations on registry qualification (1 HTA body as observer, 1 HTA body substantive) • Parallel consultation on the qualification of an IMI (Innovative Medicines Initiative) project (HTA bodies as observers and substantive)	The demand from developers exceeded the capacity by EUnetHTA JA3 members to conduct Parallel Consultations PCC hence a sustainable framework with adequate financial resourcing is necessary. An EUnetHTA Early Dialogues Financing Mechanism (EDFM) has been prepared but had to be postponed to after JA3, intermediate financing via remaining EUnetHTA project funds. EUnetHTA paused Parallel consultation in April 2020 due to COVID-19 reprioritisation. Re-launch of the Parallel Consultation Procedure in September 2020. Reviewing templates and procedures allowed to implement some HTAs requirements (i.e. PICO, PROMs.) and process (offering also a written process); flexibility of processes and documentation required is key
Facilitate learning and understanding of evidence needs	Reciprocal **observership** by EMA at HTA Early Dialogue and by HTA bodies at EMA scientific advice, respectively, was offered but rarely used.	"Observership" as form of passive participation is by now superseded by collaborative discussions on product-specific evidence generation plans. Therefore, this activity in the work plan was closed early.
"Late dialogues" / peri-licensing advice		
Gaining experience with peri-	Use of the **Parallel Consultation platform** (see above)	Early discussion of Post Launch Evidence

Activity	Achievements	Reflections
licensing advice on post-licensing data generation plans with a focus on specific products (e.g., ATMPs) or regulatory processes or tools (e.g., CMA, Adaptive Pathways, or PRIME)	to provide guidance on requirements for **post-authorisation data collection plans** (including registries). Regular review of learnings and experiences (e.g. at the November 2019 bilateral). Overview of procedures: • 2 Parallel consultations on registry qualification • 12 Parallel consultations including recommendations on PLEG • 2 Parallel consultations specifically on PLEG Scientific article on **"Regulatory and health technology assessment advice on Post-licensing and Post-Launch Evidence Generation"** published in British Journal of Clinical Pharmacology (BrJClinPharmacol 2020 Jun;86(6):1034-1051).	Generation (PLEG) requirements identified as facilitator for later decision making, however more proactive proposals from developers for discussion in Parallel Consultation needed. The identification of PLEG requirements as a result of joint REA follow-up activities needs to be expanded.
Optimise utilisation of post-licensing evidence generation for decision making	Multiple **collaborations on requirements for data collection** and analysis of real world data including registries, such as: • EMA response to the public consultation on EUnetHTA's tool on registry therapies based on tumours' genetic and molecular quality (REQueST); • EUnetHTA response to the public consultation on EMA Discussion paper on the use of registries (collated feedback of 11 EUnetHTA partners) • Discussions on synergies on work on registries at several bilateral EMA-EUnetHTA meeting (see minutes) • EUnetHTA participation in EMA registry workshops (e.g. Workshop on the use of registries in the monitoring of cancer features. November 2019) • Introduction to DARWIN EU (Data Analytics and Real-World Interrogation Network) and discussion on opportunities for collaboration; as a result,	Collaborative work on registry methodologies identified as priority. HTA representative to become member of the advisory board of DARWIN EU governance to further facilitate the collaborative work in the space of real-world evidence. The DARWIN EU Advisory Board will: - Provide strategic advice and recommendations to the project team on the establishment of the DARWIN EU capability and its use of the European Health Data Space; - Ensure continued coordination and alignment of the project with relevant European initiatives and policy as well as Member state initiatives; and - Support two-way communication on DARWIN EU with the EU Regulatory Network,

Activity	Achievements	Reflections
	invitation from EMA to EUnetHTA to nominate a representative to the DARWIN EU Advisory Board.	stakeholders and the European Health Data Space. Other regional initiatives and pilots on prospective planning of RWE and its application for decision making need engagement by both regulators and HTAs.
Information exchange between regulators and HTA bodies		

Timely provision of the outcome of the regulatory assessment to support joint REA production	• A **workflow and operational framework** for **provision of the final CHMP AR** in the context of joint REA production has been developed and implemented in 2017.
	• Based on initial experiences, the **operational framework** agreed between EMA and EUnetHTA was **fine-tuned** in 2019 as follows:
	  ○ Regular update on regulatory review timelines
	  ○ Debriefing on final indication at time of CHMP Opinion
	  ○ Clarification regarding citation of the CHMP AR in the REA
	  ○ Access to the SmPC
	• In total during JA3, for 14 products[1] the elements from the final **CHMP assessment report were exchanged** and for 13 of these subsequent **webinars** between HTA authors and CHMP rapporteurs were held (one had been cancelled due to COVID-19 scheduling issues).
	• As of the most recent webinars, REA authors are asked to present to the EMA (co-)rapporteur their PICO and considerations/challenges that may be
		Feedback from participants (regulators and HTA authors) confirmed the value of these direct discussions. Elements such as identification of evidence gaps to further align PLEG requirements need to be explored more.
		
		The administrative burden due to the need for project-specific confidentiality arrangements was considerable and should be simplified under a more sustainable framework.
		
		Earlier engagement should be explored in order to further facilitate timely REA production.

[1] Two of these joint REA productions will continue after Joint Action 3, with the authors, coordinators and processes being unchanged. In this context, the cooperation between EMA and the concerned HTA bodies in the context of this joint REA production will continue.

Activity	Achievements	Reflections
	present in the HTA assessment. This to foster mutual understanding between the two constituencies.	
Respecting the remit and perspectives of both regulators and HTABs, create a mechanism for reciprocal learning opportunities between regulatory reviewers and HTA assessors.	**Increased understanding of the regulatory outcome by HTA** assessor, as well as increased understanding of the **HTA outcome by the regulatory** reviewers was sought by: • Product-specific webinars on two applications outside the REA procedure (Zynteglo, Vitrakvi), based on publicly available information. • Subsequent to the conditional MA for remdesivir, webinar to debrief on the final regulatory outcome and to inform about the EUnetHTA PICO for the HTA review.	On the basis of the experience with webinars in the context of Joint REA production, exchanges on product-specific reviews / assessments of mutual interest are generally considered of value and should continue to be facilitated.
Further optimisation of the regulatory output to facilitate uptake of regulatory outcome by HTAB	• Review of the webinar experience in terms of questions raised by HTA authors to **identify elements for optimisation of the regulatory assessment report** through an update of the template and guidance for the CHMP assessment report See also below item on labelling	Regular experience reviews recommended, also to be complemented with information sessions / trainings.
Methodologies to identify the treatment eligible population		
Share experience on how regulators define therapeutic indications and the impact of their wordings in HTABs' definition of the treatment-eligible population.	Upon continuous exchange of experience on SmPC and EPAR, between EMA, its Scientific Committee (CHMP), EUnetHTA and representatives of the Payers' community, the value of the EMA/CHMP guide to assessors on the **wording of therapeutic indication to facilitate the interpretation of the information contained in SmPC section 4.1, e.g. for HTA purposes,** has been recognised and subsequently published on the EMA website.	To facilitate future additional exchange on the topic HTA agencies are invited to keep collecting examples of labelling and EPARs for future development of guidance on 5.1, including information on subpopulations. It has been agreed to continue sharing concrete experience from using labelling and EPARs for decision making, especially regarding subpopulations where limited data is available.

Activity	Achievements	Reflections
		Further exchanges would also cover the section 5.1 of the SmPC to consider whether the selection of information could be streamlined and ascertained compared to EPARs.
Mutual understanding of the extrapolation concept, including its application for the paediatric population	• The **draft reflection paper** on the use of extrapolation was presented and **commented by EUnetHTA** during the public consultation. • A **newly developed assessment template was shared with HTA colleagues**, for comments. • In March 2021 a **joint workshop** was held on this topic, with a special focus on the development of paediatric medicines. The objective of the meeting was exchange of experiences and mutual understanding of each other's remits and tasks.	The concept of extrapolation / evidence transfer will be relevant in certain developments, such as those affecting small populations, and would therefore require further joint methodological work. It is important to understand each other's reasoning for accepting extrapolation acknowledging the different remits.
Significant benefit vs. added therapeutic value for orphan medicines		
Understanding of the similarities and differences between the concepts of significant benefit and added therapeutic value in the context of orphan drugs	A research proposal comparing the similarities/differences between the **concepts of significant benefit and relative effectiveness assessment** was presented. An scientific article "Assessment of significant benefit for orphan medicinal products by European regulators may support subsequent relative effectiveness assessments by health technology assessment organizations" was published In Drug Discovery Today (Volume 25, Issue 7, July 2020, Pages 1223-1231) to disseminate this research.	This was not only a successful exercise with regards to the publication of an article but improved the understanding from all participants about the different concepts. Although the study focused of differences between the significant benefit assessment and REA frameworks, no major differences between significant benefit assessment and REAs were found. The conclusion was that early interactions between both stakeholders might further diminish differences in the future. Given that significant benefit and REAs serve different purposes, the ultimate outcome of the evaluations might differ even though the considerations regarding the evidence are similar. Nevertheless, because of the many similarities found in this study, HTA organizations might benefit from reviewing the orphan maintenance assessment reports, as provided on the website of the EMA.

Activity	Achievements	Reflections
Exchange on product specific reviews at time of authorisation	The concept of the Orphan Medicines Maintenance Reports (OMARs) has been developed together with HTA bodies. **These reports are regularly published** with every orphan medicine.	Following up on how the OMARs are being taken up by HTAs would need to be done in the future once more experience has been made, so that the OMARs can be updated to reflect the HTA needs better.
Unmet medical need and therapeutic innovation for priority setting		
Explore how HTABs and regulators interpret the concepts of unmet medical need and therapeutic innovation	• **Review of the status** of how the concept of unmet need **is defined** and applied by HTAs in their respective country. • Scientific article on "Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions" published in Value in Health (22(11), 1275-1282, 2019) • Discussion at the EUnetHTA forum with participation of HTA, patients, Industry and regulators. The outcome of the session was included in "The EUnetHTA Forum: highlights of the fourth edition" published in International Journal of Technology Assessment in Health Care (36(3), 191-196, 2020).	Need to explore further collaborative work on the UMN concept (e.g. in the context of the EC Pharma Strategy) to inform prioritisation by different decision makers.
Explore opportunities to collaborate on monitoring of new medicines' approvals ("horizon scanning")	In the context of EUnetHTA's horizon scanning activity "Topic Identification, Selection and Prioritisation (TISP) Pilots" a **reporting format** summarising **relevant information from EMA** on products and review timelines was developed. The basis were the information needs of EUnetHTA (short- and medium-term) to inform topic selection within WP4 and WP5B. • The provision of the report by EMA supported the TISP pilots, which led to the final EUnetHTA recommendations. Information from this work also led to the first EUnetHTA Prioritisation List (EPL). • Ad-hoc exchanges on upcoming or ongoing regulatory product review activities occurred between EMA and EUnetHTA in the context of	Provision of information by EMA allowed filling of data gaps to support planning by EUnetHTA, however this was limited to publicly available information. A more detailed reporting would potentially be needed to inform HTA work planning under a future legislative framework.

Activity	Achievements	Reflections
	prospective planning for REA joint production activities, e.g. in the context of COVID-19.	
Patient and clinician engagement		
Share respective practices and experiences related to the involvement of patients and clinicians in activities	Opportunities to exchange and **mutual learning regarding engagement practices in assessment activities**: • EMA attended HTA network stakeholder meetings for patients and healthcare professionals • Detailed discussion at the EMA/EUnetHTA bilateral in July 2019 EMA and EUnetHTA discussed engagement methodologies for patients and healthcare professionals. In addition, documents including i) Patient Input in Relative Effectiveness Assessments (REA), ii) Declaration of Interest/Confidentiality Undertaking and iii) Healthcare Professionals involvement in Relative Effectiveness Assessments have been shared by EUnetHTA for EMA information and comment. EMA shared the PCWP/HCPWP joint work plan activity on patient, consumer and healthcare professional involvement as well as updates regarding developments in stakeholder engagement and discussed mutual experiences regarding compensation of patients/healthcare professionals. EMA and EUnetHTA attended reciprocal meetings with representatives from the respective stakeholder groups.	Further collaboration could focus on sharing respective practices and experiences related to: •Compensation for expert participation •Guidance on how to incorporate expert input in the regulatory and HTA outputs
Assess the feasibility of developing a shared pool/list of contacts	The initial activity outlined in the work plan of developing a **shared list of contacts proved not to be feasible** however **EMA provided contacts for targeted consultation** on joint assessments by EUnetHTA. In total 11 of such consultations took place in and EMA provided contact details of relevant patient and healthcare professionals organisations to assist in the activities.	Such targeted consultations should continue. One of the limiting factors for identification of experts for HTA is the need to enhance awareness and understanding by experts on the differences between HTA and regulatory. To address this challenge, future collaboration could address a process and information for educating expert

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	Finally, EMA invited 17 patients to participate in 17 parallel procedures with EUnetHTA in the context of EMA scientific advice.	groups on regulatory and HTA needs.
Shared understanding of methodological approaches for design, analysis and interpretation of clinical trials and observational studies		
Provision of guidance on evidence needs for regulators and HTA bodies, through therapeutic-area-specific guidance, methodological guidance, non-product specific qualification advice and opinions, workshops.	Commenting by HTA bodies on relevant guidelines, e.g.: - 'Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle'; 'Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations'; - 'Reflection paper on the use of extrapolation in the development of medicines for paediatrics'; - Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials'; - 'Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders'; - 'Draft qualification opinion of clinically interpretable treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses'; - 'Discussion paper on the use of registries'. Discussions at different forums to **engage with developers how to generate evidence to address both regulatory and HTA information needs** , e.g. EUnetHTA Forums (2018: How can EUnetHTA predict and assists European health systems prepare for potentially disruptive innovation?, and 2019: What constitutes a medical need?), EFPIA-EUnetHTA Technical meeting, PRIME anniversary meeting, EMA/payer community meeting - Discussion of methodological issues at EUnetHTA/EMA meetings (e.g. Concepts of significant benefit and relative effectiveness, extrapolation (2017), ICH guideline updates	The joint work on methodological issues and guidelines is considered of importance even if during the current work plan activities were limited to workshop participation and commenting individual contribution, e.g. comments by individual HTA agencies on the recently published EMA Guideline on Registry-based Studies were encouraged but depended on available resources at the agencies.

Activity	Achievements	Reflections
	(2018), the REQUEST-Tool (2019)) - Discussion of methodological issues at EMA/EUnetHTA webinars on specific products (e.g. ATMPs, histology independent developments)	
Better utilization of patient-reported outcomes as part of evidence generation plans	Several discussion at bilaterals to provide update on activities, such as: • Discussion of PROs in SAs/EDs as well as in regulatory and HTA reports at the EMA/EUnetHTA in November 2019 meeting. • Development of guidance on PROs in oncology. Several **joint participations** in external events **on PRO methods**, such as EORTC meetings, FDA workshops, a DIA meeting on PROs or the SISAQoL project (2017-2020).	This is an area of great importance for future collaboration in view of the developing methodologies and stronger reliance on such data in context of decision making. Workshop on use of PROs in cancer clinical research involving also HTA participants planned by EMA for 2021.
Population-specific or Intervention-specific areas		
Address the specific needs for paediatric medicines	EUnetHTA attended the June 2018 **Enpr-EMA** workshop and presented EUnetHTA and current principles of benefit assessment of paediatric medicines by European HTA bodies.	The focus of attention diverted to the extrapolation topic, as this is about evidence that is produced. Further reflections on this topic were shared at a joint workshop in March 2021 (see above, "methodologies to identify the treatment eligible population".) For the future, it would be desirable to increase awareness of the specificities and possible limitations of evidence generation in paediatric medicines among HTA bodies. Common minimum evidence needs for benefit assessment by European HTA bodies should be defined and awareness raised among and in collaboration with stakeholders (e.g. industry, networks, PDCO).
Share practices and experiences with combination	Initial work focused on developing a combined HAS, IQWiG and NICE response to the EMA concept paper on development and lifecycle of personalised medicines and	There is agreement that this is an important topic and is still relevant and in a future cooperating post JA3 it should be considered to continue.

Activity	Achievements	Reflections
products/companion diagnostics	companion diagnostics, which is relevant in the context of the **implementation of the IVD regulation**. • Multi-HTA comment on EMA concept paper on predictive biomarker based assay development in the context of drug development and lifecycle (10/2017) • Participation in EMA multi-stakeholder workshop on predictive biomarker-based assay development (6/2018) • Participation in EMA-EUnetHTA exchange on the final CHMP review of the MAA for Vitraki (11/2019)	Priority topics for the work stream are: Trend for increased personalisation leading to smaller patient populations, smaller trials, less evidence, increased need to manage uncertainty; Companion diagnostics / other diagnostics for targeting therapeutics but where not directly related to use of specific therapeutics (e.g. genetic signatures) / Next generation sequencing (NGS); new treatment paradigms (e.g. highly individualised combinations of immune-oncology products targeted through NGS); Operational issues around patient access to companion diagnostic tests
Share information and experiences with ATMPs	A joint workshop was held in March 2021 to **increase mutual understanding of the regulatory process and the reimbursement landscape for ATMPs**. The workshop was joined by participants from EMA, IQWiG, HAS, TLV and ZIN. The workshop had three sections: 1/ background to the different partners mandates and tasks in the work with ATMPs; 2/ examples of challenges at the time of first approval; 3/ challenges after first approval (evidence generation etc).	It would be advisable to arrange a joint training session between EMA and HTA bodies on ATMPs as suggested in the EC/EMA's action plan on ATMPs. Three areas for collaboration are identified: -Alignment of evidence requirements for approval and decision-making for both regulatory and HTA. In the short term, revise the reflection of evidence available in EPARs, with benefits more clearly spelled out. -Time horizon: how long do you need to see data for a claim of curative treatment? Agreement on expectations for a one-time treatment. -Early engagement recommended, consider input at Scientific advice on PLEG collection.