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Report on the implementation of the EMA-EUnetHTA 21 work plan 2021 - 2023

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. A first EMA-EUnetHTA work plan was established for the years 2012-2015 and a report on the outcomes of this joint work published in April 2016. Subsequently, a second joint work plan for the years 2017-2021 was agreed and a report published in June 2021.

Between 2021 and 2023, subsequent to the award of the "Service contract for the provision of joint Health Technology Assessment (HTA) work supporting the continuation of EU cooperation on HTA" to the EUnetHTA 21 consortium, the European Commission invited EMA and EUnetHTA 21 to establish a joint work plan for delivering on identified priorities. On this basis EMA and EUnetHTA 21 agreed a work plan focusing on the following jointly agreed priority areas:

- Joint scientific consultation for robust evidence generation
- Exchange of information on assessments of medicines
- Generation of patient-relevant data and information to support decision-making
- Methodologies to engage patients and healthcare professionals
- Horizon scanning and preparedness of HTA and regulatory systems
- Optimisation of regulatory outputs as reference for down-stream decision-making
- Study methods and guidelines of real-world evidence
- Tools to support assessment in smaller populations
- Assessment work related to companion diagnostics

This report presents the achievements and reflections of the EMA-EUnetHTA 2021-2023 work plan.

Organisation of regular meetings of EMA and EUnetHTA representatives

Four bilateral meetings were held during the validity of this workplan and were hosted alternately by EMA and the EUnetHTA 21 Secretariat ZIN.

All meetings were attended by representatives from the EUnetHTA 21 secretariat and EUnetHTA 21 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 1: List of bilaterals

Date	Location
17 June 2022	Online
25 November 2022	Online
31 March 2023	Online
14 September 2023	Amsterdam, the Netherlands

Action by topic area

Activity	Achievements	Reflections
Joint scientific consultation (JSC) for robust evidence generation, including post-licensing/launch evidence generation		
Relaunch of a European procedure for Joint Scientific Consultation involving HTA bodies and EMA (previously known as parallel scientific advice / parallel consultation/Early Dialogue)	<u>EMA/EUnetHTA 21 Joint Scientific Consultation (JSC)</u> A revised single process for parallel JSC was launched in 2021. The underlying guidance for the parallel EMA/EUnetHTA 21 JSC procedure was regularly reviewed. Throughout the applicability of this framework: • 6-8 JSC foreseen according to the EUnetHTA 21 service contract; • 2 Open Calls to fill the slots available: first Open Call closed in December 2021 and the second Open Call closed in August 2022; • 7 completed parallel JSCs. <u>Parallel EMA/HTA body (HTAb) Scientific Advice for the interim period</u> Establishment of a new framework for the interim period from September 2023 until application of the HTA Regulation. Guidance has been published. Developers will be able to apply for parallel EMA/HTA body (HTAb) Scientific Advice and G-BA will function as the HTA Coordination Contact. The outcome of the procedure will be a scientific advice letter from EMA and individual written recommendations from participating HTA bodies.	Parallel JSC is acknowledged by all involved parties as a unique single process to facilitate an early multistakeholder exchange on pivotal trial design to generate evidence that is fit-for-purpose for both regulators and HTA bodies. The demand from developers exceeded the available slots. Reviewing the JSC process led to further improvements of the procedure: • Clarification on Post Licensing Evidence Generation (PLEG) discussion, follow-up advice and early termination, • Improved exchange between EMA and HTA bodies • Optimisation of documents The experience from the interim period process for Parallel EMA/HTA body (HTAb) Scientific Advice will further prepare the implementation of the EU HTA Regulation.
Optimise utilisation of registries for post-licensing/launch evidence generation to support decision making	Exchange of information and continuous dialogue took place on ongoing/planned regulatory and HTA registries-related activities. 4 out of 7 parallel EMA/EUnetHTA 21 JSC applications discusses	Further exchange of EMA and HTA bodies on respective requirements and experiences for post-licensing/launch evidence

Activity	Achievements	Reflections
	PLEG/registries. Joint PLEG discussion further facilitated exchange with regard to EMA's and HTA bodies's requirements, relevant data sources and experiences.	generation will help to understand different needs and evaluate possibilities for more alignment with the aim to communicate joint goals to developers with regard to PLEG that can be fit-for-purpose for both regulators and HTA.
Exchange of information on the respective assessments of medicinal products by regulators and HTA bodies		
Foster opportunities for information exchange between regulatory assessors and HTA authors on identified products of mutual interest, including ATMPs	In the absence of applications from developers for joint clinical assessment related to medicinal products under the EUnetHTA21 service contract, product-specific discussions were held between EMA and EUnetHTA21 to discuss key areas of a completed ATMP assessment for an extension of indication in Acute Lymphocytic Leukaemia. This experience served as basis for an EMA/EUnetHTA bilateral in April 2023 focusing on ATMPs, where key learnings on evidence and uncertainties with ATMPs derived from the product exchanges were discussed alongside identification of priority areas for future exchange. The outcomes of this exchange on ATMPs was presented at the CAT stakeholder meeting in May 2023.	Opportunities for cooperation on upcoming ATMP assessments should be further explored, the timing and frame of the information exchange remain to be clarified, also in view of the HTAR. Potential priority areas for exchange and enhanced mutual understanding: PLEG requirements, indirect comparisons, early identification of products/areas for exchanges. Possibility to exchange on PLEG, methodologies used for indirect comparisons and enhancement of information provided in the EPAR should be explored.
Generation of patient relevant data / information to support decision making		
Fostering development of methodologies in order to enable stronger reliance on patient relevant data in context of decision making	HTA involvement in the EMA initiative to establish an EU network of experts on PRO", particularly • Exchange between EMA and EUnetHTA in view of HTA contribution to the preparation of a 'reflection paper on Patient experience data (PED)'.	Recognising that patient relevant data is important for both decision makers, the reflection paper will cover considerations for both regulators and HTA bodies. Identified group of EUnetHTA experts is involved in the reflection

Activity	Achievements	Reflections
	• Contribution to the "EMA Qualification of novel methodologies" workshop in April 2023 (session "2: Patient-,Observer- and Clinical-reported outcomes – key elements of patient centred medicines development).	paper, which is planned to be ready for public consultation by Q1-Q2 2024.
Methodologies for engagement of patients and healthcare professionals		
Deepen the mutual experience/exchange on the involvement of patients and healthcare professionals in activities with focus on challenges of mutual interest	The collaboration between EUnetHTA 21 and EMA aimed to improve participation of patients and healthcare professionals in regulatory and HTA processes. This collaboration was marked by several initiatives and events: • EMA review of EUnetHTA 21 guidance • EMA Patient and HCP training with EUnetHTA 21 session 20.10.2022 • EMA Stakeholder meeting: PCWP/HCPWP meeting with EUnetHTA 21 session 15.11.2022 • EMA support for expert identification for JSC and JCA • Regular exchanges with relevant colleagues on sharing practices and experiences related to expert involvement in their activities, (e.g., information shared with experts regarding their involvement and how their input was being documented in the regulatory or HTA outputs). • EMA reviewed the EUnetHTA 21 draft guidance on patient and expert involvement and provided comments for consideration. Ongoing discussions included EMA's plans to remunerate experts to be continued, in order to facilitate recommendations for their work under the HTAR.	Collaboration on the involvement of patients and healthcare professionals was mutually beneficial with EMA and HTAs being able to learn from each other with respect to engaging with stakeholders and creating supporting material for these activities. While there was a clear increase in the understanding of each other's expectations for the involvement of experts in regulatory and HTA processes, different procedures and policies for the involvement of experts till exist that would benefit from further alignment with regard to future cooperation, e.g. in relation to conflict of interest.

Activity	Achievements	Reflections
Support to targeted consultations in the context of assessment activities	EMA and EUnetHTA exchanged contacts for identification of experts for HTA and EMA activities, also acknowledging the challenge of having the same experts. Awareness and understanding by experts on the differences between HTA and regulatory enhanced through a process / information package to experts. Further exchanges facilitated through participation in the EMA PCWP/HCPWP meetings and training sessions and EUnetHTA Stakeholder fora. Key events: • For 7 JSCs (2021-2023) and 2 Medical Device JCAs in the framework of EUnetHTA 21, exchange and/or cooperation with the EMA took place regarding the involvement of external experts in the procedures. • EMA participated in EUnetHTA 21 roundtable on May 25, 2022. This meeting focussed on patients and healthcare professionals and aimed to discuss the EUnetHTA 21 guidance for external expert. EMA shared their process and experience. • To enhance awareness and understanding of the difference between HTA and Regulatory processes, EUnetHTA 21 provided a training on HTA and the process for in the context of EMA's annual training of patients and healthcare professionals to inform on their involvement in JCA and JSC on October 20, 2022. • EUnetHTA 21 participated in EMA's annual meeting with PCWP/HCPWP and all eligible organisations in November 2022 and presented an overview of HTA activities and involvement	EMA and HTAs took the opportunity to invite each other to stakeholder meetings and reinforce their collaboration and clarify the different roles. Exchange and collaboration through JSCs and Medical Device JCAs underline the commitment to a common approach. EMA's active participation in the EUnetHTA 21 roundtable and the training session provided by EUnetHTA 21 during the EMA's annual expert training event aimed to promote mutual understanding between all parties involved. These are valuable experiences that can be built upon further.

Activity	Achievements	Reflections
	methods in JSC and JCA.	
Horizon scanning and preparedness of HTA and regulatory systems		
Share horizon scanning activities and outcomes	Detailed discussions on horizon scanning activities at the EMA/EUnetHTA bilateral in June 2022. This included EMA's activities in terms of business pipeline reviews, which anticipates the impact of upcoming Marketing Authorisation Application submissions on the workload and expertise needs of European regulators, as well as horizon scanning. Their methods were presented including data acquisition, data management and reporting. From HTA side, focus was on the work by the International Horizon Scanning Initiative (IHSI). IHSI has developed a database, which holds pharmaceutical compounds as of phase I of the development. Additionally, IHSI prepares high impact reports, which go into the database to predict which products could be of high impact. Any of this data is in the public domain, without any confidentiality blocking access to the information. The IHSI methodology and process was presented.	Exchange on horizon scanning is important for ensuring capacity and capability to perform respective assessment work. Both regulators and HTAs hold important information and further details of data needs and exchanges need to be developed.
Joint discussion of challenges stemming from high-impact innovative medicines that address an unmet medical need.	Agreed for EMA to provide input to EUnetHTA 21 by peer reviewing IHSI impact report against EMA pipeline.	Arrangements need to be put in place for performing such reviews and exchange information.

Continuous optimisation of regulatory outputs as reference for down-stream decision making		
Further optimisation of the regulatory assessment report to facilitate uptake of regulatory consideration in the context of HTA	Based on the 3-year experience review on webinars between EMA, CHMP Rapporteurs and HTA bodies, recommendations were made for the optimisation of CHMP assessment report (AR) template and guidance to address the findings and gaps identified. Recommendations were made to systematically justify key elements of the assessment in the CHMP ARs such as the indication, study patient selection, choice of comparator, endpoints, posology, relevance of subgroup data, validity of statistical analyses, justification of ADRs. Presentation and discussion in the CHMP ARs of evaluable QoL/PRO and their relevance were also recommended. These recommendations were communicated to the CHMP and the EMA project team in charge of revising the CHMP AR template which aims to be published in Q1 2024.	Most of the identified elements were already captured by existing templates and guidances, however they were not systematically discussed in the assessment reports. The revision of the AR template and guidance is an opportunity to further clarify the requirements and initiate trainings to assessors that will highlight the importance of the elements identified in the interactions with HTA bodies.
Continue sharing experience on labelling and EPARs information, e.g. regarding information on subpopulations	Building upon earlier cooperation during the development of the EMA/CHMP guide to assessors on the wording of therapeutic indication, EMA and EUnetHTA have continued to share experience on labelling and EPAR information, including during EMA EUnetHTA bilateral meetings. Discussions were mainly related to EPAR information.	Acknowledging the recommendations of the CHMP/EMA "Guideline on the investigation of subgroups in confirmatory clinical trials", HTA interest to obtain information on individual subgroup results in the EPAR was confirmed, on top of the rationale for wording of the therapeutic indication. Other area of HTAs' interest regarding EPAR include information on the relevance of the QoL/PRO results (both from a statistical point of view and clinical relevance of the instrument used), methodological

		aspects in relation to the evaluation of indirect comparisons, and risk minimization measures of advance therapy medicinal products.
Optimise the published information on orphan medicinal products	The EMA Survey on the Orphan Maintenance Assessment Report (OMAR), which was launched on 26 October 2021, was aimed at gathering information from various stakeholders on their current experience with the OMARs. The survey concluded on 10 December 2021. The data collected was analysed and the outcome of the survey was presented at the 8th Industry Stakeholder platform meeting on 11 July 2022. Subsequently EMA and COMP revised the summary report template as well as the process for assessing maintenance procedures. The new procedure was introduced as of January 2023 and should result in a OMARs with streamlined output and improved transparency of the assessment.	The survey results confirmed how important transparency, and in particular the scientific reasoning for the opinions by the COMP, is for the stakeholders. The updated process for assessment of maintenance procedure is more collaborative and should result in more detailed and harmonised OMARs.
Developing study methods and guidelines of real-world evidence, including for registries		
Collaborative work on registry methodologies	Detailed discussions at the EMA/EUnetHTA bilateral in November 2022. This included an EMA-funded registry-based study on Spinal Muscular Atrophy, where the HTA perspective was reflected in the protocol. Looking forward, engagement is planned in the context of the planned multi-stakeholder workshop on registries (Feb 2024).	Further reflections on opportunities for having HTA perspective in PASS/PAES protocols descriptions could be valuable.
Collaborate on establishing evidentiary value of real-world evidence	Workshop with HTAs and payers to identify use cases collaboration on RWE. This included the selection of 2 use cases addressed as DARWIN EU pilots.	

	Discussion on PLEG for CAR-T and example of the French registry DESCAR-T presented by HAS during the webinar between EMA and EUnetHTA 21 teams on an ATMP product.	
Supporting access to and analysis of real-world data	Two studies being piloted based on the feedback from the workshop: • Pilot study on multiple myeloma treatments in progress as of Jul-23 • Second pilot study on NSCLC in feasibility stage as of Jul-23	Experience from these pilots will shape future engagement opportunities.
Extrapolation / evidence transfer as a tool to support assessment in smaller populations		
Joint methodological work on the concept of extrapolation / evidence transfer to better understand each other's reasoning for accepting extrapolation	Continued dialogue and deepened collaborations, also e.g. through participation to relevant conferences. In Sept 2023, a 2nd joint workshop was held to further strengthen mutual understanding related to the use of extrapolation, particularly related to the progress made following the publication of the respective guideline.	This work helped to better understand how the concept of extrapolation is understood differently by respective decision makers when used to support the development in smaller populations. The importance of continuous dialogue, opportunities for learnings and exchange remains key.
Establish working practices in the context of the topic identification, selection and prioritisation (TISP) process for JCA on medical devices		
Develop a process for engagement in the TISP process for JCA on medical devices	Discussion between EMA and EUnetHTA21 informed the drafting of the TISP for medical devices, describing a "wish list" for information.	These have been early discussions in a new area of collaboration and need follow up under a future framework.
Support the exchange of information in the context of the TISP process for JCA on medical devices		