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HTA NETWORK REFLECTION PAPER ON "SYNERGIES BETWEEN REGULATORY AND HTA ISSUES ON PHARMACEUTICALS"

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1. BACKGROUND AND OBJECTIVES OF THE REFLECTION PAPER

In Section 2.3 of the HTA Network's Strategy[1], the Network recognised that stronger synergies between developers of health technologies, regulators, HTA bodies and decision makers can contribute to a timely and comprehensive access to information and data throughout the entire life cycle of health technology (from start to end) which can result in important benefits for healthcare systems.

Acknowledging the different remits and aims of the different processes and stakeholders, this Reflection Paper on "The interaction between regulatory and HTA issues" aims at identifying activities along the **life-cycle** of health technologies in which cooperation between regulatory and HTA bodies can contribute to facilitating efficient access to effective, safe, innovative and added value technologies while guaranteeing the sustainability and predictability for healthcare systems.

This Reflection Paper will explore areas for possible synergies and actions to put in place for a closer cooperation. It should be noted that the topic is being addressed and discussed in the framework of several EU initiatives, including EUnetHTA JA3, IMI projects and European Medicines Agency (EMA). In the European Commission the Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), composed of Member States, EMA and EEA countries, is also facilitating discussions relevant to the topics raised. This Reflection Paper will help in identifying areas that can be addressed in both the short and medium-long term in which cooperation can bring benefits. It also aims at identifying in which of the ongoing cooperation efforts such topics can be addressed. It should be noted that some of the topics addressed in the Paper are policy issues (e.g. unmet medical needs), therefore they will also benefit from policy discussions in appropriate fora.

This Reflection Paper recognises that regulatory and HTA agencies are organised differently across Member States. In regard to regulators, the Medicines Regulatory Network consists of the European Commission, the medicines regulatory authorities in the EU Member States and the European Economic Area (EEA) and the European Medicines Agency (EMA). EMA, through its Committees composed of experts from national competent authorities of the EU Member States, evaluates marketing applications for novel medicines. In some Member States the National Medicines Agency may be part of the same organisation responsible for HTA, reimbursement and pricing decisions, whereas in other Member States these bodies are separate organisations. Moreover, in some countries HTA and reimbursement may be organised at regional and/or at local levels instead of or as well as at a national level. Therefore, synergies and cooperation between HTA bodies and regulators can operate within a single Member State or across Member States and operate across different levels. The ongoing activities of the EUnetHTA Joint Action 3 will need to be taken into account in the implementation of any of the proposed actions.

[1] Strategy for EU Cooperation on Health Technology Assessment: http://ec.europa.eu/health/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf

Due to the significant differences between the pharmaceutical and medical devices sectors, the HTA Network Working Group decided to consider them separately and to **focus first on pharmaceuticals**.

2. INTERACTION BETWEEN REGULATORY AND HTA ISSUES

When analysing the interaction between regulatory and HTA issues, three phases need to be distinguished: **a)** the **pre-marketing** phase, **b)** the phase of actual **market entry** and **c)** the **post-marketing** launch phase. However, it should be also noted that in several activities, while the distinction is useful, a continuous link between the different phases will need to be implemented. For example, generation of Real World Data may need to be considered in both the pre-marketing (e.g. definition of data to be collected) and post-marketing phases.

a) Pre-marketing phase

During the pre-marketing phase the following areas for possible collaboration seem particularly noteworthy:

- Early dialogues/scientific advice with developers of pharmaceuticals involving regulators and HTAs are already in place (parallel scientific advice at EMA, early dialogues within EUnetHTA and at the national level). It is planned that the cross-European processes for parallel advice will become a single common model at the latest by the end of EUnetHTA JA3. Collaboration in defining the process of early dialogues/scientific advice would support the evidence generation suitable both for regulatory and HTA needs.
- Both regulators and HTA bodies take account of concepts such as unmet medical need and therapeutic innovation and should cooperate on the definition of these concepts and on the description of their application in various settings including the collection and integration of patient input and/or preferences into both processes.
- Where there may be evidence limitations, regulators and HTA bodies could jointly discuss with developers a plan how to generate further levels of evidence from various sources (including real world data, RCTs etc.), associated timelines and organizational responsibilities that meets the needs of all parties.
- Horizon scanning programmes for the identification of emerging therapies with potential added value, but uncertainty on clinical outcomes, could help identify critical elements that would benefit from being taken into account before marketing authorisation to optimise the likelihood of sustainable access.
- Foster research and dialogue with main stakeholders mainly in therapeutic areas with unmet medical needs.
- Foster cooperation on research needs which address regulatory and HTA issues (e.g. methodologies, such as novel study design, selection of comparators, validation and selection of endpoints and scientific guidelines, etc. [2]).

[2] EUnetHTA Letter on Research activities: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/EUnetHTALetter%20to%20DG%20RI%20on%20HTA%20in%20Horizon2020_final_20150312.pdf

Action points to be addressed:

1. Define the process of early dialogues/scientific advice in order to meet the needs of both, HTA and regulatory bodies, building on existing successful initiatives[3], in cooperation with EUnetHTA JA3[4], with developers of pharmaceuticals and other stakeholders with particular experience in this area.

Specifically, the following points could be addressed:

- financing of early dialogues/scientific advice in the long term, for example the possibility to implement a fee-for-service system taking into account existing rules in each specific member state
- defining how many and which HTAs bodies should take part in each procedure with the aim of maximising their involvement and contribution, considering that different needs may arise according to the subject of the dialogue
- handling different positions between HTA bodies and between regulators and HTA bodies (for example in the final advice document(s))
- examining the feasibility of a permanent supporting structure for coordination of HTA bodies and scientific discussion among HTA bodies performing early dialogues/scientific advice
- defining how to adequately involve relevant regional and/or local decision makers that exist within HTA whilst keeping an efficient and manageable process
- defining when and how to involve payers, health professionals and patients, as appropriate
- exploring suitable models to ensure initiation and conduct of early dialogues according to appropriate timelines based on considerations of specific needs in each particular case
- identifying and handling of interests declared.

2. Development of shared definitions for the concepts of unmet medical need and therapeutic innovation, bearing in mind the technical consequences for MSs and respecting different roles, remits and needs. Initiatives to support the development of shared definitions could include working together in specific areas, for example, connecting with EMA PRIME (PRIority MEdicines) scheme.[5] Other initiatives could include working together around adaptive pathways approach. Collaboration with IMI ADAPT-SMART and IMI GetReal projects should also be promoted in order to ensure that any new efforts are synergistic, including the use of real-world evidence.

[3] EUnetHTA Parallel Early Dialogues, SEED's early dialogues (http://www.eunethta.eu/seed), EMA-HTA bodies parallel scientific advice.

[4] EUnetHTA JA3 Work package 5:"Life cycle approach to improve Evidence Generation"

[5] PRIME is a scheme launched by EMA aiming at enhancing support for the development of medicines that target an unmet medical need and at enabling the accelerated assessment

3. Collaborate on the identification of therapeutic areas for which the medical need has not been sufficiently met yet and on the identification of emerging medicines through horizon scanning programmes for sharing early information, defining clear evidence requirements, and for identifying needs for further evidence generation (e.g. development and validation of patient reported outcomes).

4. Collaborate on the elaboration of therapeutic-area-specific guidelines, non-product specific qualification advice and opinions, and workshops in order to allow developers to generate evidence able to address both regulatory and HTA information needs.

b) Market Entry

During the market entry phase the following issue seems particularly noteworthy:

- Sharing information on the different approaches of regulators and HTA bodies to identify the eligible population for a treatment,
- Early sharing of information between regulators and HTA bodies in order to facilitate efficient mechanisms for patient access to novel pharmaceuticals,
- Optimisation of the regulatory assessment reports (for example, structure and content) to better serve as reference for subsequent HTA.

Action points to be addressed:

1. Differences may exist between populations for which the treatment is covered by health care systems as resulting from the national reimbursement decision processes, on one hand, and the labelled indication coming from the marketing authorization process, on the other hand. Consideration should be given to promoting initiatives that develop a shared understanding of how regulatory and HTA bodies develop wording for the treatment eligible population. Such initiatives could include sharing reasoning about decision making whilst respecting role, remits and needs of the different parties.

2. To support the production of joint work[6,7], identify and implement an agreement that allows for early sharing of information between regulators and HTA bodies in order to support effective, efficient, and timely HTA processes and to facilitate efficient mechanisms for patient access to novel pharmaceuticals (e.g. to allow confidential provision of the Committee for Medicinal Products for Human Use (CHMP) assessment report (210 day report) to HTA bodies at the time of CHMP opinion, before publication of the European public assessment reports - EPAR). A legal arrangement for a structured process should be defined and put in place.

3. Collaboration on the optimisation of regulatory assessment reports to further improve data displays and structure and ensure that information relevant for HTA is included in the report, including multiple therapeutic indications.

6 EUnetHTA JA3 Work package 4:"Joint Production"

7 Joint Work (definition from "HTA Strategy"): activities in which countries and/or organisations work together in order to prepare shared products or agreed outcomes. These may include, for example, literature reviews, structured information for rapid or full HTAs, early dialogues or scientific advice on R&D planning and study design. Joint Work aims at supporting Member States in providing objective, reliable, timely, transparent, comparable and transferable information and enables an effective exchange of this information.

c) Post Marketing - Real world effectiveness and safety

During the post-marketing authorisation phase the following issues are noteworthy:

- Initiatives to jointly provide guidance on the design of post-marketing authorisation studies that can fulfil both regulatory and HTA information needs in reasonable timelines,
- Develop a concept for "late dialogues" with manufacturers in order to facilitate core collaborating activities in the post marketing phase,
- Collaboration around real world data (RWD) generation, including mechanisms to facilitate greater engagement of pharmaceutical companies in data collection and maintenance and sharing of periodic benefit-risk assessment reports and therapeutic value re-assessments.

Action points to be addressed:

1. Identify processes to appropriately involve HTA bodies in the definition of data to be collected so as to avoid developers' duplication of efforts in the post-launch evidence generation phase. Examples include post-authorisation efficacy studies (PAESs) and post-authorisation safety studies (PASS). The process shall respect role, remits and regulatory requirements of the different players. It should be linked to the parallel advice platform.

2. Support initiatives addressing issues related to the quality, analysis, and (re-)use of RWD in assessments/re-assessments of pharmaceuticals as well as common methodological tools development. A further important issue to be discussed is which entities could be relied on for sharing the cost for any collaborative data collection.

3. Promote collaboration in the definition of data to be collected (i.e. minimum dataset) in registries, including medicines following the adaptive pathways approach[8]. Collaboration should also involve registry owners and should take into account the organisational differences across European healthcare systems and the need for national structures and/or regulations for the collection of additional relevant post-marketing data. Furthermore, collaboration may explore the potential for using additional sources for the collection of real world data, such as data derived from electronic patient records.

[8] Adaptive pathways is a scientific concept developed by EMA for medicine development and data generation which would allow for early and progressive patient access to a medicine. The approach makes use of the existing EU regulatory framework for medicines.
More information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

4. Identify the main barriers (practical, legal, ethical, IT) for the analysis of data coming from different registries and develop common strategies in order to overcome the barriers identified. This activity will build on the results from PARENT Joint Action[9], IMI GetReal[10] and shall ensure the cooperation with EUnetHTA JA3, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCePP) and EMA Registry Task Force.

5. Collaboration in monitoring and surveillance of novel pharmaceuticals under real world conditions including the use of post-marketing studies and registries. Initiatives could include collaborative pilot studies in specific disease areas and on specific products.

Other areas of cooperation identified by the Working Group

The working group identified a number of other areas for which cooperation between regulatory and HTA bodies would seem useful[11]:

- Orphan medicinal products (for example consultation on off label use; clinical benefit concept)
- Personalised medicine. This topic can be further developed taking into account Council Conclusions (2015) on Personalised medicine[12], especially with reference to the needs to "develop or adjust, where necessary, procedures aiming to evaluate the impact of personalised medicine, in particular health technology assessment (HTA) procedures".
- Vaccines

Additional areas might be considered in the future, depending on priorities and resources:

- Involvement of patients and health care professionals understanding patient preferences within a given therapeutic area.
- Defining which PRO (Patient Reported Outcome)/QoL (quality of life) tools would be valuable for both parties, and if necessary developing new tools that meet the needs of both parties; greater involvement of health care professionals in planning introduction of new therapies, and others.

Action points to be addressed: ***(to be further identified)***

1. For pharmaceuticals with small target patient populations such as orphan drugs and personalised medicines, there is a role for HTA and regulatory agencies to work together to provide guidance to design studies and registries so that sufficient evidence is collected to answer the research questions arising along the life cycle of the medical product, taking into account some of the inherent feasibility limitations related to small populations.

9 PARENT Joint Action: http://patientregistries.eu/

10 IMI GetReal: https://www.imi-getreal.eu/

11 Details on the objectives of each area will be defined in upcoming discussions of the HTA Network

12 Council Conclusions: http://data.consilium.europa.eu/doc/document/ST-15054-2015-INIT/en/pdf

2. The rationale underpinning the assessments for significant benefit (regulators) and relative efficacy/effectiveness (HTA) of orphan drugs might be compared and shared for the benefit of each party, while respecting its role, remits and needs.

3. IMPLEMENTATION OF COMMUNICATION BETWEEN REGULATORY AND HTA BODIES

- Acknowledging the different organisational set ups of EUnetHTA, individual HTA bodies, National Competent Authorities (NCA) and EMA, it is considered important to explore channels of communications and principles around reciprocal interaction, frequency, fora, and contact points for general and specific issues of mutual interest for both regulators and HTA bodies. This might entail observer (or other) status for EUnetHTA representatives in EMA fora and vice versa. The aim of these considerations should be to establish continuity, timely access to information during a given process, and a level playing field for regulatory and HTA experts in their interactions.

- Building on existing experiences and practices, it should be explored how key stakeholders such as patients, healthcare professionals, payers and relevant experts from academia and industry can be involved in the interaction between Regulatory and HTA bodies (for instance in early dialogues/scientific advice process), clearly defining roles and remits of each party, in order to bring about further advances in areas of regulatory and HTA cooperation.

- In the interaction/collaboration between regulatory and HTA activities, in order to avoid any conflicts of interest, mechanisms should be used to guarantee that all parties involved declare any interests and act in a fully transparent manner. Exchanges between regulators and HTA bodies should respect principles of commercial data confidentiality