Answers from EMA to questions from industry partners in the ADAPT SMART consortium regarding the EMA Adaptive Pathways pilot project

1. **Is Adaptive Pathways a concept, or a procedure, or both? If both, how do its procedural elements fit with the existing and available regulatory tools (PRIME, accelerated assessment, SA etc.)?**

   Response: *Adaptive Pathways is a concept that seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion. In so doing, Adaptive Pathways operates within the existing legal framework and aims to make optimal use of existing processes and legal tools including, as appropriate, PRIME, accelerated assessment, parallel scientific advice, conditional marketing authorization, establishment of registries (see also question 8), etc.*

Stakeholders' involvement

2. **How does EMA envision future collaboration with HTA bodies in the Adaptive Pathways framework? Who should establish the contact with HTA agencies for a joint EMA / HTA SA?**

   Note: The first sentence below in the EMA guidance seems to indicate that EMA will do it, while the second sentence states that the company should contact HTAs:

   "The EMA will share the outline of the proposal with the stakeholders designated by the Applicant, to confirm in principle their interest and availability for involvement.

   It is up to the applicant to indicate at this stage which HTAs and other stakeholders they would like to involve, and to make contact with them"

   Response: *Applicants can simultaneously notify the EMA scientific advice office and the EUnetHTA early dialogue secretariat with a request for a Parallel Consultation with both regulators and HTAs noting that intention for an adaptive approach. EUnetHTA will arrange the recruitment of HTAs taking Applicant's preferences into account.*

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If justified, an additional pre-submission meeting (within 6 months prior to the submission of the parallel advice request) may be granted in order to assist with the finalization of the content of the SA-HTA request: the Applicant should contact EMA to discuss the scoping of the meeting.

3. **Does EMA plan to undertake any further cross-stakeholder initiatives (e.g. with payers / HTAs) to ensure current barriers (challenges identified by key groups) to APs are addressed. If so, what are those?**

   Response: *Yes, EMA is leading the ADAPT SMART consortium which is a multi-stakeholder consortium seeking to facilitate availability of the AP concept. In addition, EMA is starting to discuss informally with payers how best to ensure timely access for patients to beneficial products, including the Adaptive Pathways concept.*

4. **How (if at all) will EMA use the 'Engagement Criteria' document written by ADAPT SMART when receiving a submission now for the additional pre-submission meeting offered for products considering an Adaptive Pathways approach?**

   And related to this: When and how will EMA engage with other stakeholders (e.g. HTA bodies) when a submission is received now for a possible Adaptive Pathways approach (for assessment of suitability)? Will their opinion be sought at the additional pre-submission meeting?

   Response: *the 'Engagement Criteria' document represents current consensus of all ADAPT SMART consortium members. It is not an official EMA document. However, there are no contradictions between that document and the criteria published on the EMA website. It is re-emphasized that Adaptive Pathways is a concept, not a new legal tool with formal criteria and processes (see also question 1).*

   Depending on the content of the request, the involvement of decision-makers not limited to HTAs may be useful, if the issues under discussion fall within their remit. While the procedure will remain the same, EMA is committed to facilitating the involvement of these stakeholders on an ad-hoc basis.

5. **How will EMA involve patients for diseases where there is not a well-organized patient organization (although this question applies not only to ADAPT SMART)?**

   Response: *EMA interacts with an extensive network of patient and consumer organisations, which are eligible as per established EMA criteria.*

The majority of common diseases have established patient organisations in Europe and EMA contacts them directly giving preference to those who are eligible. This includes, in the case of rare diseases, Eurordis.

In addition EMA has recently established a public database for individual patients to register their interest to work with the Agency. This constitutes an additional source of patient expertise in different diseases areas.

Finally, charities, self-help groups, and national associations identified online or through previous interaction with EMA (e.g. at conferences) are also valuable resources.

6. Will EMA actively take initiatives to get HTA-bodies more aligned?

Response: *It is not EMA's role to align EU HTA bodies with each other. However, experience with parallel early dialogues has shown that a high degree of alignment can usually be expected from such procedures.*

EMA engages continuously with HTA bodies and European network for Health Technology Assessment (EUnetHTA) to optimize the approach to interactions between stakeholders. This is evident in the announcement that EMA and EUnetHTA are stepping up their efforts to provide developers of medicines with simultaneous, coordinated advice on their development plans and facilitate alignment of data requirements.

7. Will EMA undertake initiatives to also get payers involved?

Response: *EMA is in discussion with payers about this topic; however, the outcome cannot be predicted.*

Real World Evidence

8. RWD being a key feature of the Adaptive Pathways approach, how does the patient registry initiative fit in this context?

Response: *The patient registry initiative was started in recognition of the fact that real world data (such as existing disease registries) can provide valuable information on the benefits or harms of authorized products and may provide better and more information than product-specific registries. It is hoped that the initiative will ultimately support a more proactive surveillance of many products on the market and a better informed regulatory decision-making on benefits and risks. Patient registries may be particularly useful in the context of developing a product that could be considered as following the Adaptive Pathway concept. Hence, the initiative should be considered an enabler of the concept.*

Parallel consultation including EMA and EUnetHTA, and possibly payers, on post launch evidence generation including registries is encouraged. Applicants should come for this advice as early as is feasible. Registry consortia for specific diseases are encouraged to initiate contact with EMA in relation to the Patient registries Initiative.

9. Will EMA develop any guidance documents on Real World Evidence and what would be acceptable for products where an Adaptive Pathway is deemed suitable?

Response: *EMA may impose on MAHs the conduct of post-authorization studies using real world evidence. Pharmacovigilance plans of the risk management system to be submitted by companies may also require the conduct of RWE studies to investigate or characterize safety concerns. The Good Pharmacovigilance Practice (GVP) Module VIII on Post-authorization safety studies and Module V on Risk Management plans provide guidance for such studies. Regulatory guidance on use of mobile apps for reporting of ADRs and use of social media is also under development. In the context of the Patient Registry Initiative, EMA will also provide guidance for some disease-specific registries (e.g. cystic fibrosis and multiple sclerosis) and general guidance applicable to all registries.*

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) updates and publishes every year its Guide on Methodological Standards in Pharmacoepidemiology, which covers best methodological practice for use of RWE. The 6th Revision has been published.

Concerning acceptability of RWE in the context of Adaptive Pathways, reference is made to the AP workshop briefing book examples , and the final report on the AP pilot, which outline acceptable and non-acceptable scenarios on the basis of what was submitted by companies during the pilot. Additional examples may emerge from further advice requests. While it is not possible to predict every possible scenario, at present the following elements have emerged as important:

- *Clinically robust endpoints, to offset potential bias and support decision making;*
- *Disease registries are preferable to drug registries;*
- *Sound and plausible strategy of both pre- and post-authorization data collection and analysis, considering the needs of downstream decision-makers as much as possible.*