**BACKGROUND**

Recommendation by the High Level Pharmaceutical Forum (2008): national authorities and companies to be engaged in early dialogues with the aim of improving the generation of appropriate data for products in development (Recommendation 6).

First Early Dialogue Initiatives: single HTA advice (since 2009) and parallel regulatory - HTA advice organized by the EMA with a limited number of HTA bodies (since 2010).

On this basis, early dialogues (EDs) were set up with 2 additional specificities: a collaborative approach and an extension to include medical devices.

**MULTI-HTA EARLY DIALOGUES: FROM EUNETHTA TO THE SEED PROJECT**

**EUnetHTA JA2 WPT (2012-2015):** EUnetHTA set up the first pilots of multi-HTA EDs for drugs, extending their scope to include Medical Devices (MDs) with the overarching aim to provide prospective, transparent and timely advice by HTA bodies to product sponsors so that they may integrate specific HTA needs in their product development.

**Methods Towards Defining an ED Procedure**

A draft procedure was developed based on 2 preparatory multi-HTA ED pilots undertaken by voluntary HTA bodies and companies prior to the beginning of EUnetHTA JA2. The procedure was further amended during EUnetHTA JA2 based on the results of a survey conducted on the experience from the national EDs and was presented and discussed at a meeting organized by the Medical Device industry associations in May 2014.

**Results**

- Due to high demand from developers and interest of HTA partners, the number of pilots undertaken was three times the number planned. In total, 13 early dialogues (11 on drugs and 2 on medical devices) were conducted, including 2 preparatory pilots.
- Participation of small to large-size firms, including 3 SME.

**EUNETHTA EARLY DIALOGUE FOLLOW-UP WITH THE SEED PROJECT: OBJECTIVES AND METHODS**

**Shaping European Early Dialogues (SEED)**
- **Project sponsored by the European Commission (Call for tender).**
- **Consortium of 14 HTA bodies from 10 countries, led by HAS.**

**Scopes**
- **EDs may be requested for a new technology, with supposed added benefit for patients, during the initial phase of clinical development (e.g. and of phase II) to address questions pertaining to relative effectiveness, economic aspects and other areas relevant for relative and cost effectiveness assessment.**
- **EDs are to be:**
  - prospective in nature, focusing on development strategies and not a pre-evaluation of available data;
  - limited to one indication;
  - non-binding;
  - confidential;
- **EDs were free of charge for companies.**

**Continuous Improvement of the ED Procedure (figure 1)**

The procedure used for the SEED EDs was derived from the procedure developed and refined during the EUnetHTA EDs. Further improvements were made, based on the results of short surveys conducted after each ED and the experience of parallel EDs with EMA, namely:

- A list of key issues discussed amongst HTA bodies and provided to the company prior to the face-to-face meeting;
- Change in the final outcome of the ED procedure from minutes proposed by industry, revised and validated by ED bodiess to consolidated final written answers from HTA bodies to company’s questions.

A step-by-step outline of the draft procedure is provided in figures 2 and 3.

**A collaborative approach**

The multi-HTA EDs activity has been designed to allow fruitful exchanges between HTA bodies:
- prior to the face-to-face meeting with the company, allowing HTA agencies to determine the need for additional information or clarification of the briefing document to exchange draft positions of each HTA body,
- to identify key issues to be transmitted to the company,
- on the day of the face-to-face meeting with the company,
- closed meeting to discuss differences in the positions of the different HTA bodies, reaching convergence when possible,
- after the meeting to make conclusions for the ED and proposals for future improvements.

A common outcome, comprising detailed written answers from the participating HTA agencies to company’s questions with an executive summary from the SEED coordination team.

Involvement of stakeholders: patient representatives, scientific experts, EMA representatives as observers in multi-HTA EDs and partners in EMA/multi-HTA EDs.

**SEED and EUnetHTA**

- **24 multi-HTA EDs undertaken in total within EUnetHTA and SEED projects:** 19 on drugs - including 4 EMA/multi-HTA EDs; 5 on medical devices.
- **All agencies members of SEED consortium are also partners of EUnetHTA.**
- **EUnetHTA ED procedure (amended after the survey) used as a basis for SEED EDs.**
- **ED activities planned to continue within the framework of EUnetHTA JA3 (2016-2019) before the establishment of a permanent structure.**

**SEED Partners:**
- HAS (France), B&H (Austria), NICE (France), NIOG (Israel), ISBT-TRF (Luxembourg), GDF (China), TGA (Australia), MHLW (Japan), GGMG (Germany), KCE and INAMI (Belgium), ZHA and IQWiG (Germany), AAM (Hong Kong), GDD (Spain), NICE (UK).

**SEEDs 8th ED.**
- Short discussion with SEED Consortium and EMA coordinators about the follow-up of the procedure.

**Figure 1. Continuous improvement of the ED process**

1. **D-90 / Pre-submission:** Draft application file submitted to the participating HTA bodies.
2. **D-75 / Written consolidated list of points for clarification identifying any missing information/list of points requiring additional information is sent to the company.**
3. **D-60 / Final application file sent by the company.**
4. **D-30 / Written consolidated list of key issues raised by the proposed development is sent to the company.**
5. **D-15 / Company’s answers to the list of key issues.**
6. **D-30 / Draft written answers sent by all participating HTA bodies to the coordinator and compiled and sent back to HTA partners.**
7. **D-0 / Face to Face ED Meeting: closed HTA body meeting in the morning, meeting with the company in the afternoon.**
8. **D+7 / Detailed drafting minutes provided by the company for informational purposes.**
9. **Conflated Final Written Answers with an executive summary from the SEED coordinator sent to the company.**

**Figure 2. Summary of the procedure used for SEED multi-HTA ED pilots**

**Figure 3. SEED EMA/multi-HTA ED pilots:**

In addition to the procedure used for SEED multi-HTA EDs, the procedure for SEED EMA/multi-HTA ED pilots also includes:

- **D-75 / Confidential meeting between the company, EMA and the SEED coordinator to discuss the points for clarification.**
- **D-30 / List of key issues exchanged with EMA representatives.**
- **D-0 / Face to Face ED Meeting: Short discussion with SEED Consortium and EMA co-ordinators for the given procedure and the participation of the EMA representatives to the ED meeting.**

**EUNETHTA EARLY DIALOGUE FOLLOW-UP WITH THE SEED PROJECT: RESULTS AND NEXT STEPS**

**Results**

In total, 11 SEED early dialogues (instead of the planned 10): 8 on drugs, 4 of them being parallel EMA/SEED EDs, and 3 on medical devices were conducted from May 2014 to July 2015.

The EDs concerned various therapeutic areas (oncology, cardiology, haematology, pneumology, auto-immune disease, and rheumatology), both rare and non-rare diseases and involved small and large companies.

**Main deliverables**

- 11 EDs conducted with 11 reports on the procedural aspects of each ED.
- Final report (draft available Q4 2015) including a proposal for a permanent model of EDs in Europe, to be enriched by the consultation of all stakeholders and in cooperation with EUnetHTA.
- Key elements and challenges of the sustainability of the model.
- Overview foreseen towards a fee-for-service system under the initial remit of the EUnetHTA JA3 (2016-2019).
- Permanent structure for the post-2019 period to be determined.
- Improvement of the procedure based on the experience of the SEED EDs, notably for the coverage of evidence development schemes for new technologies.
- Coordination with the definition of the needs for additional evidence generation, notably for the coverage of evidence development schemes for devices and the adaptive pathways initiative in Europe.

**SEED and EUnetHTA**

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- **All agencies members of SEED consortium are also partners of EUnetHTA.**
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**SHAPING EUROPEAN EARLY DIALOGUES: THE SEED PROJECT**

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