HTAi Conference, Oslo June 2015
Global Efforts in Knowledge Transfer: HTA to Health Policy and Practice

Panel Session Report
Multi-stakeholder collaboration in generating the best possible knowledge - the SEED experience

Key points

- Substantial experience has been gained in The Shaping European Early Dialogue (SEED) initiative and with EMA HTA parallel scientific advice processes.
- SEED has evolved with input from all stakeholders and has shown the value of open communication among the stakeholders throughout the preparatory stages to ensure an effective face-to-face meeting.
- Early and open discussion of the issues can create improved understanding among all stakeholders and increase the effectiveness and efficiency of their work throughout health technology development and approval processes.
- SEED showed that it is capable of shaping health technology development plans and has potential to improve evidence generation to meet the needs of both regulators and HTA and ultimately contribute to improved patient access.

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About HTAi

Health Technology Assessment international (HTAi) is the global scientific and professional society for all those who produce, use, or encounter HTA. HTAi has members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. HTAi is the neutral forum for collaboration and the sharing of leading information and expertise.

The HTAi 2015 conference was organized in Oslo in June 2015, gathering around 900 international delegates The theme of the meeting was "Global Efforts in Knowledge Transfer: HTA to Health Policy and Practice**"**. The scientific programme can be accessed at: http://www.htai2015.org/events/2015-htai-annual-conference.

This panel was selected for presentation by an independent review panel.

Status of this report

This report has been approved by all presenters to be presented as a public record of the HTAi panel.

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Funding

Karen Facey received a fee from Sanofi Genzyme to act as rapporteur for this panel.

1. Introduction

Dr Alicia Granados, Head Global Health Technology Assessment Scientific Strategy, Sanofi Genzyme

Dr Alicia Granados opened the panel session, reflecting on the pressures that all stakeholders in the health system are facing. Health technology developers are experiencing increasing scientific scrutiny of innovations, pricing pressures, generic substitutions and increased costs of research and development, while healthcare providers contend with financial pressures and calls for rapid decision making that puts global evidence into a local setting to deliver patient benefit. Furthermore if that patient benefit is deemed to be large, patients want access to that benefit as early as possible. Consequently, traditional models of evidence generation for new health technologies are being questioned and multi-stakeholder collaborative initiatives are being developed that seek to shape evidence generation to better meet the needs of regulators and Health Technology Assessment (HTA).

The aim of this HTAi 2015 panel session was to share with the global HTA community, experiences and lessons learned in the "Shaping European Early Dialogues" (SEED) parallel scientific advice initiative. Sponsored by the European Union, SEED included the European Medicines Agency (EMA), HTA agencies, industry, clinical experts and patients. This panel session included presentations from all the stakeholders involved in SEED, presenting the process, their experiences and reflecting how this initiative may be developed in the future.

2. Multi-HTA Early Dialogues – EUnetHTA, SEED, HTA network

Francois Meyer MD, Advisor to President of Haute Autorité de Santé (HAS), SEED Project Lead

Dr Francois Meyer presented an overview of the development of HTA scientific advice processes and discussed the review of SEED that is currently underway.

Scientific advice processes have existed in the medicine's regulatory environment since the 1990s, providing advice on the design of confirmatory clinical trials to meet the needs of regulators. In 2008, the High Level Pharmaceutical Forum suggested that HTA should engage in these processes to ensure that evidence generation was also fit for the needs of HTA. Individual HTA agencies began providing Scientific Advice in 2009 and a range of different models of Scientific Advice have evolved:

- National: One HTA body, alone or in collaboration with national regulatory agency
- Parallel: EMA and several HTA bodies in European Member States
- Multi-HTA: Collaboration of EU national HTA bodies in a project sponsored by the European Commission.

Multi-HTA Scientific Advice processes were established in 2012 to address questions about relative effectiveness and/or economic evaluation. Twelve HTA bodies and nine technology developers (large and small enterprises) have been involved and EMA was invited as an observer. The processes are confidential, non-binding and require input from the company via a structured submission. The submission contains a summary of what is known about the health technology, the development strategy, description of planned studies and questions the health technology developer wishes to pose. A face-to-face meeting is held with experts from HTA bodies and the technology developer to discuss the issues raised in the submission and a confidential report is then prepared by the HTA bodies.

Experience in these multi-HTA Scientific Advice processes has shown that similar topics arise including:

- population
- comparator
- trial design (e.g. duration, dosing)
- endpoints
- statistical analysis (e.g. subgroups, stratification)
- economic modelling (e.g. construct, utilities, resource utilization).

As this process is structured around a discussion of issues, it was recognized that such processes would be better termed as a "dialogue", rather than one-way "advice". Furthermore, when the focus is to inform the design of confirmatory trials, the term "Early Dialogue" seemed most appropriate.

The European Commission saw the success of these procedures and issued a tender for the Shaping European Early Dialogues (SEED) initiative. The grant was won by a consortium of 14 HTA partners from across Europe led by HAS, with regulators, payers and patient representatives as observers. SEED started in 2014, learning from past processes for multi-HTA and parallel scientific advice and has been a process of continuous improvement over the past three years, altering the process to respond to participants' feedback as shown in Table 1.

Table 1. Development of Early Dialogue (ED) process

Initiative	ED process changes	ED procedures
EUnetHTA JA1 (2012) Preparation	ED "draft" process created	2
EUnetHTA JA2 (2013-2014) Piloting	ED survey after 6 pilots and review meeting (January 2014) to "revise" process	8 using draft process
SEED (2014-2015)	Further amendments in November 2014 to "refine" process	7 on revised process 4 on refined process
EUnetHTA JA2 (2015)		3

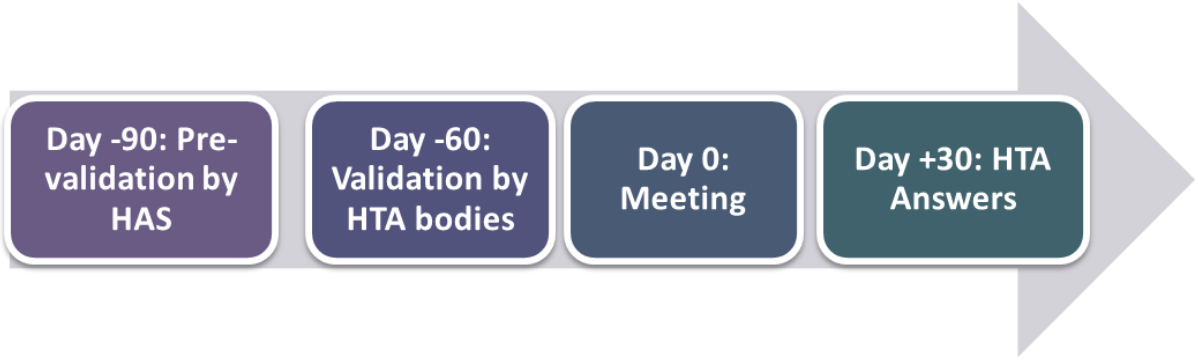
In EUnetHTA Joint Action 2, only four Early Dialogue procedures were planned, but early feedback showed the enthusiasm of all stakeholders to be involved and to help the process evolve. As a result EUnetHTA has undertaken 11 Early Dialogues on medicines and two on medical devices and SEED will undertake eight on medicines (four HTA only, four parallel with EMA) and three with medical devices.

Not all partners were involved in all SEED procedures. There were typically about 6-10 HTA bodies involved in one procedure, with some only participating in medicine related dialogues and some only in device related dialogues. As SEED was funded by the European Commission, there were no fees.

An overview of the SEED process is presented in Figure 1. Firstly, the health technology developer must submit a letter of intent, which is validated by the Lead Partner (Haute Autorité de Santé - HAS) and then by the other HTA bodies. A face-to-face meeting takes place approximately three months after the submission of the letter, with much work done in advance of the meeting. The technology develop submits a Briefing Book and issues are raised for clarification by the SEED partners. They then agree key issues to be sent to the health technology developer and draft positions of each HTA body are shared among the

partners. There is a meeting of the partners before the face-to-face meeting to discuss any divergent views and afterwards to create consolidated conclusions and proposals. A report is issued to the technology developer one month after the meeting.

Figure 1. Overview of SEED Process



After each SEED procedure, a report on process is published to allow continual learning and review. This led to the amendment of the process in November 2014 to indicate that health technology developers should provide their position on the questions in the Briefing Book. This revised process has been used with the final four Early Dialogues.

The HTA network has endorsed the life cycle approach to HTA and the value of ED and so has recommended:

- maintaining and clarifying options to perform Early Dialogue
- strengthening interactions with regulators, building on existing experience
- developing a mechanism to feed the results of ED into development of disease specific guidelines
- exploring funding and organizational models to make activities self-sustainable, including the possibility of collecting fees.

This highlights that challenges still remain, including:

- fees
  - challenge of collecting fees internationally
  - consideration of fee reductions (e.g. for small companies or orphan products)
- HTA involvement
  - choice of participating HTA bodies
  - national vs international
  - impact on HTA body and need to develop expertise
- challenge of developing disease-specific guidelines
- need to link with advice arising from processes for additional evidence generation (particularly initiatives such as Medicines Adaptive Pathways to Patients).

SEED partners are preparing a proposal to the European Commission in cooperation with EUnetHTA for a self-sustainable, permanent process for Early Dialogue in Europe. This will take account of the helpful exchanges with EMA about the evolution of their Scientific Advice process and feedback from participants, stakeholders and the HTA Network in SEED. The draft SEED proposal will be issued for consultation in July to October 2015 and all stakeholders are encouraged to provide input to make this a sustainable, valuable process that will improve evidence generation for HTA.

3. European regulatory view on multi-stakeholder collaboration in generating the best possible knowledge

Dr Jane Moseley, Scientific Officer Scientific Advice, European Medicines Agency

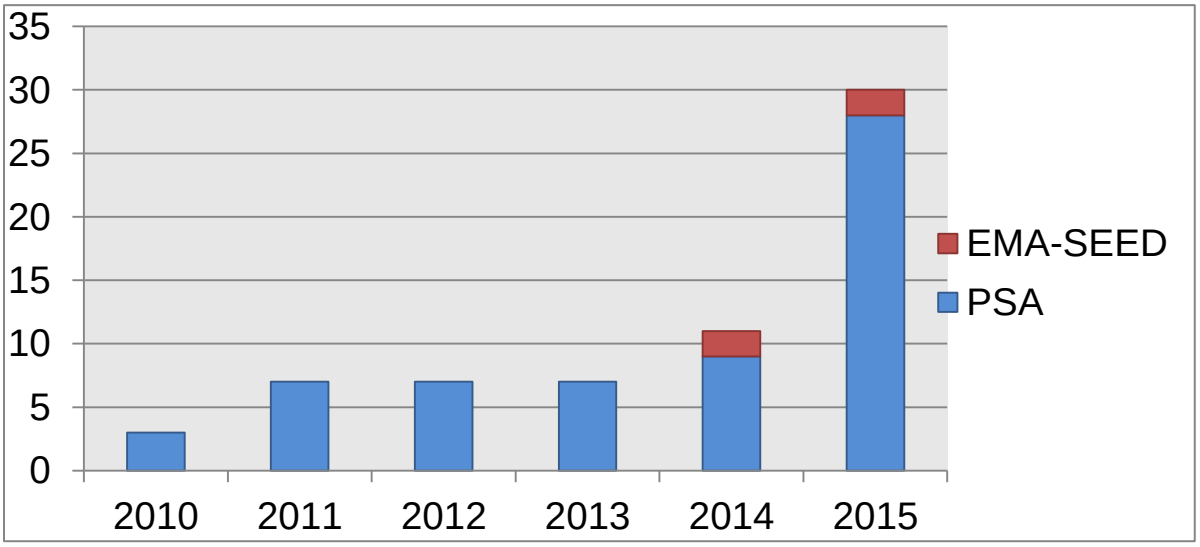
Dr Jane Moseley presented on parallel scientific advice processes and SEED in particular.

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

EMA was established in the early 1990s to coordinate work among national regulatory agencies in EU Member States to undertake regulatory assessments of the safety, quality and efficacy of medicinal products. Soon after establishment it began to provide Scientific Advice to health technology developers on their development plans for new medicines using regulatory, clinical and methodological expertise from EMA and Member States. Currently, it undertakes 500 Scientific Advice procedures per year using a structured process of notification, validation, assessment and outcome. Over time, EMA has seen a broader range of companies come forward for Scientific Advice, in particular more small and medium sized enterprises.

In 2010, EMA launched a pilot project of Parallel Scientific Advice (PSA), providing simultaneous advice with regulators and HTA bodies. Figure 2 shows the year in which the requests for PSA were received and that of the 60 PSAs, 44 were complete by June 2015 and four are part of the SEED initiative.

Figure 2. Evolution of Parallel Scientific Advice in Europe



EMA has collaborated with HAS on the SEED project to develop the optimal process for Early Dialogue before the start of the project, during individual procedures and will reflect on the completed project. The aim has been to help improve it in an iterative manner as experience has been obtained to ensure that it meets the needs of all stakeholders. One example of a process consideration is the agreements of timelines that allow sufficient time for review of the draft submission by assessors, but ensuring that this still allows the health technology developer sufficient time to update the submission before the face-to-face meeting.

The process for the SEED procedures in which EMA was included is shown in Table 2.

Table 2. SEED process, including EMA

Common Briefing Book to EMA and HTAs
HTA/EMA/health technology developer teleconference to validate submission
Independent parallel assessments by regulators and HTAs
Closed EMA /HTA interaction
Regulators and HTAs develop list of issues to clarify issues
Face-to-face meeting • Only need short overview by health technology developer • Focus on contentious issues, not all questions
HTA/regulator closed debrief
Independent written answers by HTAs and regulators

Feedback has indicated that parallel EMA SEED advice enables high-level advice about the shape of evidence plans to meet the needs of regulators and HTA. It fosters strong interdisciplinary collaboration (e.g. with regulators and clinicians), it is educational and may be particularly valuable to companies with limited experience in Europe.

EMA undertook a consultation on PSA in May 2014[1]. This received 18 responses, 13 from technology developers, (2 small-medium), 2 from HTA bodies, 1 patient/carer, 2 others. It will be published when the final parallel EMA Regulatory HTA scientific advice pilot report is available, but at this stage it shows that most agreed with:

- the process used
- proposals for an optional stage of a pre-validation teleconference
- the possibility to submit an amended development plan
- the importance of feedback to prepare for the face-to-face meeting
- identification of consensus/divergences as being critical in the face-to-face meeting.

Messages from this consultation include:

- the importance of exchanging information between EMA and HTA bodies
- the need for coordination of the HTA bodies' perspectives
- the need for one place to go to for HTA information (e.g. on prerequisites, fees, relationship with final advice)
- some requests for single point of contact and coordination
- many requests for HTA bodies' list of issues and final written advice.

A qualitative research study is also being undertaken 34 of the PSA procedures (three from SEED) to identify how the system is working and areas for improvement.

A desktop analysis has been undertaken of three parallel EMA SEED advice procedures to ascertain the level of alignment between regulators and HTA bodies (the contribution of Giovanni Tafuri and Margarita Pagnini is acknowledged) and among HTA bodies further to the face-to-face meeting. Preliminary results from the three SEED procedures show that there was a high level of alignment between HTA bodies and EMA, and amongst HTAs when looking at population, endpoints, and comparators. These results need to be confirmed by an analysis of all parallel EMA HTA advice procedures.

[1] EMA. Best practice guidance for pilot EMA HTA Parallel Scientific Advice procedures. 7 May 2014. European Medicines Agency, 2014.

The HTA Network has encouraged HTA bodies and health technology developers to participate in parallel Early Dialogue to create stronger synergies and closer interactions to improve the data available for decision-makers throughout the life cycle of the health technology. It recognises the different remits and aims of those involved and that they should be maintained, but that better interactions between HTA bodies and EMA in the EUnetHTA Joint Action would facilitate patient access to innovative, effective technologies, reduce duplication of efforts for clinical studies and data generation, and improve business predictability. In its reflection paper on joint work it recommends that maintaining and possibly clarifying different options for performing joint work seems to be the most effective way to meet the needs and capacities of both HTA organisations and technology developers. It also states that interactions with regulators should be strengthened to define a framework/process to perform Early Dialogue involving both HTA and regulators at European level, building on the experience of existing experiences (pharmaceuticals)[2].

EMA is open to future involvement in an optimized procedure for Early Dialogue with HTA bodies and notes strengths, weaknesses, risks and opportunities of the current process as shown in Table 3.

Table 3. EMA's views on current parallel EMA SEED process

Strengths • optimisation through experience (for example with list of issues and written answers) • collaborative working • experts and patients involved • good preparation • reasonable alignment • simultaneous feedback from HTA and regulators • improved understanding among all stakeholders with different views	Weaknesses (areas lacking clarity) • involvement of decision makers • relationship of advice with final appraisal • process to optimise patient contributions
Risks • capacity/funding • meeting demand without selection/prioritization • avoiding rigidity • all/some/more HTA bodies • coordination and communication with multiple stakeholders	Opportunities • shape of evidence plans at an early stage, cross-functional collaboration • reduce duplication • patient access

EMA is open to further interactions between HTA bodies and regulators and PSA/ED is one important mechanism to achieve this. It is essential that all stakeholders now get involved in discussions about how to develop the process in a non-competitive way, taking account of experience to date to determine the best processes for a sustainable system. In the longer term, tracking of the impact of PSA/ED is needed in relation to marketing authorisations and reimbursement.

[2] HTA Network. HTA Network reflection paper on "reuse of joint work in national HTA activities". April 2015; European Commission, Brussels.

4. Multi-stakeholder collaboration in generating the best possible knowledge – the SEED experience – industry experience

Ruzan Avetisyan, MD PhD, Sanofi Genzyme

In October 2014, Genzyme, a Sanofi Company, participated in the SEED multi-stakeholder EMA/multi-HTA ED procedure. This was the first SEED procedure that involved EMA. Dr Ruzan Avetisyan presented insights from this experience.

From an industry perspective the aims for participation in the SEED process were to:

- obtain feedback about the clinical program plans and additional data generation needs
- gain perspectives of EMA, HTA bodies, payers, patients and clinical experts about evidence requirements to streamline the development program
- contribute to the development of a permanent multi-stakeholder Early Dialogue model.

The ultimate goal was to help patients gain timely access to the new therapy and have a better management of their condition. The company recognized that there could be different perspectives among the stakeholders about the evidence development needs and development program plans. Therefore, it was important that the meeting provided an open discussion among all participants, to help reduce uncertainties and bring clarity, and thus produce translatable knowledge to facilitate decision making.

When deciding on the compound to put into the SEED process, several potential candidates were considered by the company. A compound in development for a rare disease was selected based on several factors. The disease under consideration is multi-systemic, heterogeneous, progressive and life-threatening and has a substantial impact on quality of life. The only currently available treatment option is symptomatic/palliative care, so there are high unmet medical needs in patients with this rare disease. There is limited published evidence about the disease, and due to rarity of the disorder challenges arise in all areas of research including the ability to enroll sufficient number of patients into the studies and subsequently collect sufficient clinical data. The phase II/III trials for the new treatment were being planned at the time of opportunity to participate in SEED was presented. Thus, it appeared to be the optimal time to seek input from the external stakeholders on the design of the pivotal study and to inform the overall development programme.

From the company perspective, the SEED process followed closely the activities and timelines presented by SEED coordinators as shown in Table 4. This process was subsequently reviewed after each procedure and iteratively amended.

Table 4. SEED process

Days (calendar)	Action
D -105	The company submits the Briefing Book to the SEED coordinator (HAS) for pre-validation. This pre-validation is specific to SEED.
D -90: START	Updated Briefing Book is submitted by the company to EMA and to the SEED coordinator. The SEED coordinator ensures its distribution to all participating HTA bodies.
D -75	➢ HTA bodies establish a consolidated list of points for clarification. ➢ A teleconference between the company, EMA and the SEED coordinator is organized to discuss the points for clarification. ➢ The SEED coordinator and EMA send the list(s) of clarification points to the company.
D -60	The company provides to EMA and to the SEED coordinator responses to the list(s) of clarification points. The SEED coordinator forwards the responses to participating HTA bodies.
D -30	EMA sends a list of main issues to the company.
D -15	Each HTA participant sends to the SEED coordinator written answers to company's questions. The SEED coordinator releases individual HTA positions to participating HTA bodies in the format of a compiled document.
D -10	The SEED coordinator organizes an e-meeting with participating HTA bodies to discuss the key issues of the dossier. The list of key issues is sent to the company.
D 0: ED Meeting	➢ Preliminary discussion among HTA bodies (closed meeting) ➢ Face-to-face meeting of EMA and HTA bodies with the company ➢ Closed debriefing among EMA and HTA bodies
D +10	The company provides the draft detailed minutes of the meeting to the SEED coordinator.
D +20: END	The draft minutes are reviewed by the SEED coordinator and by participating HTA bodies. The Coordinator checks the whole document and sends finalized minutes to the company. In case of remaining uncertainties, a teleconference or e-meeting with HTA organizations may be organized by the coordinator.

In relation to preparations by the company, careful planning was required to ensure that all relevant internal departments could contribute in a timely manner throughout the process. The key steps in the internal processes used by Sanofi-Genzyme are presented in Table 5.

Table 5: Company internal activities and timelines leading to October 2014 SEED meeting

March-June 2014: Briefing book and questions development	
March:	Start developing Briefing Book including questions and company position
May:	Internal meetings to finalize the Briefing Book
June:	Deliver pre-submission version of Briefing Book to SEED
June-September 2014: Pre-submission reviews and feedback	
June:	Pre-submission teleconference with EMA and HAS
July:	Submission of final Briefing Book to EMA and HTAs
Sept:	Receipt of EMA and HTA final questions and prepare responses
September-October 2014 – Early Dialogue SEED meeting and feedback	
8 October:	SEED face-to-face meeting
16 Oct/17 Oct:	Submission of minutes to EMA and HAS/ HTAs*
31 October:	CHMP outcome letter/EMA formal feedback received

**Note: The detailed minutes were further reviewed and validated by the HTAs and became a formal HTA feedback document*

Specifically, the Briefing Book was required by SEED about 3.5 months before the face-to-face meeting, to allow the participants to review topics and prepare questions for further clarification. The Briefing Book prepared by the company followed the template provided by the SEED consortium. Table 6 presents the topics included in the Briefing Book..

Table 6. Outline of key topics included in the SEED Briefing Book

Topics included
Disease background • Overview of the disease • Treatment options
Background information on the product • Indication • Form, route of administration, dose, dosage • Characteristics of the product • Mechanism of action • Quality data on the product
Non-clinical development
Status of the clinical development program • Clinical development up to date • Planned clinical trials
Economic aspects • Economic evaluation plan
Regulatory status of the product
Rationale for seeking advice
Discussion on added benefits

The Briefing Book also included specific questions to health authorities and by the company related to:

1. Indication and target population
2. Primary and secondary endpoints
3. Pivotal trial design issues
4. Patient reported outcome (PRO) strategy (generic PROs and development of disease specific PRO instruments)
5. Economic evaluation plans.

After the delivery of the preliminary version of the Briefing Book, a pre-submission teleconference between the health authorities and the company teams took place which helped addressing questions related to the background materials. The final briefing package was submitted in July and covered areas requested for clarification.

The face-to-face meeting among the stakeholders took place at EMA offices in London on 8 October 2014, including 19 representatives of 12 HTA bodies from 9 countries, 10 representatives from EMA, two external clinical/ science experts and two patient representatives. The meeting was co-chaired by EMA and HAS, and started with company presentations followed by feedback from all stakeholders. There were many areas to discuss, but the half-day meeting was well structured to allow effective dialogue.

After the meeting there was a post-meeting debrief in the company with internal follow-ups, minutes and written feedback prepared for SEED.

The SEED process provided validation of the development program plan with specific advice on:

- phase II/III clinical endpoints
- trial population and inclusion/exclusion criteria, target population
- additional evidence generation (i.e. natural history, sub-populations, supportive care patterns etc.)
- economic modelling requirements for different HTA bodies.

Overall, the company felt that involvement in this SEED process was a valuable experience, not just for the development program of the particular compound being discussed, but it also identified generic topics and advice that could inform also other development programmes.

There were several factors that contributed to the success of the project from company's perspective.

In terms of internal organizational factors, having a strong inter-departmental team involving clinical development, medical, regulatory, HTA/health economics and outcomes research and other members, was important. Senior leadership support and input was essential to help with internal resourcing and development of internal alignment across departments. Streamlined communications and coordination internally was identified as a key factor. It was also noted that it was important to spend time early in the process developing a clear Briefing Book and preparing for the process.

As for the important external factors contributing to the overall success of the SEED process, the company identified the following:

- transparency in processes and communications among stakeholders, during the preparations and the meeting itself
- opportunity for a pre-submission clarifications and feedback to finalize the Briefing Book, as this allowed for the provision of further detail about the disease and the program, allowing well informed discussion
- having specific questions with company positions (as opposed to open ended questions)
- well-structured meeting, covering many topics in detail
- duration of meeting was appropriate and allowed for interactive discussion (for future procedures time may need to vary dependent on timing in clinical development programme and number of questions asked)
- an environment that enables sharing of perspectives, mutual learning and understanding
- participation of patient representatives and external medical experts provided important perspectives
- HTA internal discussion to align/harmonize feedback prior to meeting with the company was helpful.

In conclusion, Sanofi Genzyme is supportive of the concept of multi-stakeholder dialogues and the approach taken in SEED. The feedback provided to the company on the product development programme was helpful, educational, informative and valuable. Specifically, it provided advice about the pivotal trial and additional evidence development needs. The company believes that it is also efficient to have all stakeholders together to allow direct interaction as this enables in-depth discussion of difficult issues and generates mutual understanding. It also needs to be noted that while alignment was gained for many issues among the stakeholders, there was some variability in economic modelling requirements across some HTA bodies, mostly due to differences in national policies. The opportunity to discuss issues related to development programmes for products for rare diseases was particularly welcomed. In the area of rare diseases, the stakeholders participating in these early dialogues would provide input and also benefit from learning early on about the disease areas and challenges associated with developing an orphan therapy.

Given this experience, the development of a permanent, sustainable, consistent model for multi-stakeholder Early Dialogue is welcomed. This should be transparent and involve all relevant stakeholders, while recognizing that there will always be some differences among Member State requirements for HTA given the devolved nature of health care delivery and differences in priorities and processes across HTAs. Areas for future consideration include: the potential to establish a model for the ED process that can be customized to reflect specific situations and needs, development of an effective mechanism for follow-up procedures and activities and clarification of the implications of such early dialogue procedures for the specific audiences including the national and local HTAs.

5. Patients @ Early Dialogue (HTA/regulatory)

Mr François Houÿez, Treatment Information and Access Director, EURORDIS

Due to unforeseen circumstances, Dr Facey presented Mr Houÿez's slides, reviewing the experience of patients involved in SEED and the work of his organization to support them.

The European Organisation for Rare Diseases (EURORDIS) was founded in 1997 as a non-governmental patient-driven alliance of organizations and individuals active in the field of rare diseases in Europe. It represents 687 rare disease patient organizations in 63 countries. Policy engagement is a key part of EURORDIS' work. It has been working with EMA since 2000 to provide patient experts on regulatory and Scientific Advice procedures and to help develop EMA's policies for patient engagement. Since 2010, EURORDIS has represented patient groups at EUnetHTA's stakeholder forum and on the HTA Network, it has been involved in EUnetHTA training and advisory groups and has identified and supported patients to contribute to SEED.

The main challenges in identifying patients to participate in SEED were:

- the need to explain the context and process; explaining what HTA, EMA and SEED
- to relate the medical device with a group of patients who could be users. (Unlike indications for pharmaceuticals, indications of medical devices do not always target a precise group of patients, or their organizations are not yet prepared to identify experts.)
- the short time to sufficiently prepare the patient experts, as briefing materials are received shortly before the meeting.

To date, EURORDIS has tried to support 12 medicine or device SEED processes since September 2014, covering a wide range of topics as outlined in Table 7. Over the nine-month period to June 2015, 48 organizations were contacted to find suitable patients. This led to 28 patient contacts. To date, after discussion, 10 of these patients have been involved in seven SEED procedures. Three procedures are yet to run and there were two procedures where a patient could not be identified to contribute, the first on non-small cell lung cancer and one of myasthenia gravis (despite contacting three national patient organizations).

Table 7. SEED procedures with patient involvement

Date	Type	Health technology
8 Oct. 2014	EMA-HTA	Medicine
15 Jan. 2015	SEED	Implantable device
22 Jan. 2015	SEED	Medicine
12 Feb. 2015	SEED	Medicine
13 Feb. 2015	SEED	Diagnostic test
10 Mar. 2015	EMA-HTA	Medicine
14 Apr. 2015	SEED	Implantable device
29 June 2015	EUnetHTA	Medicine
7 July 2015	EMA-HTA	Medicine
7 Sept. 2015	EUnetHTA	Device

It was hoped to include patients in the process who had the stage of disease being discussed, but the precise population to be included in the study being discussed

sometimes changed during the pre-meeting clarifications. This meant that a patient who had already agreed to participate may not have been the most appropriate to contribute.

As has already been explained, the process prior to the face-to-face SEED meeting including clarification of issues and consolidation of HTA and EMA draft answers is important, but patients were not involved in any of these early stages. They only participated in the face-to-face meeting and did not receive the minutes of the meeting. Despite this, patients were able to provide important contributions to the discussions about the clinical trial design to improve its acceptability to patients (e.g. considering frequency of clinic visits, amount of testing etc) and on general scoping issues via the PICO framework:

Population – all stages, advanced, potential for off-label use.
Interventions – method of use (particularly for implantable devices).
Comparator – diversity across Europe, often confirming HTA experts, impact of choice of comparator.
Outcomes – outcomes of importance to patients.

The engagement of patients in SEED is welcomed, but the current process to identify appropriate patients is laborious and rushed given the quick process. Table 8 presents EURORDIS proposals for ways in which the process for patient engagement could be improved given its experience to date.

Table 8. Proposals to improve the process for patient engagement in SEED

Day	Action
Day -60	Coordinator announces the meeting to Eurordis
Day -59	Eurordis contacts relevant groups, social media, Summer School or Patients Academy (EUPATI) alumni…
Day -45	At least 4 patients identified. Eurordis checks their role, affiliation, disease stage. Telephone brief 30 min Eurordis sends their contact details to coordinator (+/- EMA)
Day -40	Declaration of interests & confidentiality (DoICU)
Day -32	Coordinator's response on DoICU. 2 patients invited
Day -20	Travel and accommodation arrangements made
Day -15	When available, company presentation and list of questions to HTA and regulators are shared with the patients
Day -7	Conference call to discuss the dossier (2 hours)
Day 0	Face to face meeting
Day 3	Patients fill-in the evaluation

Feedback from patients about their involvement in the SEED process raises issues of sustainability, timing of input, EURORDIS workload, training/preparation, expenses and documentation, which should be considered as proposals for a sustainable process are developed.

Sustainability of process: During this SEED process there has only been one Early Dialogue per month. This requires a lot of preparatory work, two teleconference/online meetings and one full-day face-to-face meeting. It is unclear how this process will function if there are 10 Early Dialogues per month. The full-day meeting may be too long and more teleconference/online meetings may be required. However if the face-to-face

interaction is reduced, patients are less likely to be able to engage effectively in the discussion, particularly around HTA issues, which are new to them.

Timing of input: HTA experts have 90 days to become familiar with the Briefing Book, contribute to issues for clarification and are experienced in the issues under discussion. Patients, even when trained (by EUPATI or EUnetHTA), have little knowledge of HTA and only receive the Briefing Book 7-10 days ahead of the meeting. Consequently at the face-to-face meeting, the patient is just beginning to understand the issues and beginning to contribute, so more time is required to prepare patients. It would be helpful to have a pre-meeting with the developer or one HTA expert or for the patient to be able to send in comments or questions one day after the face-to-face meeting.

Equality of contribution: Currently patients do not receive the written answers emerging from the process or the minutes written by the developer. Given the effort contributed by patients this should be changed, to help patients understand the value of their input and to recognize their contribution.

Workload: In addition to the time spent by the SEED/EMA coordinator, each meeting takes at least four days' of EURORDIS time. This time is required not only to identify the appropriate patients but also to support them in advance of the meeting. Patients only receive the Briefing Book, which is a 50-80 page technical document, a few days in advance of the meeting. So, it takes at least two hours with each patient to discuss the Briefing Book and time in advance to prepare for the call.

Training and preparation: EUPATI and other initiatives have trained patients in the field of HTA, however the patients invited to SEED meetings are not yet likely to have benefited from EUPATI training. SEED requires patients with personal experience of the specific disease (and stage of disease) being discussed and may find the large, scientifically focused meeting intimidating. In most cases, the patents invited to participate in Early Dialogues will need ad hoc training a few days in advance. So there is a need to develop online training materials to support patients. Further work is needed to develop specific materials re HTA Early Dialogue for patients and to prepare patients to be able to express themselves in such an intense meeting environment. This requires not only training for patients, but also for other participants in the SEED process about patient involvement and best practice. In particular, the chair of the meeting needs to understand how to identify patients' issues in advance and draw them into the dialogue in a non-threatening and supportive manner.

Expenses: As the model for sustainability is considered, the issue of payments to patients or their organizations must be considered. Some HTA agencies currently provide patients with meeting fees for participating in face-to-face meetings, recognizing that patients may have to take time off work to participate. At the very least, travel and accommodation expenses need to be paid in advance by the organizer as these may represent one-third or one-half of a person's monthly income. Furthermore, these expenses need to be paid upfront to ensure that the individual is not out of pocket.

In conclusion patients value participation in SEED and feel welcomed. This has been a great "learning by doing" phase and EURORDIS and the patients involved thank the ED coordinators for their support. EURORDIS offers these reflections on the process and how it may be improved in a spirit of hopeful cooperation so that in future patients' input may have greater impact.

6. Panel discussion

The audience posed questions to the panellists, covering a range of issues.

Generalisability of advice to form disease specific guidance

Question: It is clear that the ED process needs to be confidential when advising on a specific technology development programme, but over time will there be any aspects that can be shared – surely there will be issues that are generalisable?

- After there have been a few ED procedures for one type of technology/disease it may be possible to publish general guidelines. However, disease specific guidance is more difficult to develop, so it may be more feasible to publish some focussed guidance on specific issues.
- EMA has experience of balancing requirements for confidentiality with providing more generic guidance as shown in its Notes for Guidance, which include themes that have arisen in different regulatory fora along with wider scientific issues. For challenging issues, EMA has also found it helpful to have a workshop with stakeholders. Another possibility yet to be explored is parallel advice on novel methodologies and biomarker qualifications. So several approaches are possible.

Resolving disagreements

Question: As we all want to improve outcomes, can we find processes for resolution of obvious disagreements between regulators and HTA?

- We need to spend more time identifying the divergences between HTA bodies and between HTA bodies and regulators. We also need to be clear about what can be resolved and what cannot be resolved. For example off-label use of a comparator is acceptable in some countries but not in others.

Question: It was noted in the Sanofi-Genzyme case study that discrepancies arose in relation to economic modelling. What was the source of those discrepancies and will it be possible to come to some consensus on economic evaluation?

- A range of different issues arose in relation to economic evaluation across Member States. Some countries require cost utility analysis, others do not and some only require budget impact. Other differences also exist in relation to the perspectives modelled (health service vs societal). However, it is possible to create one economic model that can be adapted for different countries.
- Countries that require cost utility analysis prefer generic quality of life measures that can be used to create utilities, other countries that focus on quality of life as a measure of effectiveness prefer disease specific measures. Hence both are needed.

Impact

Question: Is there a mechanism to evaluate the impact of the ED on company strategy?

- This is an important issue and to date we have no formal evidence of impact, but it is early in the process. It will be important for industry to share their experiences of the impact that ED has made, not just on the design of the pivotal study, but on wider aspects as well.
- The Background Paper of the 2015 HTAi Policy Forum meeting gave one company's reflection of their engagement in HTA and parallel several scientific advice processes. This company felt that not only did it highlight important changes needed to the phase III programme to take account of HTA issues, but that it was helpful internally to bring the clinical development and market access teams together and to change company culture about the need to consider HTA requirements early.

Openness and patient involvement

Question: Why aren't the minutes of the meeting shared with the patient?

- There are concerns about confidentiality.
- Surely, these concerns can be overcome with use of confidentiality agreements and appropriate processes.
- In future it may be possible that EMA final advice letters could be sent to patient experts.

- Overall in terms of effective patient involvement, capacity building of patient experts and learning from others who have been involved is important. Capacity building is one of the five values of the HTAi Values and Quality Standards for Patient Involvement in HTA and they could all be applied to these Early Dialogue processes.

Application to in-vitro diagnostics

Have in-vitro diagnostics been considered in SEED, and if not, will they use the same process?

- The medical device industry has shown less enthusiasm to engage in SEED, but it is hoped that this will change in the future.

7. Conclusion

The presentations and discussion confirmed the importance of multi-stakeholder Early Dialogues to help inform the design of health technology development programmes. The thorough, inclusive approach used in parallel EMA/SEED process created a shared understanding of some of the challenges and led to open discussions of solutions. All stakeholders were keen to see a sustainable model developed that ensured effective engagement of all participants, with a clear and transparent, but flexible process that would improve the effectiveness of evidence development for HTA and regulation and give patients faster access to effective health technologies.