



EMA-multiHTA Scientific Advice: SEED pilot project

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Agenda

- The larger scheme of things
 - Early Dialogue, Networks, EU Commission call for tender
- SEED
 - Consortium, Consortium members, Objectives, Procedure
- Genzyme experience
 - Considerations, SEED milestones, General experience, Internal experience
- Concluding thoughts
- Further reading and reference

The larger scheme of things

- Various initiatives ongoing in Europe:
 - Early dialogue between authorities and companies on product development
 - Resulting from high level Pharmaceutical Forum on Pricing and Reimbursement
 - Several pilots of early dialogue set up since 2010
 - Cooperation of authorities in networks to surpass limitations of national reimbursement assessments
- These initiatives formed the basis of a Call for Tender from the European Commission to develop a procedure for early dialogue
- The tender was granted to the SEED consortium

The larger scheme of things – early dialogue

The High Level Pharmaceutical Forum on Pricing and Reimbursement (2006-2008)

- High-level political platform:
 - Ministers from all (27) European Member States, representatives of the European parliament, pharmaceutical industry, health care professionals, patients and insurance funds
- 3 working groups:
 - (1) Information to Patients
 - (2) Relative Effectiveness
 - (3) Pricing and Reimbursement
- Goal is to improve the performance of the pharmaceutical industry in terms of its competitiveness and contribution to social and public health objectives
- Conclusions and Recommendations (amongst others):
 - “promote the exchange of information to improve data availability/transferability”
 - “improve the understanding of scientific evidence by sharing best-practice of data requirements and processes”
 - “explore better avenues for dialogue between assessing bodies and/or decision-makers and the marketing authorisation holder”
 - “consider ways of having early dialogue during product development to improve the generation of appropriate data as far as possible”

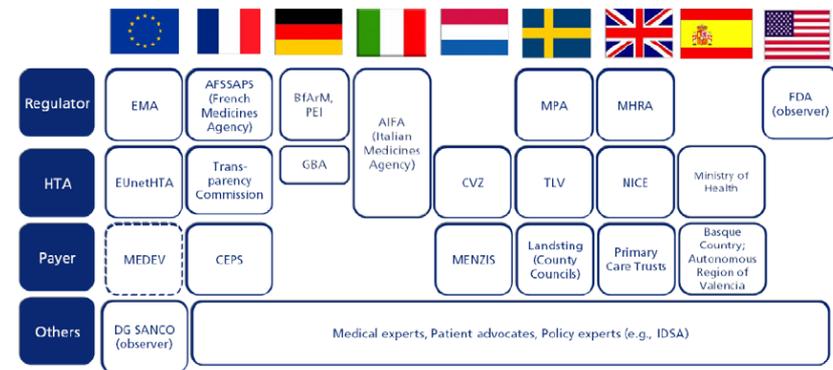
The larger scheme of things – early dialogue

- Overall goal, in line with the conclusions of the Pharmaceutical Forum:
 - Improving and anticipating the collection of clinical evidence before licensing (i.e. at the end of phase II of a clinical trial for a medicinal product) would enable easier and quicker HTA processes after licensing, leading to quicker decisions on uptake of new products.
 - Early dialogues are supposed to bring benefit to HTA authorities, regulators and companies.

The larger scheme of things – early dialogue

Several pilots for early dialogue during product development were set up to improve the generation of appropriate data:

- July 2010, EUnetHTA: 6 pilots on multi-stakeholder consultations in drug development by the European Healthcare Innovation Leadership Network, lead by Tapestry Networks
- July 2010: EMA parallel scientific advice with health-technology-assessment bodies (ongoing)
- Dec 2013: SEED



Parallel HTA-EMA SA experience so far

HTAs and payers from UK, Sweden, France, Italy, Netherlands, Spain, Germany, Belgium

Most big companies, 2 SMEs.



The larger scheme of things – networks

DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare

- “**Article 15: Cooperation on health technology assessment**
- 1. The Union shall support and facilitate cooperation and the exchange of scientific information among Member States within a voluntary network connecting national authorities or bodies responsible for health technology assessment designated by the Member States. [...]
- 2. The objectives of the health technology assessment network shall be to:
 - (a) support cooperation between national authorities or bodies;
 - (b) support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy as well as on the short- and long-term effectiveness, when applicable, of health technologies and to enable an effective exchange of this information between the national authorities or bodies;
 - (c) support the analysis of the nature and type of information that can be exchanged;
 - (d) avoid duplication of assessments.”

The larger scheme of things – networks

EU Cooperation in HTA – today:

- HTA Network (art 15 Directive 2011/24)
 - strategic level (1st meeting 16 October 2013)
 - Member State representatives (mainly MoH); EMA
- EUnetHTA
 - scientific level (on-going)
 - HTA doers (mainly HTA Agencies)

The larger scheme of things – networks

Also several other projects initiated in these networks:

- Development of common HTA methodologies
- Development of IT tools and training facilities

Goals:

- Adoption of a **long term vision** on HTA cooperation and priorities for next phase of scientific cooperation
- Reflection paper on synergies between HTA and regulatory process
- Reflection paper on conditions to facilitate take up and re-use at national level of joint HTA production including information and joint assessments

The larger scheme of things – call for tender

- Call for tender from European Commission:
http://ec.europa.eu/eahc/health/tenders_H09_2013.html
 - **“Call for tender n° EAHC/2013/Health/09 concerning pilots on early dialogue between health technology assessors and healthcare product developers during the development phase of medicinal products**
 - The purpose of this call for tender is to give support to conducting early dialogues aiming at improving the data collection during the development phase of the technology. The contractor will develop a number of methodological protocols and test them through 10 early dialogues pilots.
 - The maximum volume of this call for tender is 500 000€.
 - The deadline to submit tenders is the 7 June 2013.
-  Tender granted to SEED Consortium.

SEED Consortium

- Shaping European Early Dialogues
- Launched in December 2013.
- Led by the French Haute Autorité de Santé (HAS)
- Consortium consists of 14 national and regional HTA bodies:
 - Spain, Italy, Netherlands, Germany, Hungary, France, Ireland, Austria, Belgium, UK.
- All SEED consortium members are also partners in the EUnetHTA network.

SEED Consortium members

Acronym	Organisation	Country
HAS	Haute Autorité de Santé (Lead Partner)	FR
RER-ASSR	Regione Emilia-Romagna, Agenzia Sanitaria e Sociale Regionale	IT
AIFA	Italian Medicines Agency	IT
AVALIA-T	Consellería de Sanidade de Galicia	ES
GB-A	Gemeinsamer Bundesausschuss (Federal Joint Committee)	DE
GYEMSZI	National Institute for Quality and Organizational Development in Healthcare and Medicines	HU
HVB	Hauptverband der Österreichischen Sozialversicherungsträger	AT
ISCIII	Instituto de Salud Carlos III	ES
AETSA	Regional Government. Fundación Pública Andaluza Progreso y Salud	ES
CVZ	Health Care Insurance Board	NL
IQWiG	Stiftung für Qualität und Wirtschaftlichkeit im Gesundheitswesen	DE
NICE	National Institute for Health and Care Excellence	UK
KCE	Belgian Health Care Knowledge Centre	BE
HIQA	Health Information and Quality Authority	IR

SEED objectives

- Perform 10 independent multi-HTA Early Dialogues:
 - 7 pharmaceuticals
 - 3 combined EMA – multi-HTA Early Dialogues with face-to-face meeting
 - 3 medical devices
- Highlight differences in requirements:
 - between HTAs
 - between HTAs and regulators
- Create platform to share views and provide advice
- Develop a consolidated procedure for permanent model:
 - prospective and timely advice
 - improve data quality → quicker HTA decisions → quicker access to market
- Involve regulators (EMA), payers, and patient representatives

SEED Procedure for Early Dialogue

- Main characteristics:
 - Confidential, non-binding
 - For new products with expected added benefit
 - One indication per procedure
- Main procedural steps:
 1. Company to send letter of intent for selection
 2. Company to provide briefing book and questions
 3. Validation of briefing book and questions and submission of final briefing book
 4. Face-to-face meeting between HTAs and company
 5. Company to prepare minutes, which are reviewed by HTAs
- Briefing book and company questions:
 - Clinical development strategy, incl. cost-effectiveness studies: planned studies
 - Prospective questions and company's position for each question
- For combined EMA – multi-HTA advice: EMA uses Sc.Advice Procedure

Genzyme experience – considerations

- Reasons to participate:
 - Engage in piloting new initiatives to gain early experience
 - Ability to meet and engage in discussions with multiple HTAs
 - Essential for orphan products to include reimbursement needs into regulatory dossier
- RA Europe to lead initiative within Genzyme:
 - European initiative
 - Regulatory authority involved (EMA)
 - Experience with these types of projects (scientific advice)
- Product/project chosen for discussion:
 - prior to pivotal studies to gather data to support MA and reimbursement dossier
 - significant supporting information already available

SEED milestones for pilot

- Dec 2013: Genzyme sr. management request to apply for SEED EMA-multi-HTA Early Dialogue
 - 27 Jan: submission Letter of Intent to HAS
 - 12 Feb: acceptance by HAS
 - 28 Feb/4 Mar: procedural discussions EMA/HAS
 - 4 Mar: start development questions and briefing book
 - 3 June: submission draft briefing book
 - 18 June: pre-submission meeting with EMA and HAS
 - 7 July: submission final briefing document
 - 10 Sept/1 Oct: receipt EMA and HTA questions
 - 26 Sept: submission written responses to EMA questions
 - 8 Oct: meeting at EMA with SAWP and HTAs
 - 16 Oct/18 Oct: submission minutes to EMA and HAS
- 
- ~9 months

Genzyme experience with pilot

- This was the first pilot for combined EMA-multi-HTA Early Dialogue
- Align procedures and requirements of HTAs and EMA; a flavour:
 - Different preference for communication by EMA and HAS
 - Different timelines
 - Different templates for briefing document
 - Different validation of briefing document
 - Different outcome documents (minutes)
 - Different requirements for information:
 - Example: alternative treatment options to be described for HTAs: including off-label and symptomatic treatment
- After multiple discussions between all parties a harmonized procedure was agreed on

Genzyme experience with pilot

- 3.5-4 hour face-to-face meeting!
- Many parties present:
 - EMA -SAWP -clinical experts
 - HTAs -PDCO -patient representatives
- Meeting co-chaired:
 - EMA on behalf of SAWP/PDCO
 - HAS on behalf of HTAs: HAS summarized consolidated positions of HTA
- Company questions discussed one-by-one
- Chair consistently asked first for feedback and positions from clinical experts and patient representatives
 - views of experts/patients were very influential to the discussion
- SAWP/PDCO asked questions
- HTAs individually asked questions and provided positions

Genzyme experience with pilot

- Questions asked and topics discussed:
 - Population to be studied
 - Pivotal study design
 - Selection of pivotal study endpoints
 - Overall development plan
 - PRO tools
 - Economic evaluation to support reimbursement
- Different meeting outcome documents:
 - EMA: formal SAWP/CHMP outcome letter to company
 - HTAs: detailed ratified company minutes describing HTA positions

Genzyme internal experience with pilot

- Periods of heavy workload:
 - Preparation of questions and briefing document
 - Preparation for face-to-face meeting
- Team members and management must be:
 - available,
 - supportive of the project and the timelines,
 - pro-active
- Need dedicated team, with sufficient resources:
 - Regulatory Affairs
 - Medical Director
 - Biostatistics
 - Health Economics
 - Global Safety Officer
 - Market Access
 - Medical Writing

Genzyme internal experience with pilot

- Project management is joint responsibility and cooperation between Regulatory Affairs and Health Economics:
 - Who is contact person with EMA and HAS
 - Regular meetings between departments and with the team
- Team mutual understanding of clinical and health economic worlds:
 - separate expertizes
 - different views
 - different requirements
- Ensure alignment of views of all departments involved

Overall conclusion – on procedure

- Pilot procedure overall went well
 - Several practical issues had to be overcome
 - Further refinement in final procedure
- EMA and HAS were flexible in finding procedural solutions
- Team worked together very well in stressful times

Overall conclusion – on concept of EMA-HTA advice

- Productive, informative and valuable
- Useful early stage advice for planning clinical development plan
- Reduces uncertainty
- Efficient to have all (HTA) stakeholders together
- Direct interaction with stakeholders (in depth and real time)
- Provides for mutual understanding
 - EMA and HTAs
 - Internally within the company
- Opportunity to explain disease and product: important for orphan products and rare diseases
- HTA feedback varies per country: no harmonization
- This is the future, so embrace and implement!
 - Use depending on development stage and type of product and potential topics for discussion

Concluding thoughts

- Parties must not confuse roles and responsibilities
 - Regulatory authorities: B/R based on efficacy, safety and quality
 - HTAs: therapeutic benefit based on relative effectiveness
- How to deal with any contradictory advice?
 - Regional regulatory (EMA) vs. country-specific reimbursement (HTA)
 - One HTA vs. another HTA
- Complexity of implementing all advice:
 - In pivotal clinical trial or in separate effectiveness trials
 - Complexity of the pivotal trial
- Authorities to develop one common procedure and follow-up or written procedure
- Next step: ...harmonization of advice across HTAs?

For further reading and reference

- European Commission Tender:
http://ec.europa.eu/eahc/health/tenders_H09_2013.html
- SEED: <http://www.earlydialogues.eu/has/>
- EMA scientific advice (including combined EMA-HTA):
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9
- EMA Early Dialogue:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001979.jsp&mid=WC0b01ac058004d5c1
- EMA-HTA cooperation:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57