Early Scientific Advice from Regulators and HTA: The EUnetHTA Perspective

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KEY POINTS . . .

Timely advice on HT development will increase the quality of data submitted and meet HTA needs.

Early dialogues between HTA bodies and manufacturers are the key for adequate evidence generation.

EUnetHTA and SEED project are shaping early dialogues process as a permanent activity in Europe.

A EUnetHTA Perspective

The following article is based on a presentation given during the Second Plenary Session, Early Engagement Between Manufacturers, HTA Assessors, and Regulators, at the ISPOR 16th Annual European Congress, 2-6 November 2013, Dublin, Ireland

Introduction

Since the publication of Article 15 of the directive on the application of patients' rights in cross-border health care, there has been a clear mandate for European collaboration in the field of health technology assessment (HTA). Based on this directive, the European Network for Health Technology Assessment (EUnetHTA) has implemented many relevant actions, one of which is to raise the standards for assessment by elaborating general methodology guidelines and to trying to improve the quality and appropriateness of the data produced by specifying requirements for initial evidence generation and elaborating on disease-specific guidelines. This article will present the EUnetHTA perspective on the early dialogues between manufacturers, HTA assessors and regulators on initial evidence generation for relative effectiveness and cost effectiveness assessment.

Multi HTA Early Dialogues

Scientific advices between developers and regulators have been in place for some time. They began at the European Medicines Agency (EMA) and have continued very successfully for regulatory issues. In 2009, the National Institute for Health and Care Excellence (NICE) began regular activity on national HTA advice. They have since been followed by the Federal Joint Committee (GBA) in Germany, the Italian Medicines Agency (AIFA) in Italy, and other agencies in Europe. In addition, there is a recent initiative ongoing on parallel regulatory and HTA scientific advice at EMA premises in London.

Early dialogues between multiple HTA bodies and health technology developers were put in place within the framework of EUnetHTA Joint Action 2 and have been supported by the European Commission (EC), especially by recently financing the call for tender for 10 additional early dialogues.

The current process for multi HTA early dialogues generally resembles a procedure that already exists within EMA with some important modifications. Notably, HTA bodies send their written answers to the questions asked by the companies; these answers are compiled into one document and sent to all HTA participants for consideration and discussion before a face-to-face meeting.

The face-to-face meeting is divided in two parts. First, there is an internal discussion among HTA bodies without the company and with or without external clinical experts, on key issues that have been raised by a particular development and consequences that HTA concerns may have on the proposed study design(s). Later in the day, there is a face-to-face meeting with the company and the HTA bodies. This meeting includes an open dialogue and discussion on alternative approaches for each question posed by the company. At the close of the meeting detailed minutes, including clear conclusions with similarities, agreements, disagreements, and heterogeneities among HTA bodies and companies' positions together with possible impact on the study design are completed and reviewed by the Chair and by all involved parties in order to create the final document.

HTA Participants in early dialogue EUnetHTA Joint Action 2 pilots included: **AIFA, ASSR, IQWIG, GBA, NICE, HVB, CVZ, KCE/INAMI, GYEMSZI, TLV,** and **HAS**

The current procedure for early dialogues has been tested and improved by ten preparatory EUnetHTA pilots, two in 2012 and eight in 2013, with two final EUnetHTA pilots still in progress as of November 2013. Within these pilots there were 12 HTA agencies participating from 9 countries. An EMA representative was invited as observer of the process. All documents remained confidential. The pilots covered various therapeutic fields, orphan and non-orphan drugs, involved both small and big companies, and included questions on relative and cost effectiveness of the

product in development. This experience was considered important with regards to the improvement of the collaboration between HTA partners and the efficiency of the process. The next step to improve the process is to analyze an ongoing survey, which is the first deliverable from EUnetHTA Joint Action 2 in this field. The survey was addressed to all HTA bodies, developers, and observers that have participated to at least one early dialogue with 45 questions on each step of the process. After receiving answers a final analysis will be completed and EUnetHTA shall use it to improve the process for additional dialogues to perform in the Shaping European Early Dialogues (SEED) Project.

The Seed Project

The SEED Project is financed by the European Commission in order to perform additional 10 early dialogues, 7 dialogues on drugs (4 multi-HTA and 3 parallel EMA-multi HTA dialogues) and 3 on devices, diagnostics, or procedures, with at least 10 HTA organizations (as conditioned in the call for tender). Thirteen partners from Europe formed the consortium for this project led by the HAS, France. One of the main tasks of the SEED project includes the proposal for sustainable process for early dialogues in Europe involving HTA bodies, payers, and possibly patient representatives, as well as collaboration with the EMA. The kickoff meeting was held in Brussels on October 21, 2013, at which point the work began to establish procedures and templates for briefing books, both for medicines and medical devices, as well as to schedule 10 early dialogues. An interim report was set to be due after five early dialogues in order to discuss all improvements that should be made for the remaining early dialogues. A call for interest to developers was published in November 2013 and all companies who were interested in a dialogue could formalize their request by sending a letter of intent. At the time this article is written, the SEED coordination team has received 22 requests for early dialogue, out of which several on invasive medical devices, which illustrates a huge interest from companies for this project. For companies that have their request accepted, the dialogue will revolve around a supposed added benefit as well as relative effectiveness and cost effectiveness of the product in development.

EUnetHTA survey on early dialogue gathered answers on questions including:

1. When to get advice?
2. What is the minimal number of HTA bodies to be included?
3. Which areas should be covered?
4. What are key factors for successful early dialogue?

As with EUnetHTA early dialogues, for the time being SEED early dialogues will remain free of charge for companies. Scenarios that are being tested in the SEED project include independent multi-HTA advice and parallel EMA-SEED advice. Each early dialogue will be followed by a report and subsequent proposal for improvements in order to help create a permanent model for this process.

Preliminary Survey Results

The final analysis of the ongoing survey was presented in November 2013 at the EMA and published at the EUnetHTA website. As previously mentioned, this ongoing survey included information gathered from twelve HTA agencies across nine countries as well as nine participating companies. Some of the questions for which results have been gathered are 1) when to get advice?; 2) what is the minimal number of HTA bodies to be included in the process?; 3) which areas should be covered?; and 4) what are some key factors for successful early dialogue? It was suggested that advice be received prior to Phase III, and even before Phase II when there is a question on the choice of the most appropriate endpoints. When determining the best number of HTA agencies to involve, it was proposed to have less than ten but not less than five. There was also a proposal to mix agencies focused on relative effectiveness assessment with agencies more concerned with cost-effectiveness assessment. Important areas to cover included primary and secondary endpoints, patient relevant benefit, added benefit, relative effectiveness, cost-effectiveness, as well as guidance to companies on information to present in the briefing book and in the HTA submission file. Some factors determined or a successful dialogue were the quality and level of detail in each company's question, detail of HTA written answers, sufficient time for HTA bodies answers to be exchanged before the face-to-face meetings, and productive internal face-to-face discussion of the HTA agencies before meeting the company.

Based on the fact that some HTA agencies may have different points of focus, relative effectiveness or cost-effectiveness, and different data requirements, it has been suggested that a Chair should lead the discussion and summarize consensus and divergences resulting from the meetings as well as possible impacts on the development proposed. The role of HAS Chair to accomplish this task was praised by all participants. The opinions were split when asked if HTA written answers should be sent to the company and it was decided to keep compiled HTA answers as an internal working document for the time being. EMA's role as an observer was generally supported. It was suggested that EMA should cover regulatory issues only and be prevented from incorporating bias into the process by providing undue comments related to the HTA in the development program. Overall parallel EMA-multi HTA early dialogues appeared generally supported as one of the possibilities for an early dialogue with product developers.

Development on the permanent model of early dialogues is being continued within the SEED project; the results gathered from this survey as well as from the surveys after each SEED early dialogue will be further discussed with SEED partners in order to optimize future procedures. After the last SEED early dialogue (March 2015), the results and conclusions of the SEED project will be elaborated and discussed with all participating parties: EUnetHTA, HTA bodies and companies involved, as well as EMA for early dialogues on drugs. ■

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