# Early Scientific Advice from Regulators and HTA: An EMA Perspective

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## KEY POINTS . . .

Engage early and repeatedly with regulators and HTA bodies so that advice can be built into the development programme.

Provide clear questions and comprehensive background information to allow for a full understanding of the stage of development.

It is important to approach the discussions with an open manner and preparation, in order to explore and present alternative approaches, rather than just defend the position that was adopted initially.

An EMA Perspective

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## Introduction

Scientific Advice from the European Medicines Agency (EMA) is developed within the Scientific Advice Working Party (SAWP), which has been running for over ten years (Fig. 1) and is issued by the Committee for Medicinal Products for Human Use (CHMP). Over the course of the past ten years, the number of applications seeking scientific advice has grown steadily with an estimated figure of over 450 applications for 2013. The purpose of this article is to provide a brief overview of how scientific advice is obtained from the EMA, the people and processes involved, and the recent focus on the parallel health technology assessment HTA-EMA procedure for acquiring scientific advice. Additionally, this article will touch upon the advantages and challenges associated with the current procedure as well as future potential for the program.

The SAWP is a multidisciplinary group of 28 experts and their alternates, drawn from both the national competent authorities and academia. In order to ensure a good relationship during the advice process and in the subsequent decision-making, various EMA committees are represented within the working group. Some of the committees represented include the Orphan Medicinal Products Committee, the Committee for Advanced Therapies, and the Pediatric Committee. Additional advice is contributed through a network of experts at the European national agencies. In order to build the scientific advice, the SAWP coordinates with various working parties including the Safety Working Party and the Quality Working Party, and actively seeks patient representative involvement in a number of applications, particularly those associated with orphan medicinal products. Preliminary scientific advice reports are discussed on a regular basis and companies participate in face-to-face discussions concerning their applications. Following these discussions, a scientific advice letter from the CHMP is issued within a 40 or 70-day time line.

## Parallel HTA-EMA Scientific Advice Process

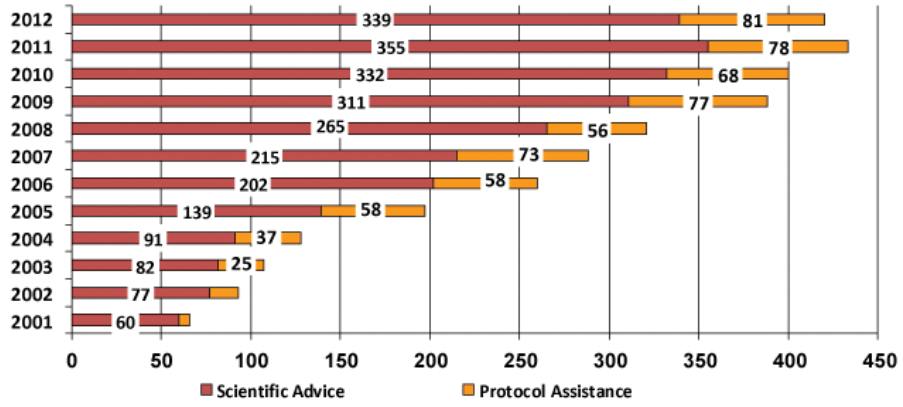
With growing recognition that EMA's evidence requirements as regulators and the requirements required by HTA bodies were quite different; a pilot project was set up in 2010 (Fig. 2), whereby a parallel HTA-EMA scientific advice procedure, based on the template of the well-oiled machinery of the EMA scientific advice process, would be run.

> Because both the EMA and the HTA bodies are represented throughout the process, an understanding of each other's role is effectively gained, leading to constructive advice and an ability to change the development program at a particular stage.

In terms of the application process, it is important to emphasize that this parallel scientific advice requires some months for discussion and planning prior to validation. This pre-validation time is attributed to the recruitment of HTA bodies, to the review of a draft briefing package as well as establishing a timeline that can meet all involved party's needs. The process has three built-in discussion meetings, two of which involve all parties and one closed session between the EMA and HTA bodies prior to the final discussion meeting with the applicant. The final discussion meeting consists of a four-hour, face-to-face meeting with the EMA followed by a detailed scientific advice letter from the CHMP detailing the application outcome and providing answers to all of the questions posed. Separately, the minutes of that final discussion meeting are circulated to the HTA bodies for agreement.

Since 2010, the EMA has finalized 19 applications with several applications still ongoing. The EMA has received >

**Figure 1. Scientific advice is given by the Committee of Medicinal Products for Human (CHMP) on recommendation of the Scientific Advice Working Party (SAWP).**




involvement from HTA bodies and payers from the UK, Sweden, France, Austria, Italy, The Netherlands, Spain, Germany, and Belgium, with NICE in the UK being the most frequent participant. On average, there are about three or four HTA bodies involved per application. The majority of the applications thus far have been from big pharmaceutical companies, with just two small and medium-sized enterprises (SMEs) seeking advice, mainly involving new mechanisms of action in their respective therapeutic areas. The point at which the companies apply for the advice is dependent upon their stage of development. With non-clinical proof of concept, it is best to seek advice very early. At this point the company can present their pharmacological concept and general study design and receive broad advice and multi-stakeholder views on what would be needed to demonstrate benefit/risk or benefit/value. Similarly, applicants can come later in development once they have clinical data and when they are planning late Phase II and Phase III clinical studies. In that case, the applicant will receive more precise responses on study design, duration, populations for inclusion, comparators, endpoints, and so on. At this stage in development, the applicants seek advice from the HTA bodies concerning cost-effectiveness and added therapeutic value.

One example of an application for this advice process concerned a novel agent for the treatment of a rare condition known as pouchitis. Pouchitis is a condition that affects patients who have had surgery in connection with inflammatory bowel disease. As this condition is rare, there was no authorized treatment for the condition across Europe at the time of application. The use of antimicrobial agents for this condition, however, is frequent. The applicant was proposing in its pivotal study that the primary treatment comparison would be to placebo and they would additionally allocate a number of patients to an active treatment arm for a secondary comparison. Broadly speaking, this was found to be acceptable to the regulators, but from the HTA point of view, the key value benefit was in showing comparable efficacy and safety with what are currently used therapies, while containing costs. Because of small study numbers, the applicant argued that it was not feasible to conduct a fully powered study comparing their agent against an active comparator.

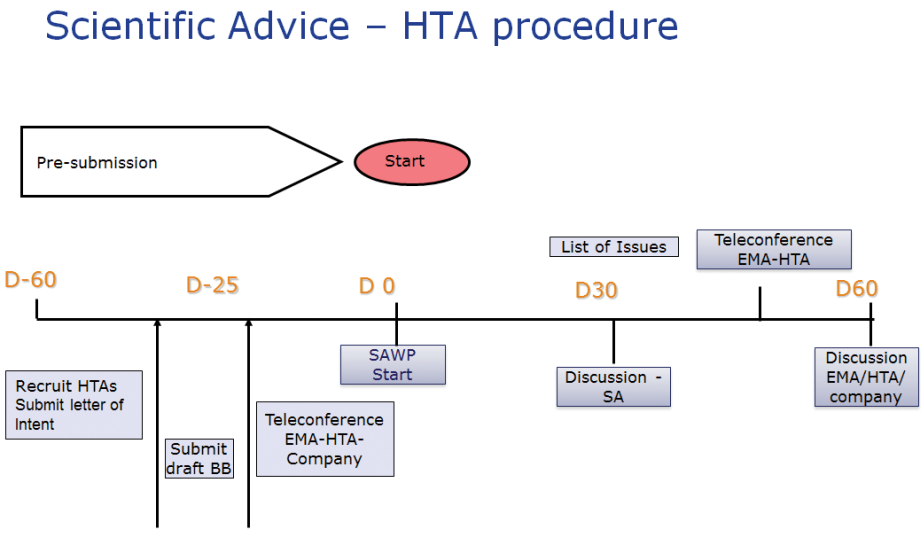
However, after many discussions, all parties were able to reach agreement on a less stringent statistical approach, which would still incorporate an active comparator arm, and would meet the requirements of both the regulators and the HTA bodies.

There have been many other occurrences where the applicant has been able to modify their study programs within the advice process. These proposed modifications were then reviewed before and during the final discussion meeting, allowing the applicants to then make final changes to their development plan. It is these instances in which the advantages of the program are discovered. This parallel process builds on the well-established years of experience with the scientific advice at the EMA and provides a unified regulatory approach, which is applicable across Europe. Though this process has yet to be established, it allows for very good cooperation between the EMA and the HTA bodies. Because both the EMA and the HTA bodies are represented throughout the process, an understanding of each other's role is effectively gained, leading to constructive advice and an ability to change the development program at a particular stage.

## Concluding Thoughts

So where does this parallel HTA-EMA advice process go from here? Until now, industry feedback on this process has been relatively informal. In the long term, this advice process should lead to

**Figure 2. Scientific Advice – HTA Procedure.**



more efficient use of resources by industry; however it is probably too early to say whether or not this has had a real effect on marketing authorizations or on HTA appraisals. Applicants seeking advice should establish contact very early with the EMA, providing precise questions and all necessary supporting documentation. Once validation is complete, it is best to only make changes to accommodate issues that arose during the advice process. It is important to approach the final discussion meeting with an open manner and preparation, in order to explore and present alternative approaches, rather than just defend the position that was adopted initially.

As this advice process is further developed, workshops can be held with stakeholders, in order to review results of the process and aid in the addition of improvements or changes to the current procedures in an effort to build on meeting the scientific requirements of HTA bodies and the EMA. Additionally, the EMA will be involved in the SEED (Sharing European Early Dialogue) project with HTA bodies and welcomes cooperation with our HTA colleagues in meeting the needs of patients. ■

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