EMA-HTA Parallel Scientific Advice

Early Dialogue to Support Marketing Authorization and Market Access

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Drug development is a multi-year and cost-intensive process in which marketing authorization is not the final step on the route to optimal market access. Maximum market availability of medical products to patients depends on pricing and reimbursement assessments and agreements made during the health technology assessment (HTA) process, which can take anywhere from six months to more than a year. Recognizing that there are two sets of standards being considered for drug market access, in 2010 the European Medicines Agency (EMA) launched a parallel scientific advice program in which sponsors can obtain input on value decisions from the EMA as well as various HTA bodies. The scheme was permanently implemented after the pilot ended in May 2015 due to the success of the program.

The EMA or the national regulatory agencies, depending on the marketing authorization procedure, determine whether the evidence provided supports a positive risk-benefit balance and warrants the granting of a marketing authorization. Any product approved by the EMA in the centralized procedure will automatically hold a marketing authorization in all the European Economic Area (EEA) member states. Regulators evaluate the evidence generated during the rigorously controlled product development for conformity with applicable scientific, therapeutic, and product specific guidelines. Products need to meet the regulators' expectations for internal validity, quality, safety, and efficacy, while having a positive benefit-to-risk ratio for patient outcomes. Additional evaluation criteria include the impact on the quality of life, the degree of innovation, and whether the medicinal product addresses an unmet medical need. Ideally, new medicinal products should elevate the benefits over existing therapies.

National Health Technology Assessment Bodies (HTAs, including, for example, third-party payers, patient and public representation, pricing and reimbursement agencies) evaluate the value and patient benefit of the approved drug to grant access to health systems at a certain price. Almost all products approved centrally by the EMA will be evaluated by national or regional HTAs following the country's requirements and policies. Some of the criteria used during the marketing authorization stage are considered during the evaluation of the value proposition against evidence requirements and criteria for what constitutes value. HTAs will consider the patient benefit, and selected markets consider cost-effectiveness and/or budget impact of a new medicine. Particularly

with the high price tag of some of the newest, most innovative medicines (e.g., newer antibodies, advanced therapies), affordability influences the decision of making a drug available and setting the specifications for use in the healthcare system. The HTAs may also be responsible for the price, subsequent price renegotiations, and price erosion in the case of real-world effectiveness data.

Sponsors of new medicinal products have to meet the criteria from regulators and HTAs in order to be able to make the product available to patients in a particular market. Swift market availability is supported by the generation of both sets of evidence - in parallel when possible and sometimes consecutively - required for positive decisions as early as possible during the drug development process. The regulatory evaluation is supported by guidelines issued by the regulators. The HTA evaluation is based on guidance and criteria for demonstrating clinical benefit, and where applicable social benefit, and economic benefit.

Several initiatives between the EMA and HTAs led up to the implementation of the EMA-HTA parallel scientific advice.[1] The initial focus sought to improve the alignment of information handling and included the assessment of how European Public Assessment Reports (EPARs) provide benefit and risk of medicines by the European High Level Pharmaceutical Forum. Recommendations to improve the HTA effectiveness evaluation were published in a 2008 report.[2] Directive 2011/24 (article 15) also allowed the European Commission (EC) to establish the HTA network (comprised of all member states plus Norway and Iceland) calling for stronger interaction between the EMA and HTAs, timely exchange of information to form stronger synergies, and interactions for all stakeholders.[3] In 2010, the EMA, in collaboration with HTAs, started the pilot program offering parallel advice on evidence requirements for either organization to support market authorization and reimbursement/ pricing decisions. Four EMA-HTA parallel advice procedures were conducted under the Shaping European Early Dialogue for health technologies (SEED) umbrella. The EC-funded SEED project involved a number of HTAs to explore various ways for collaborative early dialogue.

During the EMA-HTA parallel advice meetings, stakeholders can learn about the common and divergent requirements of the agencies involved, to drive a more efficient evidence collection during the development stage.

The EMA-HTA parallel scientific advice procedure follows a four-step process.[4,5] *(Figure 1)*

- **Pre-Notification:** The pre-notification phase starts about six months prior to the intended meeting. During this phase the sponsor engages with the EMA and the chosen HTAs for confirmation of the meeting date, preliminary planning of the type of questions to be asked, and whether a pre-submission teleconference is needed. However, the individual HTAs will decide whether to participate in the parallel scientific advice procedure. The pre-notification phase lasts about six weeks.
- **Pre-Submission:** Submission of the letter of intent and draft briefing document to the EMA and applicable HTAs signals the start of the pre-submission phase. The pre-submission phase lasts about three weeks if the sponsor does not request a teleconference or about seven weeks if a teleconference is requested. A pre-submission teleconference generally is recommended for more complex and/or controversial

Figure 1. Timeline for EMA-HTA Parallel Scientific Advice

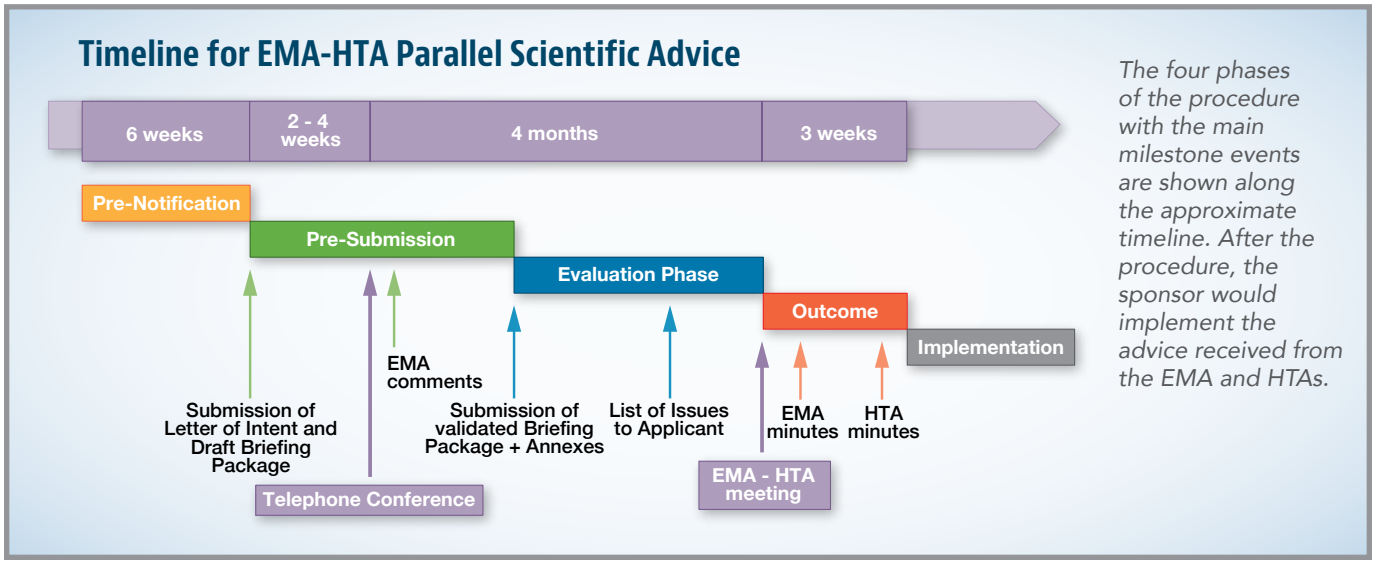
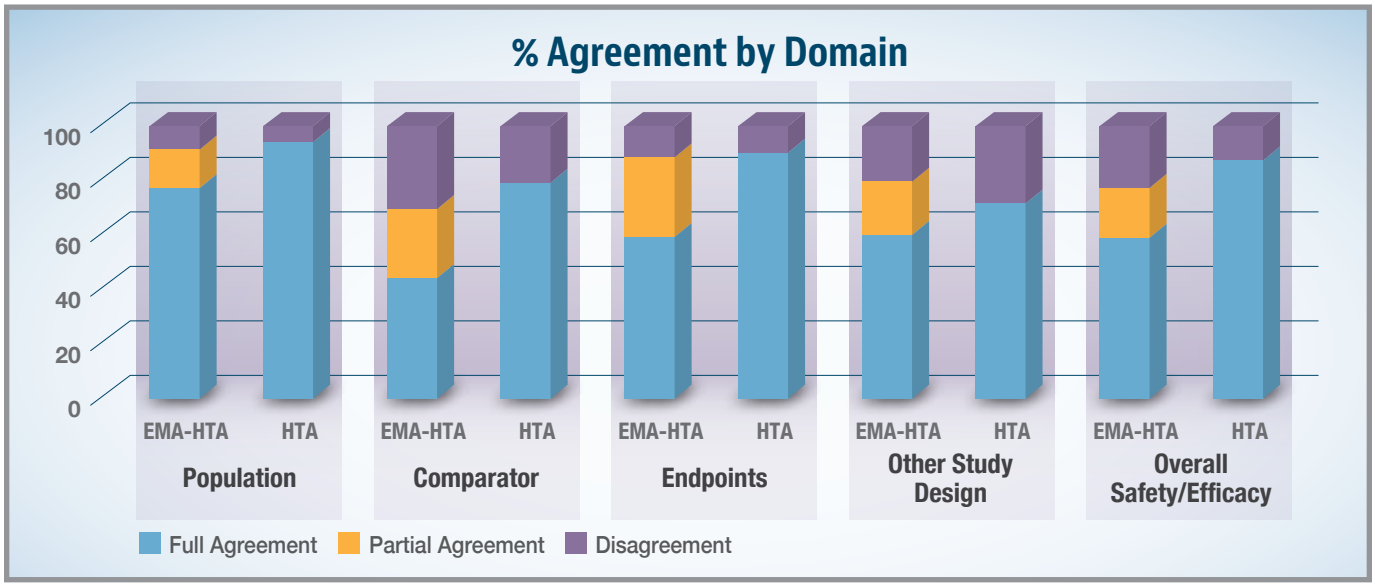


Figure 2. Degree of Agreement between the EMA and HTAs



The agreement in responses to questions was analyzed by domains and evaluated by agreement between the EMA and HTAs (EMA-HTA bars) or among HTAs (HTA bar).

programs. It allows for a discussion of the scope of advice and the appropriateness of the preliminary questions. Any comments on the briefing package following the pre-submission conference will be sent to the sponsor in writing by the EMA. The applicant will then send the final, revised briefing document with all annexes for EMA and HTA validation.

- **Evaluation Phase:** Once the briefing package has been validated, the applicant sends it to the EMA and all applicable HTAs via EudraLink. The submission of the briefing package marks day one of the scientific advice procedure. The EMA and HTAs evaluate the briefing package independently and may send lists of issues to facilitate the discussion. The evaluation phase culminates in a face-to-face meeting to discuss the questions and provide the appropriate feedback on available and further required evidence for positive outcomes in a future marketing or pricing/reimbursement application evaluation.

- **Outcome:** The EMA and HTAs will provide their advice independently. The EMA will provide written meeting minutes within five working days, whereas the HTAs provide their responses within 15 working days in their individually preferred format.

The advice provided by the EMA and HTAs is non-binding.

During the procedure, the sponsor can direct questions to the EMA and HTAs or only to the EMA or the HTAs. Regional and national regulations, as well as other factors, will influence the responses of the HTAs and/or the involvement of further relevant advisory bodies.

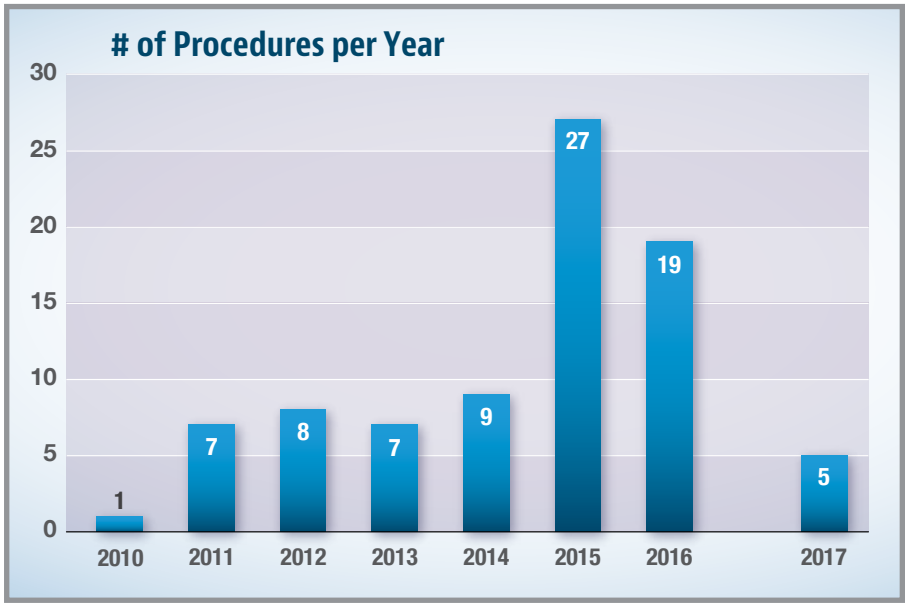
Tafuri, et al.[6] conducted an analysis of the agreement level for 31 EMA-HTA parallel scientific advice procedures conducted between the launch in 2010 and 1 May 2015 (cutoff date for the evaluation of the pilot).[6] The procedures were analyzed based on the meeting minutes and only included those where the evaluation of agreement between EMA and HTA advice was directly possible. A total of 375 questions with 588 answers from HTAs were evaluated for their agreement with the EMA. Some 70 answers were not 'assessable', leaving a total of 518 answers for evaluation. The majority, 61% (317 of 518), were regarded as full agreements, while disagreements only accounted for 16% of the answers (83/518 – *Figure 2*).

The analysis further groups the questions into domains: population, comparator, endpoints, other study designs, etc. The population domain includes questions regarding the inclusion/exclusion criteria, therapeutic indication, biomarkers/subgroups, and extrapolations, while the endpoint domain includes considerations regarding primary efficacy endpoints, patient-related outcomes, health-related quality of life secondary endpoints, and clinical relevance to effect size. Other study design considerations include randomization, treatment duration, dosing, and analysis methods. Tafuri, et al.[6] and the EMA's Report[1] find the highest level of agreement for the population domain with 77% in full agreement and 14% in partial agreement. The lowest level of agreement - 44% in full agreement and 25% in partial agreement

- was found for comparator-related questions. The agreement level in other domains ranged between the population and comparator domains. On the other hand, the HTAs agreed among themselves in 94% of cases for the population domain and 90% for the endpoints. The lowest agreement among HTAs was for other study designs (71%) and again the comparator domain (74%). The agreement level for the remaining domains was in the high 80%.

Since the start of the initial pilot in 2010 and up to March 2017, 92 EMA-HTA parallel scientific advice procedures were conducted (*Figure 3*).[1,7]

Figure 3. Number of EMA-HTA Parallel Scientific Advice Per Year



Although the initial years saw a limited number of procedures conducted, the number of EMA-HTA parallel scientific advice procedures significantly increased in recent years. Five procedures were conducted up to March 2017.

Of the 63 procedures conducted (59 non-SEED and 4 SEED) between 2010 and 31 December 2015, 38% addressed antineoplastic immunomodulating drugs, 13% the nervous system, and 11% were general anti-infectives for systemic use. The remaining therapeutic areas generally accounted for less than 10% of the total procedures. The majority of procedures (31) were conducted for chemical entities (49%), with 27 products (47%) being bio (technology) derived and 5 (8%) being advanced therapies. Patient representatives participated in 40% of the procedures with almost 60% of those (17) stemming from 2015, after the routine invitation of patient representatives was initiated in December 2014.[1]

The National Institute for Healthcare and Excellence (NICE) from the United Kingdom (86%), the Federal Joint Committee (Gemeinsamer Bundesausschuss - G-BA) from Germany (66%), and the Agenzia Italiana del Farmaco (AIFA) from Italy (37%) participated in the most of the 59 parallel advice procedures conducted by the end of 2015.[1] On average, three HTAs (range 1–5) participated per scientific advice procedure.

Of the participating HTAs, NICE was by far the most frequent participant, perhaps at least in part based on their long-standing experience in providing scientific advice to inform sponsors from the value-driven perspective used by HTAs to determine market access. NICE started providing single country scientific advice in 2009.[8] By the end of 2015, NICE had completed 166 scientific advice procedures, including NICE-only scientific advice and single-country Medicines and Healthcare Products Regulatory Agency (MHRA)-NICE scientific advice, and contributed to multi-country scientific advice under the EMA-HTA pilot program. Of the 166 scientific advice procedures conducted by NICE, 146 products remained at the development stage or failed during development. Of the remaining products, 16 products were authorized; one was pending authorization at the time of analysis, and three did not gain a marketing authorization. Of the 16 authorized products, 12 products underwent the post-marketing authorization NICE technology appraisal and nine received a positive opinion. Two evaluations are still ongoing, and for one, NICE could not make a determination since the manufacturer did not submit any materials.

Although it is impossible at this stage to draw conclusions about the success rate of receiving market access due to an HTA scientific advice procedure, the data presented for the NICE procedure would suggest a positive correlation. NICE and EMA have noticed an increased interest in the HTA scientific advice procedure and note that the process and interactions will continue to evolve as stakeholders gain insight into each other's requirements and assessment methods. The EMA's early access tools, PRIority MEdicines (PRIME)[9] and Adaptive Pathways[10] (see also *PRIME turns One* article in this issue) recognize the importance of receiving HTA advice at an early stage during drug development to optimize evidence generation to support marketing authorization, as well as market access, through the pricing and reimbursement determination. ■

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