To Seek or Not to Seek Parallel European Medicine Agency and Health Technology Assessment Scientific Advice?

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KEY POINTS . . .

Pharmaceutical manufacturers are often challenged to balance the evidentiary expectations of regulatory and health technology assessment bodies with time and resource constraints.

The parallel scientific advice program provides the opportunity for early, simultaneous engagement with regulatory agencies, HTA bodies, and other key stakeholders.

In order to maximize the utility of parallel advice, strategic planning and timing of its reception is key.

The parallel scientific advice (PSA) process allows pharmaceutical developers to receive simultaneous feedback from both regulatory and health technology assessment (HTA) bodies on their development plans for new medicines. This process seeks to reduce redundancies and identify trade-offs due to overlap between the two entities, potential for conflicting expectations for evidence and data analysis along the product life cycle, duplication of effort, and delayed patient access. This article summarizes the pros and cons of seeking advice from regulatory and HTA bodies separately versus in parallel.

Regulatory versus Reimbursement Issues

Pharmaceutical companies are faced with many challenges when designing global clinical development programs for their products. Multiple objectives need to be addressed to achieve regulatory approval, including safety, efficacy, health outcomes, pharmacokinetics/pharmacodynamics, biomarkers, and subgroup analyses. A robust clinical program is ideal but is typically limited by time and financial resources.

Aside from seeking regulatory approval from the European Medicine Agency (EMA), the pharmaceutical companies assume a significant burden to synthesize sufficient evidence to position their products favorably for reimbursement purposes by the HTA bodies. Global manufacturers must aim for a balance between meeting requirements from the EMA and the HTA bodies while doing so in a feasible manner given time and financial constraints.

EMA Advice for Regulatory Approval

It is standard practice for pharmaceutical companies to seek EMA advice on the design of their clinical trial programs. Recommendations that arise from the EMA are "binding," meaning that the pharmaceutical manufacturers must do everything that the EMA asks in order to get regulatory approval for their products in a given country/region.

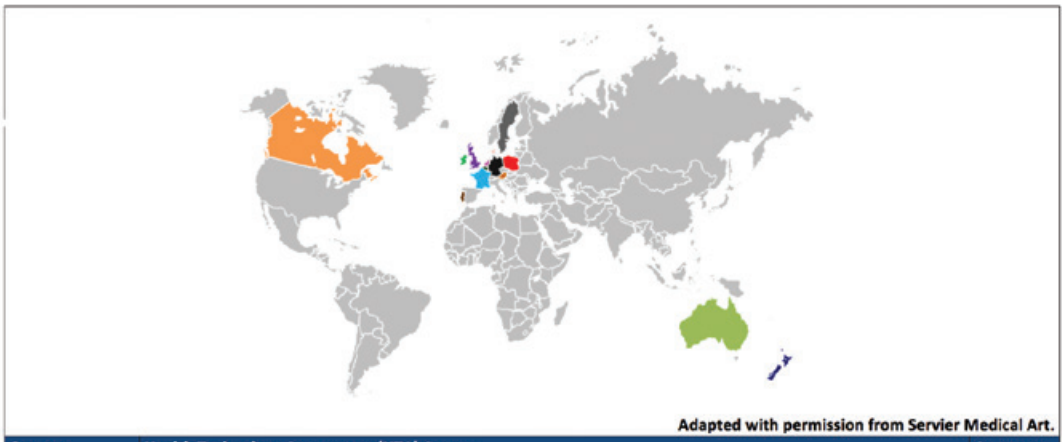
The EMA focuses on the safety and efficacy of a medication in order to grant market authorization. The question that the EMA seeks to answer is 'Does the new medicine work?' Once the efficacy data based on specific patients, setting(s), comparator(s), measures(s), and follow-up are established, the question then becomes: Is the balance of risk to benefit acceptable (i.e., is it sufficiently safe given the expected health benefits)?

Requirements for regulatory approval of a new pharmaceutical product are generally consistent for FDA and EMA, but HTA requirements are highly variable. In the United States, the Food and Drug Administration (FDA) is becoming more "adaptive" by placing a strong focus on clinical context. Strides have been made to establish an "evolving approval" process based on safety, efficacy, and quality. As a result, the FDA has created a breakthrough therapy designation to address unmet needs. This breakthrough therapy designation is granted based on preliminary clinical evidence of substantial improvement over existing therapies for drugs intended to treat a serious or life-threatening disease [1]. In addition, the FDA has instituted an accelerated approval process for medications for serious conditions using surrogate endpoints. Both the breakthrough therapy designation and the accelerated approval process have sped approval timelines, but these have also created challenges in satisfying HTA evidence requirements at the time of launch. Some would argue that these approval processes increase the need for seeking HTA scientific advice.

HTA Scientific Advice Programs for Reimbursement

In a similar fashion, pharmaceutical companies may elect to arrange briefings through HTA Scientific Advice Programs. These advice programs are intended to foster scientific collaboration to ensure appropriate evidence collection. HTA advice is "non-binding," so the pharmaceutical companies are not required to address all of >

Figure 1. Selected HTA Agencies [2]



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Country	Health Technology Assessment (HTA) Agency	Acronym
Australia	Medical Services Advisory Committee	MASC
Australia	Pharmaceutical Benefits Advisor Committee	PBAC
Austria	Gesundheit Oesterreich GmbH	GOEG
Belgium	Belgian Federal Health Care Knowledge Centre	KCE
Canada	Canadian Agency for Drugs and Technologies in Health	CADTH
Canada	Medical Advisory Secretariat within the Ontario Ministry of Health and Long-Term Care Health Strategies Division	MAS
Denmark	Danish Centre for Health Technology Assessment	DACEHTA
France	Haute Autorité de Santé	HAS
Germany	Institute for Quality and Efficiency in Health Care	IQWiG
Ireland	Health Information and Quality Authority	HIQA
Netherlands	Dutch Health Care Insurance Board	CVZ
New Zealand	Pharmaceutical Management Agency of New Zealand	PHARMAC
Poland	Agency for Health Technology Assessment in Poland	AHTApol
Portugal	National Authority of Medicines and Health Products	INFARMED
Scotland	Scottish Medicines Consortium	SMC
Sweden	Tandvårds- och läkemedelsförmånsverket	TLV
United Kingdom	National Institute for Clinical Excellence	NICE
Wales	All Wales Medicines Strategy Group	AWMSG

the recommendations in order to achieve regulatory approvals for their product in a given market region. Rather, it serves as a forum for feedback on how the clinical trial program may answer (or not answer) clinical and economic questions related to outcomes, patient population, and selection of comparator(s). However, these meetings are fee based and may present considerable preparation time and expense to the pharmaceutical manufacturer, particularly when multiple sessions (e.g., in different countries) are requested.

The HTA bodies in each country focus on reimbursement. The question that the HTA seeks to answer is 'Does the new medicine work in practice?' In addition, "how does the new medication compare to existing treatment in terms of costs and outcomes?"

In recent years, HTA agencies have become more rigid about the evidence expectations. The role of the HTA agencies is inherently different from that of a regulatory perspective. The HTA agencies serve as the final gatekeeper to ensure that a new product will appropriately use limited health budgets compared to other treatments available for funding. One way that HTA bodies try to ensure cost-effective use of treatments is by limiting the population that will receive the treatment to those for which there is good evidence of efficacy, normally following

> "Although it may be impractical to expect full alignment between EMA and HTA scientific advice, there are benefits in having consolidated insights from all stakeholders."

the inclusion/exclusion criteria of the trial. Thus, HTA agencies and payers often will not extrapolate clinical endpoints to patient benefit or to populations outside the clinical trial. Some payers will allow initial coverage while the pharmaceutical manufacturer gathers additional evidence. Other payers have suggested pay-for-performance arrangements. Some of the more prominent HTAs are shown in Figure 1, with their respective regions.

The caveat to HTA scientific advice is its specificity for a given market region; for instance, the requirements for Germany may differ vastly from the requirements for the United Kingdom. There are some very clearly outlined and established procedures for specific key markets. Even the stated purpose of each organization differs (see Table 1). As a result, it is often difficult to achieve an aligned understanding of the type of evidence required among the different HTA countries/regions. This is partially due to salient variations in the application of population health, since financing for medical coverage heavily hinges on taxation. Factors that local HTAs need to consider in their decision making include local clinical practice, local burden of disease and unmet need, local health priorities, cultural values, "fair access," legal constraints, relative costs and cost effectiveness, and affordability.

The primary approach for HTA evidence requirements may be any one of the following:

- ***Therapeutic benefit assessment:*** Clinical benefits of therapy assessed and price negotiated by a single, central organization (Arzneimittelmarkt-Neuordnungsgesetz [AMNOG])
- ***Formal health economics:*** Pharmacoeconomics data utilized in a national price regulation scheme to control reimbursement and drug utilization (NICE, SMC, and AWMSG)
- ***Decentralized pricing/reimbursement negotiations***: Primary focus on price and reimbursement control, with negotiations at the institutional and regional levels

Table 1. Comparison of the Stated Purpose of Various HTA Agencies [3-5]

Australia	Canada	United Kingdom	Scotland	Sweden	Netherlands
PBAC (1987)	CADTH (1989)	NICE (1999)	SMC (2002)	TLV (2002)	CFH at the CVZ (2005)
The PBAC ensures that all Australian residents have access to necessary and life-saving medicines at an affordable price	CADTH is an independent, not-for-profit organization responsible for providing health care decision makers with objective evidence to help make informed decisions about the optimal use of health technologies, including drugs, diagnostic tests, and medical/dental/surgical devices and procedures. Among other things, we: • Help health care decision makers keep pace with technological change • Review and make recommendations on new and existing health technologies • Undertake comprehensive HTAs that leverage the full depth and power of today's evidence-rich environment • Examine practices, processes, and protocols to provide a better understanding of the current landscape in health care • Scan the horizon to give health care leaders a glimpse of what the future might bring	NICE's role is to improve outcomes for people using the NHS and other public health and social care services. We do this by: • Producing evidence-based guidance and advice for health, public health and social care practitioners • Developing quality standards and performance metrics for those providing and commissioning health, public health, and social care services • Providing a range of information services for commissioners, practitioners, and managers across the spectrum of health and social care	The remit of the SMC is to provide advice to NHS Boards and their ADTCs across Scotland about the status of all newly licensed medicines, all new formations of existing medicines and new indications for established products (licensed from January 2002)	The TLV is a central government agency whose remit is to determine whether a pharmaceutical product or dental care procedure shall be subsidized by the state. It also has the responsibility for monitoring profitability on the pharmacy market. The TLV strives to create the greatest possible improvements in health using the tax revenues that are allocated for medicines and dental care	Common tasks include the following: • Provide advice on the sum of the contributions and the budgets for health insurers • Manage contribution funds and distribute them over the health insurers • Provide guidelines for carrying out new and existing legislation • Monitor adherence to the regulations of international conventions • Keep care insurers, care providers, and citizens informed; • Monitor feasibility and efficiency of government plans; • Detect and report bottlenecks in the practice of implementation

CADTH indicates Canadian Agency for Drugs and Technologies in Health; CFH, Commissie Farmaceutische Hulp; CVZ, Dutch Health Care Insurance Board; NICE, National Institute for Clinical Excellence; PBAC, Pharmaceutical Benefits Advisor Committee; SMC, Scottish Medicines Consortium; and TLV, Tandvårds- och läkemedelsförmånsverket.

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For details regarding any specific HTA guidelines, refer to www.ispor.org/peguidelines/index.asp for a review and classification of approximately 35 guidelines. The purpose of these guidelines is for reimbursement submissions (both mandatory and voluntary submissions) and general improvement of methods used in evidence synthesis. It has been reported that 75% of methodological principles across various HTA guidelines are in agreement [5]. The main difference between health economic assessment frameworks revolve around the study perspective (e.g., inclusion of non-health care costs), measurement of economic outcomes (e.g., assessment of only clinical outcomes, use of quality-adjusted life years [QALYs], use of stated preferred measures), handling uncertainty, and role of pharmacoeconomic modelling. Variations in HTA guidelines exist, particularly in the level of rigor required for evidence even for closely related markets such as England and Scotland. In a comparison of decisions made by NICE and the SMC (Scotland), 25 cases were examined involving 22 medications in 18 indications [6]. Important differences were noted between the two HTA agencies, with NICE placing more restrictions on the use of technologies.

Traditionally, HTA advice is sought for individual markets. Discussions can be tailored for local evidence requirements, and regional variation in standards of care and health care financing can be accounted for. However, there is a significant investment in time and expenditures to engage multiple agencies as separate, standalone meetings. When conflicting advice arises from different markets, it is a challenge to simultaneously satisfy the evidence requirements of different agencies.

Parallel Scientific Advice on Relative Clinical Efficacy/Effectiveness Questions

Rationale

Early engagement and scientific advice with regulatory agencies, HTA bodies, and other stakeholders can be a key driver of patient access and commercial success. The pharmaceutical industry's ability to deliver valuable health technology for areas of high-unmet need is dependent on reliable and valid payer signals in terms of pricing and conditions allowing for reimbursed access. As a reflection of societal preferences, it is important to assess criteria for access required by HTA bodies *vis a vis* those of regulators.

Process

In 2010, the EMA implemented a pilot project of PSA to allow pharmaceutical developers to receive simultaneous feedback from both regulatory and HTA bodies on their development plans for new medicines. This pathway seeks to bring all stakeholders together early in order to optimize development plans and, ultimately, to improve access for patients. Since implementation of the pilot project, there have been 31 procedures as of 2015 [7]. Topics of drug development have included diabetes, heart failure, Alzheimer's disease, oncology, asthma, chronic obstructive pulmonary disease (COPD), orphan conditions, etc. Due to the overlap between regulatory and HTA interface, challenges along the product life cycle include the potential for conflicting expectations for evidence and data analysis, duplication of effort, and delayed patient access (see Figure 2). The PSA process seeks to reduce these redundancies and identify trade-offs. The commonalities important to both regulators and HTA bodies in these discussions have included choice of comparators, clinical endpoints, duration of the trial, and patient population. Topics of interest unique to the HTA bodies include cost-effectiveness models, impact on the caregiver, and modelling the natural course of the disease. >

Figure 2. Regulatory-HTA interface along the product life cycle [8]

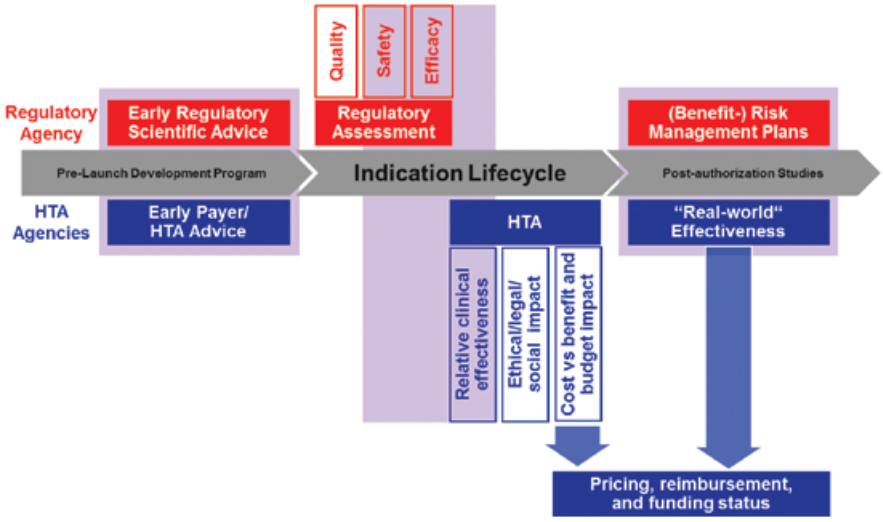

Table 2. Pros and Cons of Seeking and Obtaining Parallel EMA and HTA Consensus

Pros	Cons
- Reduction in delays to patient access as advice for different data needs is sought in parallel rather than in sequence	- Regulatory capture may present a conflict of interest as early interactions can imply that regulatory and reimbursement authorities are becoming co-developers of medicines
- Contemporaneous evolution of development to satisfy all parties before development plans and HTA and EMA decisions have been finalized	- Additional financial hurdles for pharmaceutical companies to ensure meeting additional demands of parallel advice
- Minimization of discrepancies and identification of trade-offs	- No process for bridging divergences that are identified since all HTA bodies have different priorities
- One collaborative discussion with simultaneous feedback	- Clear output from HTA advice needed
- Input on which HTAs are invited	- Timing of engagement may be difficult as some HTAs are not willing to meet pre-phase II data
- 4-hour face-to-face meeting that allows for open discussion with expression of personal opinions	- Role of HTA bodies as final gatekeepers may be undermined with early involvement

Pros and Cons

One of the potential drawbacks with parallel scientific advice from EMA and an HTA is that there is potential for conflicting regulatory versus affordability recommendations. For instance, in Germany where the HTA focus is on evidence-based medicine, the Institute for Quality and Efficiency in Health Care (IQWiG) indicated, "It is very difficult to protect the public and the individual patient from the threats to health and to the health budget (simultaneously) by the wide use of drugs with unknown benefit-harm relation [9]."

In spite of this potential contention, the rationale for parallel EMA-HTA advice includes the fact that new medicines do not reach all patients in need. By aiming to bring all stakeholders together early, there is a greater likelihood that the clinical development program can be appropriately tailored to address the different evidence requirements (benefit risk required by regulators versus benefit required by HTA) [10]. Ultimately, the goal is to improve access for patients.

Although it may be unrealistic to expect full alignment between EMA and HTA scientific advice, there are benefits in having all the stakeholders in the same room, to at least hear firsthand the concerns expressed by the other party. With a coordinated decision on how to approach the clinical development program, the upside of reaching an agreement is consolidating the evidence requirements, avoiding the need to invest research and development funds in areas of less interest. The risk of joint advice is settling on an "average" evidence requirement that ultimately does not meet any market's specific needs. Note, therefore, the advice is provided "in parallel" which explicitly allows diverging view to be captured and fed back to the company. The company then can decide if and how to incorporate diverging evidence requirements. Additional pros and cons of seeking and obtaining parallel EMA and HTA consensus are illustrated in Table 2.

With parallel EMA-HTA scientific advice, the pharmaceutical manufacturer expects to be able to align the clinical trial design, specifically concerning endpoints, comparators, patient inclusion, and study duration. Informed decisions can be made with better and earlier understanding of all stakeholders' concerns, allowing for a more complete understanding of the opportunities, limitations, and tradeoffs of potential clinical evidence-generation plans for a new medication. Although not legally binding, parallel EMA-HTA scientific advice enables the pharmaceutical manufacturer to get some "endorsement" for the clinical evidence program.

Timing: When Should Parallel EMA-HTA Scientific Advice Be Sought?

When parallel EMA-HTA scientific advice is sought very early (during the nonclinical proof-of-concept stage), the advice typically is limited to high-level responses regarding the general study design and views on what would be needed to demonstrate benefit/risk and added value [10].

When parallel EMA-HTA scientific advice is sought later (prior to phase III trials), the responses will be more precise regarding endpoints and comparators, how much is required, and what is feasible and focused on pharmacoeconomic questions [10].

Case Examples

Several reports of successful compromises in product development have resulted from parallel EMA-HTA scientific advice thus far [10]. In one instance, a company preparing to launch a novel therapy for COPD proposed utilizing a licensed comparator in its pivotal trial. The EMA agreed with this proposal; however, an HTA representative who was present requested a different comparator not licensed for use, yet routinely used. The solution was to introduce a new arm of the pivotal study to include both comparators, meeting the recommendations from both advisors. In another case, a pharmaceutical company had developed a novel therapeutic as a first-in-class treatment for a rare oncology. With no other product previously licensed for this indication, the company proposed standard of care as its comparator and the EMA agreed. However, other HTA bodies requested the use of an off-label,

active comparator and the pharmaceutical company opted for this pathway [10].

Key Insights on Parallel EMA-HTA Scientific Advice

Rather than a formal setting, these meetings have become more of a dialogue, with each party having the opportunity to highlight their expectations. The advice itself is usually very constructive, as all parties are generally willing to consider alternative designs with its implications. At times, expectations from different parties reach alignment. The most useful advice is related to clinical evidentiary standards, as this topic is a common interest among different HTA agencies.

Planning is critical, as it is becoming increasingly more difficult to schedule these parallel EMA-HTA Scientific Advice meetings. HTA agencies have limited resources and are often challenged by the need to prioritize their workload.

Shaping European Early Dialogues (SEED) for health technologies has been a European Commission-sponsored self-sustaining model most likely depending on a fee for service. This was limited to a certain number of pilots, concluded in 2015. [11,12]. There will be a new process that involves a standing committee for early dialogue and scientific advice, which is set by a dedicated work stream in EUnetHTA Joint Action 3 with focus on pre- and post -launch evidence requirements. The new process is anticipated to build on the experience gathered in SEED and the EMA parallel scientific advice process.

Summary

There are three concepts to remember when it comes to seeking early regulatory and reimbursement advice as listed in Figure 3.

Whether the pharmaceutical manufacturer decides to seek advice from EMA and HTA separately versus in parallel, either process can work; assess the pros and cons with the team. It may be most critical to seek parallel EMA-HTA scientific advice when there is a significant need to clarify and potentially align clinical evidentiary expectations of EMA and HTA agencies.

Planning is critical because timing of the advice matters. If sought too early, signals that may arise after the clinical trials have begun may not be addressed. If sought too late, there may be insufficient time to complete the clinical trials before the target market date. Note that with complicated clinical development programs, it may be challenging to address both regulatory and HTA questions in one session; multiple HTA scientific advice sessions may be necessary. It remains difficult to engage specific HTA agencies considered most relevant in light of the questions, anticipated business case, and within the timeframe when you need it given their limited resources that are currently dedicated to EU-level early scientific advice activity.

Continue to engage with national HTA agencies in order to understand how to best address the vast majority of other context-specific aspects of HTA (e.g., health economic modeling questions [HTA in its "true" sense]). There will be many facets of the advice that is given. Remember—if you ask for the advice, be prepared to use it. The best way to approach this is to focus on actionable items.

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Additional information:
The preceding article is based on an Issues Panel given at the ISPOR 18th Annual European Congress.

To view the authors' presentation, go to: https://www.ispor.org/Event/ReleasedPresentations/2015Milan#issuepanelpresentations

Figure 3. Key Concepts for Parallel EMA-HTA Scientific Advice