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EARLY DIALOGUE WITH HEALTH TECHNOLOGY ASSESSMENT BODIES: A EUROPEAN PERSPECTIVE

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Introduction: Evidence requirements may differ across HTA bodies, and so pharmaceutical companies must plan to synergize their evidence generation strategy, across global regulatory and HTA bodies. Until recently, companies had no official platform to discuss the clinical development of a drug with HTA bodies; however, this is changing.
Objectives: To achieve broad usage in the EU, products must achieve both regulatory and reimbursement approval, the latter of which is based on HTA appraisal in many markets. The objective of this study is to present and evaluate the different options available for early HTA consultation (during drug development/Phase III) in the major European markets from the industry perspective.
Methods: An exploratory (nonsystematic) literature review was performed to identify the European markets offering early HTA consultations, and each process was analyzed using a set of predefined metrics that are relevant to industry (the ability to consult with the regulatory body in parallel, consultation fees, length of consultation meeting, language of consultation meeting, maximum number of pharmaceutical company employees attending, procedural timelines, nature of data for which consultative advice can be sought, the output of the process, and the ability to involve external experts).
Results: Four different types of early HTA consultation processes were identified across the major European HTA markets. The nature of these processes varied in terms of the types and number of questions that can be addressed, the length of the meeting, the reporting output, and the ability to involve external experts.
Conclusions: The availability of various options for early HTA consultation may help to avoid a mismatch between the evidence generated by means of a product's clinical development program, and the evidence expected by HTA bodies and payers, which can facilitate the pricing and reimbursement process upon a product's market authorization.

Keywords: Reimbursement, Decision making, Technology assessment, Biomedical/economics, Health policy/economics, Insurance, Health, Reimbursement/economics, Scientific consultation, Early dialogue, Clinical development, Market access

Until approximately 10 years ago, reimbursement of new drugs in most European countries followed its regulatory approval relatively easily, as the requirements for reimbursement were quite straightforward. More recently, however, with major European markets facing budget constraints, obtaining access at the country level—at a price reflective of a drug's innovativeness and clinical benefit—is increasingly challenging. Reimbursement decisions by European payers are typically driven by health technology assessment (HTA) bodies' appraisals (Table 1), each of which has imposed a set of evidence requirements that can be divergent from the requests of other HTA bodies and the regulators.

If pharmaceutical companies do not effectively plan for the evidence requirements stemming from these HTA bodies, it is possible that a drug may yield a negative return on investment, as reimbursement and patient-level access is not optimized: a negative HTA appraisal can lead to a new agent's delay in launch, or even its complete withdrawal from the market. Two recent examples highlight this phenomenon. While ipilimumab received EMA approval July 2011 for metastatic melanoma (1), due to initial unfavorable HTA assessments by the Scottish Medicines Consortium (SMC) (2) and the National Institute for Health and Clinical Excellence (NICE) (3)—which were subsequently overturned (4;5)—the product essentially did not receive full access in Great Britain until 18 months following marketing authorization. In Germany, linagliptin's manufacturer failed to submit data in its reimbursement dossier for type II diabetes that aligned with the *Gemeinsamer Bundesausschuss* (G-BA)'s choice of comparator (6); faced with therapeutic reference pricing to a generic agent, the company decided not to launch the molecule in Germany (7). It seems clear that explicitly planning for anticipated payer evidence requirements during the preparation of a product's clinical development plan can serve as an opportunity to both improve patients' access to new innovations and reduce an asset's commercial risk.

However, individual HTA bodies may have differing requirements (e.g., in terms of how evidence should be presented, which data should be included, and whether a strong emphasis is placed on Patient Reported Outcome (PRO) data), and so pharmaceutical companies must plan accordingly to synergize these needs, across both regulatory and HTA bodies globally. Some of the more important aspects underpinning positive and

Table 1. HTA Bodies Assessed in this Report

HTA body	Full name of HTA	Country/IES	Remit
NICE	National Institute for Health and Clinical Excellence	United Kingdom (UK)	Provides advice for England and Wales; well-reputed institution with global impact; positive recommendation means *proposed* reimbursement on a local level
G-BA	Gemeinsame Bundesausschuss (Federal Joint Committee)	Germany	Provides reimbursement recommendations for Germany; positive recommendation means reimbursement
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)	Germany	Provides advice for Germany; Well-reputed institution with global impact; does not make reimbursement decisions
TLV	Tandvårts och LäkemedelsförmånsVerket (Dental and Pharmaceutical Benefits Agency)	Sweden	Provides advice for Sweden; positive recommendation means reimbursement
CVZ	College voor Zorgverzekeringen (Health Care Insurance Board)	Netherlands	Provides advice for the Netherlands; positive recommendation means reimbursement
HAS	Haute Autorité de Santé (French National Authority for Health)	France	Provides reimbursement recommendations for France; positive recommendation means reimbursement
EUnetHTA	European Network of HTAs	Pan-EU	Recommendation needs to be adapted to country recommendation by local HTA agency in order that advice is considered for reimbursement purpose.
EMA/HTAs	European Medicine Agency/European HTAs	Europe	Parallel Regulatory and HTA advice where EMA allows for invitation of HTA experts, aiming to let marketing authorization and reimbursement authorization coincide

Note. Source: Agency Web sites.

negative HTA decisions are described in publically available sources (8), and typically focus on ensuring appropriate endpoint, comparator, and trial site selection. The hurdles at the HTA level tend to be higher than those at the regulatory level: for example, while HbA1c reduction is a commonly accepted endpoint in the diabetes space by the EMA, recent decisions in Germany indicate this endpoint is unacceptable to G-BA due to a lack of prospective correlation between HbA1c and downstream hard endpoints (6). Each of these evidence dimensions represents a potential point of disagreement with the HTA agency, should the company not plan accordingly; these requirement dimensions therefore have profound potential implications on a product's evidence generation strategy and consequently on its pricing and reimbursement outlook.

Given these concerns, some companies already solicit HTA bodies' advice early on in a product's development to help internal decision makers reduce the risk of the drug's clinical program (9), especially before proceeding with the execution of a drug's Phase III trial program, which can cost upward of €100 million (10). Since the end of 2010, some European HTA bodies have started to formalize such early HTA consultative opportunities for companies seeking advice for their development-stage drugs, with the objective to increase the likelihood that the company's planned evidence generation strategies will meet payer evidence requirements. The objective of this study is to present and evaluate the different options available for HTA consultative advice in the major European markets, using the perspective of the pharmaceutical industry.

METHODS

An exploratory search for information around the early HTA consultative process, as well as for examples of companies having engaged in this process, was conducted using the following approach:

First, to understand which established European HTA bodies conduct early advice consultations, the Web sites of the major national-level HTA bodies in Europe (Table 1) were searched. Countries assessed included only those European markets with national HTA decisions that are publically available in English. Regional HTA agencies (e.g., Agencia de Evaluación de Tecnologías Sanitarias de Andalucía in Spain) or HTA agencies from countries with fewer than six million inhabitants were not included within this assessment.

Second, the EMA and the EUnetHTA Web sites were solicited for information on pan-European HTA processes.

Third, a pragmatic review of the literature was performed to elicit specific examples of companies publishing their early HTA consultative efforts by means of the search strategy described in Supplementary Figure S1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000713. Exclusion criteria included studies published before 2005, or

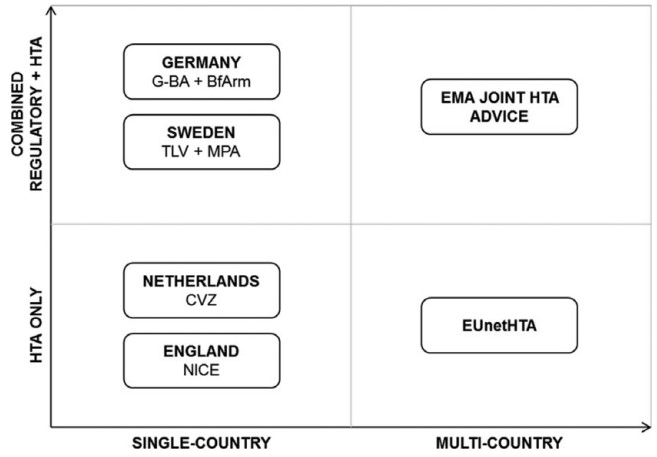

Figure 1. Identified models for HTA advice.

returned citations that were considered irrelevant to the early HTA consultation process (for example, "Adapative e-learning to improve dietary behavior"). 29 citations were identified by means of this search, and after applying the exclusion criteria as described above, four references were reviewed in-depth. This pragmatic literature review was performed by one reviewer.

An "early HTA consultative pathway" was characterized as a defined process by which manufacturers can seek scientific advice for an asset still under development (i.e., in Phase II or Phase III clinical trials). Once an early HTA consultative pathway was identified, information around the following parameters was collected (11–14): the ability to consult with a HTA body in parallel with the relevant regulatory body, consultation fees, length of consultation meeting, language of consultation meeting, number of pharmaceutical company employees able to attend, procedural timelines, nature of data for which consultative advice can be sought, the output of the process, and the ability to involve external experts.

RESULTS

In the search, eight HTA bodies were identified that met the selection criteria (Table 1). Amongst those, four main models for companies seeking early consultative HTA advice were identified (Figure 1) and will be presented through examples: single-market HTA advice, single-market parallel regulatory and HTA advice, multi-country HTA advice, and parallel regulatory and multi-country HTA advice. The respective capabilities and capacities of each model varied, and are reviewed according to the parameters as summarized in Table 2 and described further below.

Single-market HTA Advice: NICE's example

In October 2010, NICE published their procedure for companies seeking HTA advice for drugs in development. Following the need highlighted by the pharmaceutical industry, NICE was the first HTA body to establish a formal process for early HTA consultation. The stated objective of NICE's scientific advice is to increase the likelihood that clinical trials and other research activities undertaken during drug development will meet NICE's eventual evidence requirements.

Throughout the consultation process, NICE proposes the use of a 'briefing book', a document presenting the company's key questions for the asset and the corresponding company position for each question. Questions related to any parameter within the scope of NICE's HTA are accepted. NICE does not limit itself to input from its internal experts, but invites external experts to provide specific analysis and feedback on some topics, allowing for a high quality consultation.

It can cost up to EUR 60,000 for a company to access NICE's advice during this process. According to NICE, this fee structure is determined by the complexity of the advice request and the number of questions asked by the company, qualifying the project as small, medium or large. Therefore, careful time and consideration should go into the questions proposed and the development of the briefing book. Furthermore, NICE has a limited number of early consultation slots available, and so it is advisable to plan for this interaction well in advance. The consultation meeting itself is conducted in English and lasts approximately 3 hours.

The ultimate output of this consultation consists of NICE's recommendations around optimal trial design, comparators, patient follow-up, the appropriateness of outcomes data collected, the economic modeling approach and the collection of relevant costing data. NICE will provide the company with a comprehensive written report of the topics discussed during the consultation.

Single-market Parallel Regulatory and HTA Advice: G-BA / BfArM's example

As of September 1, 2012, it is mandatory for companies seeking early HTA advice from the G-BA to do so in parallel with regulatory advice from *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArm). Key areas to consult upon with G-BA include the use of surrogate endpoints, and the company's validation plan if the surrogate endpoint is not yet likely to be considered adequately validated by *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (*IQWiG) and / or the G-BA. Possible subgroup analyses—and especially their statistical analysis plan—are recommended to be discussed as well. Given recent market access issues in Germany (6), perhaps the most important question in the mind of many companies is the G-BA's preferred choice of comparator, which is another aspect of the development plan upon which the G-BA is willing to provide advice. For companies seeking to undergo this process, it is important to note that the G-BA and IQWiG have communicated that they will not alter their recommendations if regulatory requirements differ from their own due to a different understanding of "benefit".

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Table 2. Consultation Findings by HTA Body

	GER G-BA / IQWiG	SWE TLV	UK NICE	NLD CVZ	Pan-EU EUnetHTA	Regulatory / EU HTA EMA / HTAs
Conjoint regulatory advice	Mandatory	Mandatory	Possible	Not possible	Not possible	Possible
Consultation timelines (months)	2	2	4	2	4.5	4.5
Fees (Euros)	10,000 – 20,000	5,000	20,000 – 60,000	0	0	20,000 – 60,000
Output	Meeting minutes	Meeting minutes	Report	Report	Meeting minutes	Variable based on HTA body
Ability to assess health economics	N / A	Yes	Yes	Yes	Yes	Variable
language of meeting	German	English	English	English	English	English
Length of meeting	1 to 2 hours	1.5 hours	~3 hours	Unknown	3 hours	~4 hours
Number of 'company attendees' allowed	4 to 6	No limit	Variable	1 to 2	<10	Variable
Involvement of external experts possible	No	No	Yes	No	No	No

Note. This table excludes the HAS, which was not found to have individual early consultation pathways, although the HAS does participate in the pan-EU procedure. Source: Agency Web sites.

Similarly to NICE, the G-BA also requests that the company utilise a briefing book during the consultation process, which must be submitted between 8 and 12 weeks before the meeting. The fee for the consultation has been estimated at EUR 10,000–20,000 depending on the number of questions asked by the company; further costs may be incurred for the translation and preparation of the briefing book in German. At the moment, only the questions and company position need to be translated (~EUR 2.00 per line), while all other documentation can be submitted in English. Given these considerations, the budget for external support can be up to EUR 50,000.

The G-BA meeting itself typically lasts one to two hours, and is preferably conducted in German. A maximum of six company attendees are allowed to attend the meeting. At the end of the process, a written report of the interaction (in German) is provided by the G-BA, as well as a possible written agreement on further updates and study design. It is presently unclear how the G-BA might react if their early consultation recommendations are not factored into the asset's clinical development program; however, past precedence has shown that companies declining to build their dossier around the G-BA's choice of appropriate comparator have faced difficulties in the pricing and reimbursement process (6), although it is unclear whether these companies had taken advantage of the early consultation process.

Multi-country HTA Advice: EUnetHTA Joint Action 2 Pilot

In March 2012, the European network for HTA "EUnetHTA" communicated their plan to establish a pan-European advice process for drugs in development, led by the French HTA body (*Haute Authorité de Santé*, HAS). This project aims to combine the efforts of the majority of European HTA bodies, with four pilot assessments completed so far; six further pilots are scheduled for completion by November 2013 (15;16). Currently, representatives from the following HTA agencies are participating in the pilots: Italy (Agenzia Italiana del Farmaco, AIFA), Germany (IQWiG), Austria (Hauptverband der Österreichischen Socialversicherung, HVSVT), Sweden (TLV), Netherlands (College Voor Zorgverzekeraars, CVZ, now called Zorginstituut Nederland, ZIN), Belgium (Federaal kenniscentrum voor de gezondheidszorg KCE, Institut National d'Assurance Maladie, INAMI), France (HAS), and the UK (NICE). Other HTA agencies might also express their wish to take part in this exercise.

EUnetHTA has published a draft procedure detailing the desired content and format for the company briefing book, timelines and administrative requirements (15), which are very similar to the NICE requirements described above. At the present time, no fees have yet been established for this process. At least 2 months before the face-to-face meeting, a complete briefing book should be sent to all participating HTA bodies. Two meetings are included throughout this process—one teleconference to facilitate a preliminary discussion of the relevant issues, and a second in-person meeting with the HTA bodies involved to focus on addressing the most pertinent issues coming out of the teleconference. The meeting with the company lasts for 3 hours, and the preferred language of the interaction is English. No more than ten company attendees may participate in the consultation. At the end of the process, the minutes from both meetings are produced and shared by the pharmaceutical company, which are reviewed and validated by all HTA body participants.

Parallel Regulatory and Multi-country HTA Advice: EMA Pilots

In this procedure, the HTA bodies from which to solicit advice are chosen by the company, and HTA advice is given in parallel with the EMA's regulatory scientific advice procedure. If this parallel procedure option is chosen, the EMA recommends having at least two HTA bodies represented.

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To participate in this procedure, the company must prepare a briefing book addressing the company positions for the asset and distribute this material to the EMA and all HTA bodies involved; Germany and Sweden request that these materials be translated into the local language. Manufacturers should allow one additional month for this parallel process as compared to the CHMP regulatory scientific advice procedure alone, resulting in a total of 4.5 months from start to finish. Fees for this procedure will vary based on the HTA bodies involved, but can be up to EUR 20,000 per HTA body. The meeting itself lasts approximately four hours, and the type of output will depend on the HTA bodies involved. The company will circulate minutes to all participants and some HTA bodies may return clarifying comments on the distributed minutes, whereas others may independently produce a full report.

To date, eighteen pipeline assets have undergone this process (17). From mid-2010 through to early 2012, six of these efforts were facilitated by Tapestry Networks (18): three companies, AstraZeneca, GlaxoSmithKline, and Johnson & Johnson took part in this pilot consultation program assessing joint regulatory and HTA advice for six assets spanning several therapeutic areas, including type II diabetes, breast cancer, Alzheimer's disease, infection, melanoma, and nonsmall cell lung cancer (NSCLC) as described in Table 3. Regulators (the EMA), HTA bodies, and payers from France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom participated in the pilots. The recently published final report assessed that the pilot consultations were effective in highlighting the commonalities and differences in evidence requirements among the stakeholders that participated; most differences concerned the HTA bodies' choices and requirements for active comparators. The companies involved seem to believe the pilots were successful in gaining additional clarity around payer evidence requirements for their assets; as a result of these pilots, several pharmaceutical companies adapted their existing development programs to meet the payer evidence recommendations emergent from the stakeholder consultations (18).

DISCUSSION

Benefits and Risks

There are clear benefits to undergoing an early HTA consultative process, both for pharmaceutical companies and payers / HTA bodies. Documented advantages for the company include the ability to forego investment in studies unlikely to be useful in securing a product's reimbursement; a potentially easier internal alignment process around an asset's clinical development strategy; and the possibility of reducing the risk of an asset's development program (18). From a payer perspective, aligning with companies on the evidence to be generated from the development program may eventually increase the number and quality of medicines available to patients in their market, by helping the company to successfully navigate the pricing and reimbursement process. Furthermore, for the payer, decision making based on better-quality data—which is likely to be the outcome of such a process—is more straightforward, with reimbursement outcomes more easily justified to different stakeholders.

From the company's perspective, the early advice pathway is not without risk, and thus they must balance excitement about these new consultation opportunities with the potential risks involved in undergoing this process. For example, although seeking scientific advice from CVZ in the Netherlands is not mandatory, it is seen by this stakeholder as an outreach to assist companies in optimally preparing their reimbursement dossier; it has been informally communicated that not implementing the CVZ's recommendations can lead to unnecessary delays in reimbursement negotiations, or even a negative reimbursement decision altogether (Personal Communication to RB). Before consultation, manufacturers should seek to understand the degree to which early HTA advice is considered binding, even if such reassurances on the part of the HTA body can be only informally documented.

It should be noted that the early reimbursement advice process is a new process. To date, only few products have undergone assessment. It remains to be seen whether the early consultations will be aligned with the actual reimbursement that is given once the drug is available on the market.

Keeping this benefit-risk balance in mind, it is possible that companies may want to pursue this process only for certain drugs in their portfolio. For example, it may be most optimal to purse this avenue to align with stakeholders on the development of drugs for diseases that are less understood, where significant variability exists within the standard of care, or when disease epidemiology precludes the ability to run a robust clinical program (e.g., in the case of orphan diseases, for example).

Which Option to Pursue?

As described above, four different models for HTA consultative advice exist, and a company's preference for which type of HTA consultation to pursue will depend on the needs of the company and the asset in question. In certain situations—for example, if the input needed is minor or clearly market-specific—it may be preferable to seek more streamlined advice from an individual HTA body (e.g., IQWiG), versus seeking a more robust assessment, leveraging external expertise, from a body such as NICE.

In other scenarios, it may be preferable to seek parallel HTA and regulatory advice, given the discrepancies that can arise between the requests of HTA bodies within the context of increasingly stringent FDA and EMA requirements. Can the differing needs of these stakeholders ever be reconciled? It appears that at least one company has used a parallel consultative process model to their advantage when faced with this

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Table 3. Overview of Multi-HTA Stakeholder Pilot Consultations to Date

	Sponsor	Therapeutic area	Approach	Phase
Pilot 1 23 Oct 2010	AstraZeneca	Type 2 Diabetes	New strategy to create value in a disease area in the context of global risk with multiple risk factors	I
Pilot 2 2 Dec 2010	GlaxoSmithKline	Type 2 Diabetes	New mechanism of action with proposed novel endpoints to assess value	NA
Pilot 3 3 Feb 2011	Janssen	Breast Cancer	Two development strategies focused on targeted subpopulations with accompanying diagnostic; no precedence for one area	II
Pilot 4 1 Jul 2011	Janssen	Alzheimer's Disease	Strategy for new indication and approach to patient identification	II
Pilot 5 2 Dec 2011	GlaxoSmithKline	Melanoma / NSCLC	Application of data to new indication and development of a companion diagnostic	III
Pilot 6 3 Feb 2012	AstraZeneca	Antibiotics	Approach to new indications for two new drugs; valuation of antibiotic stewardship, reimbursement strategy for emerging infections	II

Note. Source: Tapestry Networks (18).

situation (9). In his publication, Backhouse describes the process of seeking early advice from several different HTA bodies and reconciling this advice with those of the regulator, which can add efficiency to the development and regulatory process. For some assets, and in Backhouse's case, the key difference between the advice emerging from the regulator relative to the HTA bodies is the stakeholders' perspectives around the acceptability of submitting a placebo-controlled pivotal trial. Seeking advice from a joint regulatory and HTA process may be useful to reconcile differing opinions around essential aspects of the pivotal trial's design; an open dialogue may be the key to satisfying the needs of all stakeholders involved. Furthermore, pursuing a parallel procedure may allow for relatively short timelines and lower resource expenditure, if compared against a process seeking advice from each HTA body individually.

It's not surprising that past experience (9;18) has shown that a more fragmented consultative approach can lead to divergent advice on key aspects of trial design, such as appropriate active comparators, endpoint selection, and other important development parameters. It may seem, then, that a centralized approach would be the most beneficial avenue for pharmaceutical companies to pursue when seeking early advice, given that the outcome should theoretically be applicable for all of Europe. From a company's perspective, if the advice given is positive, this applicability will certainly be beneficial; however, in the case of negative feedback, the upside to pursuing a more fragmented consultative approach is that it leaves the door open for a more positive view of the asset's development program in the remaining markets. Furthermore, as described by Hutton et al. (19), one consequence of centralizing the HTA process is the risk of losing country-level control over the HTA consultation and consequently on pricing and reimbursement decision making. This may represent a limitation to the harmonization from a country perspective, as despite a centralized procedure, different evidence requirements may be necessary to meet the needs of local healthcare environments.

Future Outlook

This review has focused on select examples that showcase the early HTA consultation process in Europe. however, markets in Latin America and Asia are increasingly using HTA in their evaluation and reimbursement of new medicines (8) and in these regions, with the exception of Australia (20), the availability of an early consultation process remains limited. As the advice stemming from European HTA bodies may not be relevant outside the region, due to differing standards of care and treatment modalities across markets, pharmaceutical companies may find early HTA consultations in both Europe and the emerging markets becoming a requirement to meet the needs of a global evidence generation strategy.

Furthermore, as the healthcare landscape in the United States continues to rapidly evolve, HTA is becoming a tool increasingly used by U.S. commercial payers as they make formulary and coverage decisions. To this end, some companies already conduct "mock Pharmacy & Therapeutics committee meetings" with payers for pipeline assets, to better understand what plans are looking for in their decision making (Authors' experience). This allows the company to "pressure test" the product development plan in a low-risk environment, and can serve as a means for prescribers and payers to provide advice on study design as relevant to the American market.

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CONCLUSION

From an industry point of view, the availability of various options for early HTA consultative advice poses an improvement when compared to the historic situation, where HTA advice could only be obtained after completion of an asset's development plan. It seems clear that seeking early advice can help to avoid a mismatch between the outcomes of an asset's clinical development program and the expectations from HTA bodies and payers, potentially facilitating the pricing and reimbursement process upon a product's launch. However, a longer-term evaluation of the early consultation process is necessary to understand whether it has had a discernible impact on patient access.

European HTA bodies are becoming increasingly challenging to satisfy with regards to evidence requirements. Many companies are citing payers' unrealistic expectations, including a lack of recognition of their development efforts and product innovation, as the most pertinent difficulties in navigating the current process, which has become time consuming—and expensive—for the pharmaceutical industry. In light of these challenges, it is possible that in the not too distant future, Europe may potentially be considered as an add-on market by some global pharmaceutical companies. Taking advantage of the early HTA consultation processes that are in place may help to better align internal and external stakeholders involved in the drug development program, by enabling companies to better anticipate and plan for to the evidence requirements of payers and regulators.

SUPPLEMENTARY MATERIAL

Supplementary Figure S1
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CONFLICTS OF INTEREST

R.B. and C.C. have received consulting fees from Novartis, Pfizer, Amgen, Genentech, Merck Serono, Astellas, Millennium, Takeda, Sanofi-Pasteur, and others. M.C. is a current employee of Covidien. M.v.W. is a current employee of Ferring.

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