Building HTA insights into the drug development plan: Current approaches to seeking early scientific advice from HTA agencies

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There is a growing trend for pharmaceutical companies to seek scientific advice on drug development from a Health Technology Assessment (HTA) perspective, to improve the efficiency of their studies, enable better trial design, and support the goals of positive HTA recommendation for reimbursement. This study uses information collected directly from companies on individual products to assess their strategies and practices for seeking HTA-related scientific advice in terms of which stakeholders to engage and for what purpose, when to seek scientific advice, and whether to implement that advice within global clinical development.

Keywords: Health Technology Assessment; Early scientific advice; Drug development; Reimbursement; Regulator; Parallel scientific advice

Seeking scientific advice from regulatory agencies to facilitate evidence generation is a crucial development strategy for companies. The implementation of regulatory advice has been proven to be one of the success factors for market authorization.[1] With the increasing use of HTA in drug reimbursement decisions, companies have adjusted their internal structures and development strategies to accommodate both regulatory and HTA requirements.[2] As a result, stakeholder interactions during development have expanded beyond regulatory advice to include HTA insights. These can be obtained from internal market access experts, external HTA/payer advisers, and formal advice meetings with HTA agencies. This advice is nonbinding, prospective in nature, and focused on development strategies rather than on pre-evaluation of data, therefore ensuring that proposed development plans can produce evidence relevant for future HTA recommendation for reimbursement.[3]

Three types of formal early HTA advice are available to companies: advice from (i) a single HTA agency; (ii) parallel regulatory and HTA agencies; and (iii) multiple-HTA agencies. Advice from a single HTA agency is sought to understand the national requirements to support jurisdictional access.[4,5] Parallel regulatory/HTA advice supports early identification of divergence between regulatory and HTA requirements and helps improve alignment. Parallel advice can be obtained at a national level in England and Sweden[6] and, more recently, in Canada.[7] In 2010, the European Medicines Agency (EMA) and several European HTA agencies initiated a pilot to provide parallel advice. The advice mechanism continuously improved through the European Network for Health Technology Assessment (EUnetHTA) and was formalized as EMA-EUnetHTA parallel consultation in 2017.[8] Advice meetings with multi-HTA agencies aim to explore different HTA perspectives and increase the probability of alignment on evidentiary requirements. Such meetings have been available in Europe since 2012 and were formalized in 2017 as the EUnetHTA Multi-HTA Early Dialogue (ED) program.[9] There is also increasing collaboration at the international level. In 2019, Canadian Agency for Drugs and Technologies in Health (CADTH) and the UK National Institute for Health and Care

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Excellence (NICE) launched a program to provide simultaneous early HTA advice.[7]

Several studies have been carried out to assess the value of advice meetings. From the perspectives of the agencies, parallel advice meetings have proven beneficial in promoting better understanding among different stakeholders, supporting the predictability of evidence requirements and also potentially facilitating the quality of review.[10,11] Tafuri and colleagues analyzed the meeting minutes of EMA-EUnetHTA parallel consultations and identified a high level of overall agreement among agencies in the advice.[12] From the perspectives of companies, early HTA advice from a single agency or multi-stakeholders is beneficial to enable a more efficient development program and improve the internal decision-making process.[13,14]

However, the proliferation of early HTA advice programs results in challenges for companies to identify the optimal pathway for planning, seeking, and implementing advice from HTA agencies. There is international variability in processes, methodologies, and requirements among HTA agencies. Therefore, it is crucial for companies to consider when, on what topics, and from whom to seek advice. This study uses information collected directly from companies on individual products, to assess their strategies and practices for seeking HTA-related scientific advice during drug development. The objectives of the study were to: (i) assess company approaches to gaining HTA insights during drug development through stakeholder interactions; (ii) identify company practices to seeking formal scientific advice from HTA agencies, including when to seek advice, from whom, and on what topics; and (iii) investigate the impact of HTA scientific advice on the drug development plan.

Method

Study design

A multi-year, annual benchmarking study has been developed by the Centre for Innovation in Regulatory Science (CIRS) in partnership with its member companies to assess the impact of HTA during drug development and jurisdictional access. The study was developed in 2011 and structured in the form of a questionnaire to collect HTA-related metrics on individual products. Pilot studies were carried out in 2012 and 2013 to refine the methodology, with the final questionnaire established in 2014 and data collection conducted annually afterwards. The selection of companies and steps carried out to develop and validate the tool have been published.[15] Each data collection year, pivotal trial projects launched within the year, and products licensed in Australia, Canada, and Europe within the data collection year, are included. The projects and products include both new active substances (NASs) and major line extensions (MLEs) that require a new clinical trial.

The structure and the rationale of the final questionnaire was listed in a previous publication.[15] This paper was based on a subset of the benchmarking study and focused on assessing company practices for seeking HTA insights during development. The following multiple-choice questions were asked for each product:

1. Product characteristics (generic name, novelty, indication)
2. Date of first pivotal dose of the product
3. Whether HTA-related insights were sought in relation to the design of global clinical development.
4. Type of HTA-related consultation employed
5. Scope of the discussion
6. Name of the HTA agencies that provided advice
7. Date of the meeting when HTA advice was provided
8. How influential was the early HTA advice on the global development plan? If the advice did not influence global development, please provide the reason why
9. If no HTA-related insights were sought, please provide the reason why

Key definitions

'Date of first pivotal dose' was defined as the date of the first dose in the first large-scale clinical safety and efficacy study necessary to support marketing authorization of a product. 'Global clinical development' was defined as any clinical trial conducted as part of a multinational drug development program.

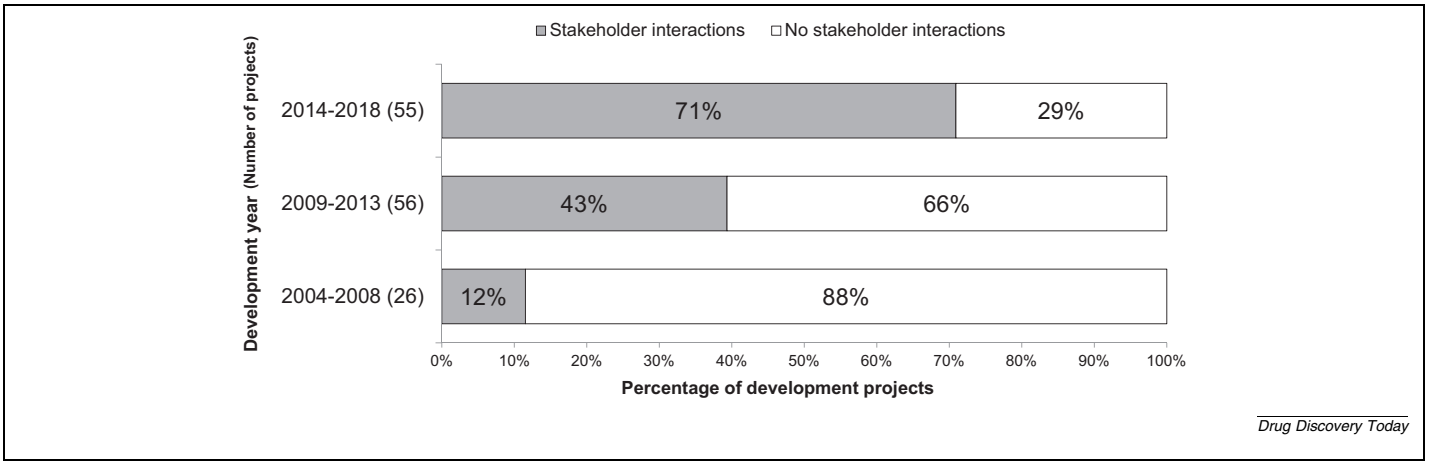

FIGURE 1
Stakeholder interactions providing insights from Health Technology Assessments (HTAs) for inclusion in development plans.

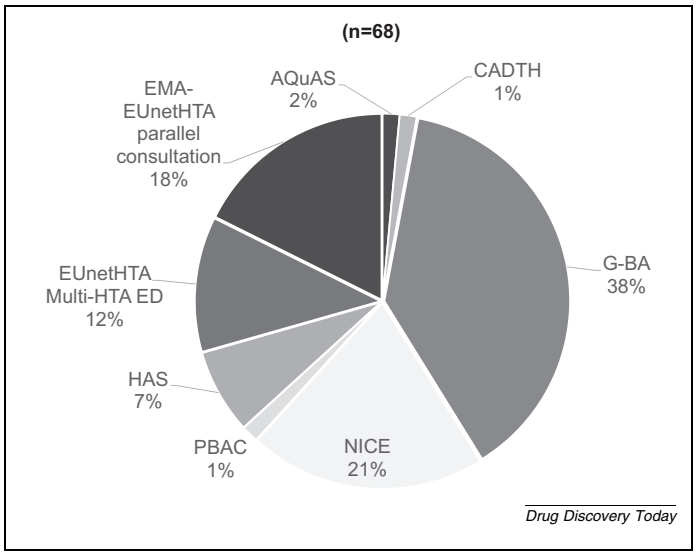

FIGURE 2

Scientific advice meeting according to the Health Technology Assessment (HTA) agency involved (N = 68). Abbreviations: AQuAS, Agency for Health Quality and Assessment of Catalonia; CADTH, Canadian Agency for Drugs and Technologies in Health; ED, Early Dialogue; EMA, European Medicines Agency; EUnetHTA, European Network for Health Technology Assessment; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee.

Data processing and analysis

The study questionnaire was built into a secure online platform developed by CIRS. Information was exported into an Excel file and analyzed using descriptive statistics by CIRS. The analysis was conducted by the first author to quantitatively describe the uptake, timing, topic, and impact of HTA advice. The second author reviewed and audited the results. For each analysis reported in this paper, the cohort of products included in the calculation was based on the company-provided data. To protect the confidentiality of the individual data submissions, only aggregated results are presented.

Results

We excluded data from pilots and reported on information provided by nine international companies that continuously participated in the study between 2014 and 2018. Information on HTA insights was collected on 153 compounds from these nine companies. The time of the pivotal trial of these compounds ranged from September 2004 to June 2018. Seven of the nine companies were ranked in the top 25 pharmaceutical companies by R&D expenditure and all nine had R&D budgets greater than US$1 billion in 2019,[16] reflecting their research intensity.

Trend of seeking HTA insight during drug development

For the past decade, there has been an increasing trend to seek HTA insights from external stakeholders to understand HTA requirements on evidence generation, with 71% of products developed between 2014 and 2018 having obtained HTA insights, compared with 12% between 2004 and 2008 (Fig. 1). Overall, advice from a single HTA agency was the most utilized format of stakeholder interactions (40%), followed by company-sponsored payer advisory boards (35%). The mechanism of multiple agencies presenting at the same advice meeting was also recorded in the study, with eight meetings among multiple HTA agencies (7%), and 12 parallel advice meetings with Regulatory and HTA agencies (10%).

For products that did not seek external HTA insights, there were two types of reason: (i) internal reasons, including well-conducted internal payer research, internal expertise and established knowledge in the therapeutic area, and different priorities among pipelines; and (ii) external factors, such as the limited availability of formal advice meetings at the time of development.

Scientific advice from HTA agencies: when, whom, and on what topics

We then focused on the advice obtained from HTA agencies to analyze company interactions with agencies during development. In total, 68 scientific advice meetings were recorded across 46 products from November 2009 to June 2018 (Fig. 2). Of these, 35 products were NASs (76%), and 11 products were MLEs (24%). For each product, companies could use more than one scientific

TABLE 1

Questions discussed at HTA advice meetings.

Topic of questions discussed	Type of HTA advice meeting (number of consultation meetings)		
	Single HTA agency advice (48)	Parallel regulatory and HTA agencies advice (12)	EUnetHTA multi-HTA ED (8)
Therapy area level	23% (11)	8% (1)	13% (1)
Efficacy/effectiveness evaluation	77% (37)	75% (9)	50% (4)
Safety	44% (21)	42% (5)	25% (2)
Trial design	77% (37)	100% (12)	50% (4)
Patient selection	56% (27)	75% (9)	50% (4)
PROs	60% (29)	83% (10)	38% (3)
Economic evaluation	38% (18)	58% (7)	25% (2)
Value to healthcare system	23% (11)	17% (2)	25% (2)

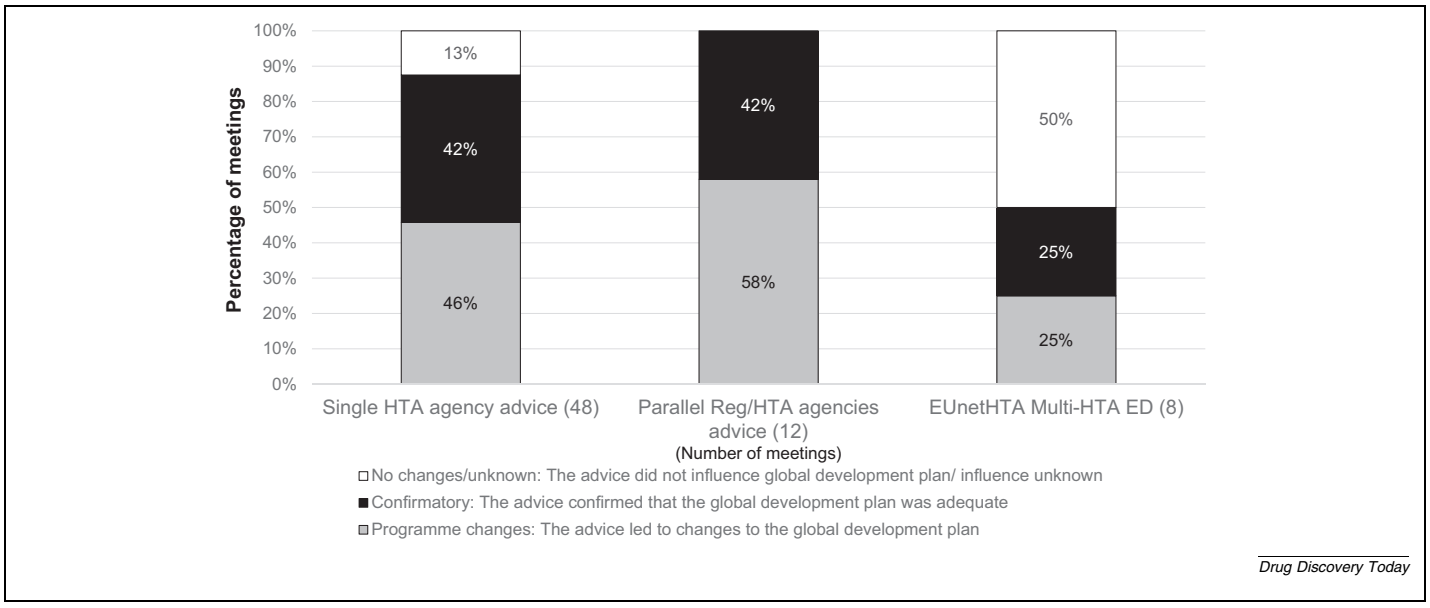

FIGURE 3
Impact of Health Technology Assessment (HTA) advice on the development plan. Abbreviations: ED, Early Dialogue; EUnetHTA, European Network for Health Technology Assessment.

advice approach with different agencies; 14 of 46 products used this strategy. In this study, the maximum number of formal advice meetings for a single product was five; however, no specific pattern could be established in terms of the order of agency interactions. Advice meetings were sought frequently for oncology products (58% went for formal advice from HTA agencies). The most frequently used format was advice from a single HTA agency (48 meetings), with the Gemeinsamer Bundesausschuss (G-BA) and NICE being the most common providers (Fig. 2). The multi-HTA agencies advice included in the study were all EUnetHTA ED programs. The parallel regulatory/HTA advice included 11 EMA-EUnetHTA parallel consultations meetings and one national advice meeting.

We assessed the timing of advice during development. Overall, 60% of advice occurred before the initiation of the pivotal trial, with a median time of 303 days. The median time between the advice to the launch of the pivotal trial was 367 days for the EUnetHTA multi-HTA EDs, 301 days for the single HTA advice, and 290 days for the parallel advice.

There were different types of question that companies wanted to address at each type of advice meeting (Table 1). Trial design-related questions were asked at all the parallel advice meetings in this study. The parallel advice also focused on the patient-reported outcomes (PRO) instrument, efficacy/effectiveness evaluation, and patient selections. The advice from a single HTA agency showed a similar pattern on efficacy/effectiveness evaluation and trial design. In addition, questions at the therapeutic level were raised at 11 national advice meetings, which could be related to the current clinical care pathway in the jurisdiction, current clinical outcome, and national guidance. Questions raised at the EUnetHTA multi-HTA EDs in this study covered a variety of topics, with an equal emphasis on efficacy/effectiveness evaluation, trial design, and patient selection.

To identify the trend of advice over time, we analyzed the types of question raised by companies by the timing of the advice meeting, for the period 2013–2015 compared to the period 2016–2018. There was a decrease in discussing therapeutic area-related questions, from 19% to 4%, as well as a reduction in the number of questions on economic evaluation, from 62% to 39%. An increasing trend of discussing which instrument should be applied to measure PRO was observed, from 67% to 78%.

Impact of scientific advice from HTA agencies

Parallel advice were the most influential meetings, leading to 58% of projects changing their development program (Fig. 3). Advice from single HTA agencies showed similar importance for changing the development program, as well as for confirming the evidence generation plan. Only four out of the eight EUnetHTA multi-HTA EDs had influenced the development plan. For products that had more than one advice meeting, the advice meetings sought earlier had an impact on program changes, whereas the last advice meeting was confirmatory. Most of the advice sought for MLEs was for confirmatory purposes (64%, seven products), whereas more than half of advice provided to NASs led to program changes (54%, 19 products).

The relationship between the timing of advice and its impact was also explored. For advice meetings occurring before the launch of the pivotal trial, 56% of advice led to changes to the development program. For advice sought after the launch of the pivotal trial, 39% resulted in a change to the development plan. When the scientific advice was not implemented, the main reasons were stated as 'unfeasible advice' or 'timing of advice was too late to impact development plan'.

Discussion

The past decade has witnessed the fruition of HTA-related advice, in particular the establishment of formal advice provided by HTA agencies at both national and international levels. This annual benchmarking study identified current approaches of companies to seeking HTA insights during drug development, assessed the

impact of the HTA advice, and provided practical implications for future strategic planning.

Practical implications for taking early HTA advice

The results revealed that companies used a mix of options to seek HTA-related insights during development, with a preference for single HTA agency advice (71% of the total 68 advice meetings assessed in the study). We also observed 11 EMA-EUnetHTA parallel consultations and eight EUnetHTA multi-HTA EDs taken between 2012 to 2017. In general, companies welcomed the multi-stakeholder advice, which raised awareness of evidentiary requirements from different perspectives.[14,17–20] However, it was also emphasized that a single HTA advice meeting can address questions relevant to national healthcare systems and standard of care and should not be replaced by parallel advice.[5] We found that the most frequently sought-after single agency advice was from G-BA and NICE. This result reflected the focus of companies on these two markets as a business priority. The two agencies apply different value frameworks for HTA: G-BA uses added clinical benefit as a key decision criterion, whereas NICE uses cost-effectiveness.[21] Therefore, taking advice from G-BA and NICE could provide a representative view for other agencies using similar value frameworks. The result was consistent with previous research, which identified the regular use of the advice service provided by the two agencies at a national level, as well as their frequent representation in the EMA-HTA parallel advice meetings.[4,5,12] Seeking HTA insights during development required additional resource from companies. Therefore, a decision not to seek early advice was also an important strategy. This has been observed in our study when there was 'internal expertise and established knowledge in this therapeutic area', and/or 'different priorities among pipeline'.

In the study, the majority of formal HTA advice (60%) occurred before the launch of the pivotal trial, with a median time of 303 days. Advice taken before the pivotal trial was more likely to enable development program change. This might not be surprising, given that the main reason stated by respondents for non-implemented advice was 'timing of advice was too late to impact development plan'. In previous research, companies indicated that the most efficient time for early advice was after the establishment of the proof of concept for a new product.[19] NICE evaluated the timing of all their advice meetings, and 61% were in Phase II of development.[4] A study focusing on G-BA early advice suggested that advice taken before the pivotal trial starts had higher completeness regarding the endpoints and study duration.[13] Therefore, it is crucial for companies to understand the logistics and requirements of each meeting format to request, prepare, and undertake the advice at the right time during development to maximize the utilization of advice. This is particularly important if companies plan to seek advice involving multiple stakeholders, because agency resources and availability differ.

We assessed the topics of questions addressed at different types of advice meeting. All three types of meeting focused on the efficacy and effectiveness evaluation, and trial design. A preference to discuss questions at the therapeutic level was seen in the single HTA advice meeting format, although this decreased in the period 2016–2018. One explanation could be that experience from previous advice meetings might apply to new products in the same therapeutic area; therefore, further advice is no longer needed. The PRO instrument was identified as a key topic in the advice meetings. In a 2016 survey of perceptions, both agencies and companies reported that PRO was the area that Regulatory and HTA requirements could be most strongly aligned with, and that parallel advice would add value in the designing of PRO.[20] Our results confirmed the importance of PRO and showed an increasing trend in this topic in meetings during the period 2016–2018 (78%) compared with 2013–2015 (67%). The results suggested that companies have been carefully considering the discussion topics to ensure the added value of advice to the development plan.

In addition to the development plan, agencies also welcomed the discussions on postlicensing evidence generation (PLEG) at early advice meetings. PLEG is a continuum of evidence development for a pharmaceutical product after market authorization. It is recommended that companies identify the potential evidence gap at the time of licensing or HTA assessment and discuss at an early advice meeting how to fill the anticipated gap.[22] With this continuous annual metrics study, any future questions on PLEG in advice meetings will be recorded in the results.

Measuring the value of early HTA advice

From a company perspectives, the value of HTA advice will be ideally reflected through a favorable HTA recommendation.[14] Nevertheless, there are challenges to this expectation, because reimbursement is a multifactor decision that is not limited only to early scientific advice. For example, a recent study conducted by NICE explored the relationship between the provision of NICE early advice and the Service Médical Rendu/Amélioration du Service Médical Rendu (SMR/ASMR) scores by Haute Autorité de Santé (HAS) as a surrogate measure. The results suggested a link between the NICE advice and a higher proportion of products with the HAS classification of added clinical value.[23]

In our study, we measured the utilization of early HTA advice. Parallel advice was the most influential meeting format, leading to changes for most products (58%). This was followed by single HTA advice (46%). Tafuri and colleagues assessed the uptake of EMA-EUnetHTA parallel consultations and showed a good level of compliance with advice on primary endpoint by companies.[24] We showed 42% of advice outcomes of a single HTA meeting and of parallel advice meetings to be confirmatory. Although these meetings did not influence the development, the confirmation was beneficial to pressure-test the evidence generation plan. Therefore, in addition to measuring the direct impact of advice on development, further indicators could be developed to assess the value of early HTA advice for companies, such as repositories of information gained from advice meetings and enhanced internal knowledge. Long-term optimization of early HTA advice is also needed. For example, HTA agencies should list frequently asked questions from advice meetings to share their perspectives on common topics, such as comparator choice, and companies should disseminate their learnings and exchange experiences in a collaborative fashion.[25]

Future opportunities

More recently, early HTA advice meetings have been affected by the ongoing Coronavirus 2019 (COVID-19) pandemic, which

has moved most meetings to a virtual format. The challenges for agencies are related not only to the change of format, but also to resource constraints because the clinical experts who usually participate in the meetings might need to work on the frontline of the pandemic response. By contrast, early HTA advice has become more crucial as a platform for companies and agencies to interact early, because both new medicines and repurposed medicines for COVID-19 are being developed, and their assessment accelerated. Therefore, new opportunities have emerged. For example, NICE initiated a free fast-track advice program for companies developing therapeutics for COVID-19.[26] Considering the lost opportunity to be involved in the future EMA-EUnetHTA parallel consultations after Brexit, NICE has also launched a new process to provide concurrent early advice, with similar timeframes to EMA advice. This new opportunity allows companies to request advice simultaneously from EMA and NICE.[27]

Recent research suggested that payers were concerned about medicines on the market through adaptive regulatory pathways, using limited evidence such as single-arm trials and biomarkers as clinical endpoints.[28] Challenges also emerged for payers in relation to PLEG, reimbursement decisions, and exit strategies. Consequently, payer organizations and patient groups have actively participated and been piloted in early dialogs. Payers have also indicated the need to further engage in early discussions with regulators, HTA agencies, and companies to support evidence generation.[29,30] The evolution and experience of existing HTA advice programs can also support the future initiation of similar activities in other jurisdictions, where HTA is being piloted or expected.[14] This ongoing study will continuously collect product-specific metrics on early HTA advice and capture changes and improvement of these activities.

Limitations of the study

This study collected HTA insights during development from nine participating companies. Therefore, the data sets do not represent all the advice meetings provided by HTA agencies mentioned in this study. However, this paper focused on approaches and strategies from the company perspectives, rather than on the overall advice services from agencies. We believe that the companies included in the study were representative of international companies that focus on innovative medicine development; therefore, the results demonstrated the current approaches to seeking early scientific advice from HTA agencies. In addition, this study only collected high-level information on the impact of HTA advice; further research into the qualitative details of each advice might give a deeper understanding of the impact of HTA advice on clinical evidence generation that is relevant for future HTA recommendation for reimbursement.

Concluding remarks

Our study showed an increasing trend for companies to seek HTA insights, with 71% of products developed between 2014 and 2018 having external stakeholder interactions. We observed diversity in the types of advice, including both national advice and international multi-stakeholder advice, with an emphasis on NICE and G-BA. In general, advice was taken before the launch of the pivotal trial (median of 303 days). The most influential advice on trial design was provided from single HTA agency meetings and via EMA-EUnetHTA parallel consultations.

This ongoing study provides a baseline of current company practices and strategies. With further experience and follow-up data collection, we would hope to suggest indicators that measure the value of early HTA advice. There is also potential to capture new areas of topic discussion and new initiatives, and to reflect the changing environment that calls for closer interactions of regulators, HTA agencies, and companies during development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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