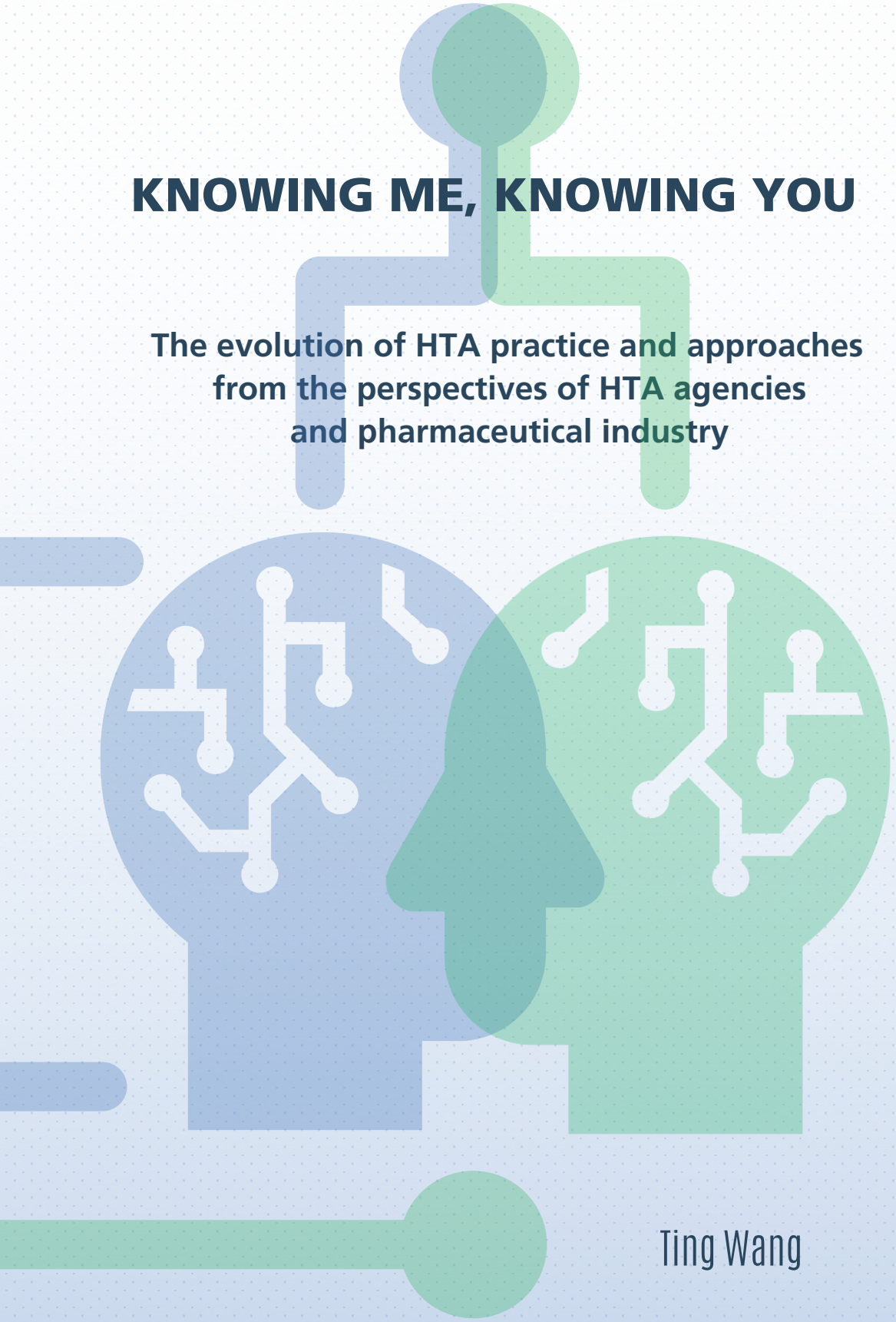
KNOWING ME, KNOWING YOU

The evolution of HTA practice and approaches from the perspectives of HTA agencies and pharmaceutical industry



Ting Wang

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Ting Wang

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PROMOTOREN

Prof. dr. Marie L De Bruin
Prof. dr. Hubert GM Leufkens

COPROMOTOREN

Dr. Wim G Goettsch
Dr. Neil McAuslane

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CHAPTER 1

INTRODUCTION

PATIENT ACCESS TO NEW MEDICINES

Every jurisdiction with regulatory agency capacity undertakes the review of medicines as the first step for patient access to new medicines. This step is intended to verify a product's quality, safety and efficacy and establish that its benefits outweigh its harms within the context of its proposed indication. Products that receive a positive regulatory approval can be made available within a country via a variety of access mechanisms: through public payment by national and/or regional coverage systems, through private payers or out of pocket payment by patients. In many jurisdictions such as Australia, Canada and European countries where the healthcare expenditure is primarily covered by the national health insurance, the access of new medicines is depending on reimbursement decisions by public payers.

The reimbursement decisions at each jurisdiction are taken at the macro- and meso-levels based on their own healthcare systems (OECD 2005). In response to the economic challenges of funding medicine access via national healthcare systems with finite budgets, it is then vital for decision-makers to ascertain where to spend and on whom to spend based on the available healthcare budget (Porter 2009). With the purpose of informing decision-making, to promote an efficient health system, Health Technology Assessment (HTA) has emerged as a tool to inform the reimbursement decisions by assessing the relative and cost-effectiveness of new medicines in comparison to existing technologies within a local context (Goodman and Ahn 1999). Since then, the concept of HTA has evolved and has now been defined as a multidisciplinary process that uses explicit methods to determine the value of health technology (O'Rourke, Oortwijn et al. 2020).

The role of HTA agencies as advisors to reimbursement decision-makers is crucial for the application of funding by the health care system (Claxton, Palmer et al. 2016). There is increasing interest by a variety of stakeholders in comparing HTA agencies and their outcomes, and there needs to be a clear understanding of how the different processes and practices within the HTA environment are evolving. Divergences were identified regarding the remit, scope, structure of HTA agencies, as well as variability in HTA requirements across jurisdictions. These differences in the HTA setting are rooted in the divergence in the national healthcare systems, such as the national economy, healthcare resources, and political and social conditions (Banta and Jonsson 2009, Nagy, Kamal-Bahl et al. 2013, Kalo, Gheorghe et al. 2016). Complexity in different recommendations were observed to be related to rapid changes in clinical practice and standard of care, and divergent economic environments (Akehurst, Abadie et al. 2017, Allen, Walker et al. 2017). These studies have contributed to the awareness and identification of different HTA practices. They have reinforced the need to bring alignment across HTA to improve patient access to new medicines.

HTA agencies continuously improve their processes, procedures, and methods for efficient and quality decision-making. This is particularly important for healthcare systems that are publicly funded. At the highest level, there is a societal and political expectation

that reimbursement decisions where public money is spent are justifiable and often a need for accountability of agencies involved in the healthcare decision-making. In addition to making rational, evidence-informed reimbursed decisions for an individual new medicine, there is an emphasis of HTA for selecting a new medicine in line with the healthcare priorities of the societies (Seixas, Regier et al. 2021).

The changing landscape of HTA has become of great importance to pharmaceutical companies, who seek to create efficient, globally aligned development programmes and successful market access of their products. Historically, global development is aimed to demonstrate the quality, safety and efficacy of a new medicine, and trial design for evidence generation is driven by regulatory agencies' requirements. To adapt to the rising importance of HTA, companies have implemented cross-functional collaborations within their organisations to bring clinical, regulatory, health economics and outcomes research (HEOR) and access teams together during the drug development process to ensure the generation of evidence that supports both regulatory approval and an HTA recommendation (van Nooten, Holmstrom et al. 2012). However, challenges remained within the companies, such as lack of awareness of HTA and reluctance to consider additional HTA requirements during development (Wang, McAuslane et al, 2016). Companies continue to explore the most efficient internal practices implemented during the drug development process to ensure that the best data can be obtained to address jurisdictional HTA expectations.

Interactions between HTA agencies and companies through the form of early scientific advice have been increasingly used to support evidence generation during development. These activities have improved over the past years in terms of their format and process, and studies have been done to review the learnings of these multi-stakeholder interactions (Wonder, Backhouse et al. 2013, Tafuri, Pagnini et al. 2016).

This thesis studies the ongoing evolvement of practice at HTA agencies and companies and across stakeholders' interactions during drug development, review, and reimbursement.

EVOLUTION OF HTA AGENCIES

The concept of HTA has been first introduced in the US in the 1970s as "a comprehensive form of policy research that examines the short- and long-term social consequences of the application or use of technology". Use of HTA expanded to Canada, Australia and Europe during the 1980s and gradually transferred from academia to support policy decision-making in the areas of public health system reimbursement decisions and the development of guidelines and protocols for new technologies (Banta 2003). Three main drivers for the quick growth of HTA were identified by Stevens et al as: under-researched medical interventions; cost pressure on health services; and rising consumer expectations and demand (Stevens, Milne et al. 2003). The new and internationally accepted definition of HTA has been adapted in 2020 as "a multidisciplinary process that

uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system" (O'Rourke, Oortwijn et al. 2020).

HTA applies to any intervention that may be used to promote health and well-being, which includes a range of technologies, including pharmaceutical products, medical devices, vaccines, surgical procedures, and preventative interventions. Historically, HTA has been divided in single technology and multiple technology assessments: single technology assessments are conducted to compare one technology with an alternative, and multi-technology assessments consider a cluster of treatment options in a specific disease area (Stevens and Longson 2013). In this thesis, we focussed on the single technology assessment for new medicines.

Despite the fact that the concept of HTA originated in the United States, there is no formal national HTA agency in the US. The US healthcare system is fragmented, with a mix of public and private payers, each making the decisions on drug reimbursement for patients within their budget (Elhauge E 2010). Although independent organizations such as Institute for Clinical and Economic Review (ICER) have emerged in the US, the role is to provide an independent source of evidence review, rather than directly and officially inform the payer decision making. The current legal system in the US prohibits the use of health economics approaches in the coverage policy of the federal health insurance programme (Medicare). Outside US, formal organizations have been set up within the public sector at the national or local level to conduct HTA to inform drug reimbursement decisions. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) was introduced, and the submission and review by PBAC have been mandatory since 1993 for medicines to be subsidized by the government (Hailey 2009); The Canadian Agency for Drugs and Technologies in Health (CADTH) was founded in 1989, with common drug review process introduced in 2002, the CDR assess the new medicines for a centralized reimbursement recommendation in Canada (Salek, Lussier Hoskyn et al. 2019); In Europe, the establishment of HTA agencies has also come to fruition in the 1990s; by 2008, 14 member states had formal HTA agencies, with continues adoption and evolvement of HTA agencies in other jurisdictions in Europe (Kristensen 2009, Garcia-Mochon, Espin Balbino et al. 2019). In these countries, institutionalization of HTA has been viewed as an essential tool to strengthen national health services, hastening the dissemination of HTA principles through establishing formal activities and agencies. HTA agencies have also been developed in several Latin American countries, such as Brazil, Mexico, Chile and Argentina, as well as in Asian countries such as South Korea, Taiwan, Thailand and Singapore. An increasing number of emerging countries will likely follow the trend of HTA institutionalisation (Banta 2009, Banta and Almeida 2009, Kim 2009, Sivalal 2009). In this thesis, we focused on HTA agencies in Australia, Canada and Europe, which represent established HTA practice, and at the same time key jurisdictions for market access for pharmaceutical companies.

HTA agencies continue to review their methodology and refine processes and procedures to improve their practice (NICE, 2021). Global networks have been established to enable capacity building and shared learnings, such as HTA international (HTAi) and The International Network of Agencies for Health Technology Assessment (INATHTA) at the global level, and HTAsiaLink and Health Technology Assessment Network of the Americas (RedETSA) at regional level (Longson 2014, Schuller and Soderholm Werko 2017, Teerawattananon, Luz et al. 2018). Within Europe, the European Network for Health Technology Assessment (EUnetHTA) was established to create an effective and sustainable network for HTA since 2006. Based on the experiences and learnings from the EUnetHTA joint actions, the European Commission adopted the Regulation on HTA in December 2021, which introduces a joint clinical assessment for new medicines and medical devices among member states (European Commission, 2021) that will effectively start in 2025.

Performance of regulatory agencies is closely watched, with the time taken for regulatory review measured as a key performance metric (Hirako, McAuslane et al. 2007). Numerous studies have been conducted to promote timely regulatory assessment and approval, and transparency around these metrics may help eliminate unnecessary delays in regulatory approvals within both mature and emerging markets (Schweitzer, Schweitzer et al. 1996, Sinha 2010, Wileman and Mishra 2010, Kataria, MeHTA et al. 2013). In the HTA space, research has been done to establish 15 key principles for the improved conduct of HTA, including independence, transparency, inclusiveness, scientific basis, timeliness, consistency, and legal framework. It has been suggested that these principles could be utilised to audit questions to measure HTA agencies' performance (Banta 2008, Drummond, Schwartz et al. 2008). However, there is a current perception that cross-agency comparisons of HTA practice and performances are not feasible. This is due to the differences in agency mandate, assessment, and appraisal process and how recommendations are made based on local context. Thus, there is currently no established method to measure and systematically compare the performance of HTA agencies.

Over the past decades, the role of HTA has also evolved from a standard activity after medicine's market authorisation, to a life cycle approach. The recently established HTA definition emphasised that "HTA can be applied at different points in the lifecycle of a health technology, i.e., pre-market, during market approval, post-market, through to the disinvestment of a health technology" (O'Rourke, Oortwijn et al. 2020).

EVOLUTION OF HTA WITHIN THE PHARMACEUTICAL INDUSTRY

Following the market authorisation of a new medicine, the commercial success for pharmaceutical companies depends on how HTA organizations will assess its added value in the overall context of the national healthcare systems (Sood and de Vries, 2009). Therefore, companies need to clearly understand the HTA systems and requirements when

submitting an HTA dossier. HTA agencies produce guidance on dossier submission as well as clinical guidelines. However, previous research identified considerable divergence in the clinical guidelines and HTA appraisals. For example, differences were observed in the acceptance of clinical trial endpoints by German HTA agency G-BA compared to its clinical guidelines (Staab, Walter et al. 2018). This not only affected the marketing of the product from the companies' perspective, but it also led to limited access to the patient for the drug that was previously available on the market in Germany before the G-BA assessment. Numerous studies have pointed out the inequitable access for medicines in Europe, following the centralized regulatory approval, especially in products aimed at unmet medical needs such as oncology and orphan indications (Grandfils, Hounkanlin et al. 2013, Mardiguian, Stefanidou et al. 2014, Lipska, Hoekman et al. 2015, Adkins, Nicholson et al. 2017)

Several papers have been published comparing pharmaceutical reimbursement pathways and outcomes (Cleemput, Franken et al. 2012, Nicod and Kanavos 2012, Sorenson and Chalkidou 2012, Nicod 2014, Allen, Liberti et al. 2017, Nicod 2017, Vreman, Mantel-Teeuwisse et al. 2020). The decision-making processes across HTA agencies are heterogeneous, and findings from these publications emphasize the importance of improving the transparency of decision-making processes. To mitigate the risk of receiving restrictive or negative HTA outcomes, companies have been improving their practice at individual jurisdictions, including conducting payer research, market research, and consultation with an ex-payer group or key opinion leaders (KOL). However, this approach is company-specific and depends on the resources available. Currently, there is a lack of predictability from companies' perspective on the HTA review timelines, outcome and evidence acceptance/preference by HTA agencies. Individual companies and industry associations have published their policy statements on key HTA principles, which generally advocate for transparent, science-based decision-making by agencies (Merck, 2019; Roche, 2020; EFPIA, 2021).

In current practice, the submission to HTA agencies for a pricing and reimbursement recommendation follows shortly after the regulatory approval. In Australia and Canada, companies can submit their HTA dossier during the regulatory review to streamline the timing of the two decision-making processes. Therefore, at the time of the regulatory review and HTA assessment, regulators and HTA agencies use similar data generated from global clinical trials. As a result, companies need to consider regulatory requirements during development and generate evidence that addresses HTA needs. One of the key HTA strategies is to seek early advice from HTA agencies on the development plan of a new product. This early scientific advice can be provided either by a single HTA agency, or through a consortium of multi-HTA agencies, or jointly with a regulator (Wang, McAuslane et al, 2016). Despite the efforts from the companies and agencies to improve their communication process early during development, key questions that remain for companies are how the advice is influencing the development plans and how to adapt the requirements from different HTA agencies into a global development plan.

The upstream process of building HTA considerations into drug development and the downstream process to prepare for HTA submission are the main areas of HTA strategy for companies. The companies' practice in this respect reflects the global HTA environment and is vital for an efficient, streamlined global drug development of innovative medicines that will ultimately benefit patients. Limited research has been done to assess companies' upstream and downstream HTA practices.

MULTI-STAKEHOLDER INTERACTIONS

The evidence to evaluate the safety and efficacy of medicines is usually based on the results derived from randomized controlled trials (RCTs), which demonstrate the extent to which a drug does more benefit than harm under ideal circumstances. A positive regulatory decision is made on the basis that the assessment of evidence shows a favorable benefit-risk balance (Haynes 1999). Unlike for almost all regulatory decisions, the evidence used by HTA to make an informed recommendation on drug reimbursement is comparative in nature. The objective is to maximize health outcomes by comparing the costs and efficacy of a new product with therapeutic alternatives. This difference in decision-making responsibility thus results in an evidence gap between regulatory and payer requirements in bringing medicines to patients. Questions around the evidentiary requirements between regulatory and HTA decision-making are becoming increasingly relevant. To facilitate the development and availability of safe and efficacious medicines to patients, agencies provide early scientific advice and protocol assistance to companies on the appropriate design of clinical trials and the robustness of their development programme (Wonder, Backhouse et al. 2013, Elvidge 2014).

This thesis focuses on stakeholder interactions that address HTA needs. Currently, 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 (Wang, McAuslane et al, 2016). Advice from a single HTA agency is sought to understand the national requirements to support jurisdictional access (Maignen, Osipenko et al. 2014). 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 and, more recently, in Canada (Ofori-Asenso, Hallgreen et al. 2020). Following successful experiences through EUnetHTA joint actions, the EU HTA regulation was formalised in 2021, providing joint advice between EMA and HTA agencies in Europe (European Commission 2021). Advice meetings with multi-HTA agencies aim to explore different HTA perspectives and increase the probability of alignment on evidentiary requirements. In 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the UK National Institute for Health and Care Excellence (NICE) launched a program to provide simultaneous early HTA advice (NICE, 2019). Several studies have been carried out to assess the value of joint 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. Tafuri and colleagues analysed the meeting minutes of EMA-EUnetHTA parallel consultations and identified a high level of overall agreement among agencies in the advice (Tafuri, Pagnini et al. 2016). From companies' perspectives, early HTA advice from a single agency or multi-stakeholders is beneficial in enabling a more efficient development program and improving the internal decision-making process.

In addition to the interactions during development to support evidence generation, flexible pathways from regulatory review to HTA evaluation have been established to enable better alignment in timing. This sequence has been undertaken in several countries. Since 2011, from the date the regulatory application is accepted for review, the reimbursement submission may be sent to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. The PBAC evaluates the medicine based on the evidence of cost-effectiveness and provides recommendations to the Minister of Health for the inclusion of the new medicine in the Pharmaceutical Benefits Scheme (PBS) (Australian Government Department of Health, 2019). In Canada, a collaborative pilot between regulatory and HTA agencies was set up in 2008 to review prioritized drugs, which allows companies to submit an application to the HTA agency for eligibility screening before regulatory approval has been granted (Frønsdal K 2012). Since 2012, all drug applications can be submitted to the Canadian Agency for Drugs and Technologies in Health (CADTH) for HTA review, before receiving a Notice of Compliance (NOC) by Health Canada (CADTH, 2022). This allows regulatory and HTA processes to occur in parallel and potentially shortens the time between the regulatory approval (issue of NOC) and the HTA recommendation. More recently, the MEB-ZIN parallel review pilot has been set up in Netherlands, and in the United Kingdom the Innovative Licensing and Access Pathway (ILAP) is established to align the regulatory and HTA process and accelerate time to market (ZIN 2022, MHRA 2022).

The multi-stakeholder interactions focussing on improving evidence alignment and streamlining of processes are intended to advance patient access to new medicines. (Kristensen, Husereau et al. 2019). However, considering the fruition of interactions, concerns have been raised regarding the resources needed for taking such activities, from both agencies and companies' perspectives. Previous research has evaluated individual activities in terms of the aim, format, and value of these interactions (Wonder, Backhouse et al. 2013, Maignen, Osipenko et al. 2014, Vlachaki, Ovcinnikova et al. 2017, Dintsios and Schlenkrich 2018). A further understanding of interaction practices will be valuable for agencies to allocate the resources best and build the interactions into their common practice, as well as be helpful for companies to best plan these activities during development as part of their HTA strategy.

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RESEARCH GAP

This introduction has provided a general overview of the current HTA landscape and pointed out where research is needed to inform the practices of agencies and companies to enable better drug development and access to new medicines.

For HTA agencies, a systematic cross-agency benchmarking is needed to enable clarity regarding the differences and similarities across HTA agencies, to identify the processes and timing of processes in individual HTA agencies, and to enable comparisons to be made within agencies for quality assurance, as well as between agencies for performance improvement. HTA agencies need further insights on their performances against peer agencies and to facilitate shared learning towards a framework of good HTA practice.

For pharmaceutical companies, HTA needs to be embedded from development to jurisdictional submission to HTA agencies. Insight in the current practice across the industry is lacking. There is added value in understanding how and when HTA decisions are made during drug development, which HTA agencies are consulted for advice, and what key submission strategies are taken. This information can provide insight for HTA agencies on the challenges that companies face, and the potential role HTA agencies could play to better enable the development plan and submission.

Multi-stakeholder interactions between regulator, HTA agencies and companies need to be further mapped out and evaluated to assess the current experience, uptake, and value of such activities. Particular areas of importance are when to undertake this interaction, how it enables better evidence alignment, how it supports accelerated processes, and where the direction of evolvement is. The learnings may in turn inform the practice of agencies and companies, and support better upstream to downstream decision-making for access to new medicines.

THESIS OBJECTIVES AND OUTLINE

This research is aimed to evaluate the HTA practice of pharmaceutical companies to enable better decision-making during development and at launch, examine the processes and performance of HTA agencies, and promote good practice across both stakeholders through self-improvement and interactions.

This thesis is organized following three parts: Part A focuses on the HTA practices of agencies, Part B assesses the HTA practice of companies, Part C explores the multi-stakeholder interactions regarding to HTA. Chapters 2 to 7 are based on peer-reviewed journal publications and can be read independently.

Chapter 2 provides the methodology and performance metrics to benchmark HTA agencies. Specifically, it details the development, and establishment of a benchmarking tool, provides a systematic framework to identify areas in the HTA process in which time is spent and enables ongoing improvement in practice.

Part B addresses the HTA practices of companies during development to market access. Specifically, Chapter 3 characterizes the practices of companies that address HTA requirements by collecting specific metrics and activities for new products from development to rollout at the jurisdictional level, examines the rollout milestones that help to provide an understanding of submission strategies, and assesses the consistency and predictability of HTA decision making. Chapter 4 focuses on the HTA strategy by companies to seek advice from agencies and investigates the 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 the global clinical development. Chapter 5 assesses how companies are building HTA insights into clinical development through developing and updating target product profiles.

Part C brings together both agencies and companies by assessing the multi-stakeholder interactions. Chapter 6 provides a viewpoint on areas where potential evidence requirements could align between regulators and HTA agencies, as well as across HTA agencies. Chapter 7 assesses the landscape of current interactions and provides an outlook on the future evolvement of these activities. Finally, Chapter 8 summarizes all the study results and unifies the conclusions in light of previous research.

1

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PART A

FOCUS ON HTA AGENCIES

CHAPTER 2

BENCHMARKING HEALTH TECHNOLOGY ASSESSMENT AGENCIES—METHODOLOGICAL CHALLENGES AND RECOMMENDATIONS

Ting Wang, Iga Lipska, Neil McAuslane, Lawrence Liberti, Anke Hövels, and Hubert GM Leufkens

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ABSTRACT

Objectives

The objectives of the study were to establish a benchmarking tool to collect metrics to enable increased clarity regarding the differences and similarities across health technology assessment (HTA) agencies, to assess performance within and across HTA agencies, identify areas in the HTA processes in which time is spent and to enable ongoing performance improvement.

Methods

Common steps and milestones in the HTA process were identified for meaningful benchmarking among agencies. A benchmarking tool consisting of eighty-six questions providing information on HTA agency organizational aspects and information on individual new medicine review timelines and outcomes was developed with the input of HTA agencies and validated in a pilot study. Data on 109 HTA reviews from five HTA agencies were analysed to demonstrate the utility of this tool.

Results

This study developed an HTA benchmarking methodology, comparative metrics showed considerable differences among the median timelines from assessment and appraisal to final HTA recommendation for the five agencies included in this analysis; these results were interpreted in conjunction with agency characteristics.

Conclusions

It is feasible to find consensus among HTA agencies regarding the common milestones of the review process to map jurisdiction-specific processes against agreed metrics. Data on characteristics of agencies such as their scope and remit enabled results to be interpreted in the appropriate local context. This benchmarking tool has promising potential utility to improve the transparency of the review process and to facilitate both quality assurance and performance improvement in HTA agencies.

INTRODUCTION

All health technology assessment (HTA) agencies have the same or similar underlying objectives and obligations to ensure that the utilization of health technologies provides the best value for money (Sorenson, Drummond et.al 2008). As the HTA environment becomes more globalized and newer collaborative and integrated ecosystems develop, there needs to be a clear understanding of how the different processes and practices within the HTA environment are evolving. In order to enable increased collaboration, quantitative and qualitative comparative information on HTA agencies' processes, practices, and performance are needed as the platform on which to build trust in and across agencies.

There is a common understanding and general acceptance that HTA agencies should adhere to certain key principles including independence, transparency, inclusiveness, scientific basis, timeliness, consistency, and legal framework. Drummond proposed fifteen key principles to assess HTA activities (Drummond, Schwartz et al. 2008). Drummond and colleagues suggest that such key principles could be augmented and used to formulate audit questions to measure HTA agencies' performance (Drummond, Neumann et al. 2012).

On the other hand, there is also almost full agreement as to the existence of differences among HTA agencies in their national procedural frameworks, as well as methodologies for clinical and economic assessments (European Commission, 2018). In particular, one important output from HTA is the recommendation of pharmaceutical products to be listed on the national or local formulary (Drummond, Schwartz et al. 2008). Therefore, the challenge and the opportunity for agencies, companies, and other stakeholders are the identification of truly comparative metrics to recognize similarities and differences among HTA agencies in order to appropriately interpret different HTA recommendations for pharmaceutical products.

The move toward increased HTA transparency is unavoidable as collaborative networks grow and in fact, independent comparisons of HTA activities are already underway (Nicod and Kanavos 2012, Kleijnen, Lipska et al. 2016). Therefore, HTA organizations should facilitate open discussion of the scientific basis for their decisions, although factoring the diversity in local context, especially when diverse coverage decisions for the same new medicine occur across jurisdictions (Kristensen and Gerhardus 2010, Schelleman, Dupree et al. 2015). The most recent public consultation by the European Commission on strengthening EU cooperation on HTA, which had responses from across twenty-one member states and representatives from industry and service providers, public administrators, patients and consumers, healthcare providers, academic or scientific institutions and payers, revealed that transparency of the HTA process is seen as a relevant factor of very high or high importance (83 and 16 percent of survey replies respectively) (European Commission, 2018). As HTA agencies processes and practices have been mapped by different stakeholders, the main focus has been on outcomes and timelines.

Agencies have been measured by divergent stakeholders including academics, pharmaceutical companies, and consultancies. A set of fourteen best practice principles was constructed by Wilsdon and colleagues based on the revision of existing principles developed by Drummond and demonstrated to some extent the consensus between academia, payers, and industry (Wilsdon, Fiz et.al 2018). Although the authors concluded that it was a challenge to apply one set of HTA best practice principles because of the variety of HTA processes and mandates jurisdictions, they proposed metrics that could be modified for each principle and used to compare the role of HTA in selected healthcare systems (Wilsdon, Fiz et.al 2018). It should be noted that HTA agencies have raised objections to some of the principles outlined in the studies by Drummond and Wilsdon and colleagues (International Working Group for HTA Advancement, Neumann et al 2010). However, there was full agreement among agencies that "HTA should be timely". The results of the European Commission public consultation showed that timely delivery of an assessment report is a relevant factor of very high, high, and medium importance (51, 41 and 8 percent of replies, respectively) (European Commission, 2018). However, timely HTA delivery does not depend only on the procedural frameworks and review performance of HTA agencies, as it is also impacted by companies' practice in terms of both the quality and timing of submissions to HTA agencies.

Although HTA agencies are concerned regarding cross-agency comparisons because of differences in agency mandates and lexicons as well as in how decisions are made, the assessment and appraisal period for all agencies can be broken into detailed components of overall processes. The breakdown of processes leads to identification of common stages during HTA review between agencies, and in turn the establishment of comparative milestones at each stage. Data on quantitative metrics of timelines as well as qualitative information on HTA agencies' procedural frameworks enable comparison to be made between agencies, the results could facilitate both quality assurance and performance improvement within the agencies.

OBJECTIVES

This paper describes a benchmarking tool that was developed with active HTA agency participation in order to build with the agencies an agreed methodology that enables comparative data to be collected and interpreted. According to the Oxford Dictionary, benchmarking is "evaluating something by a comparison with a standard." Benchmarking could also be considered as a continuous systematic process for comparing performance indicators across peer organizations for the purpose of organizational improvement.

The specific objectives of the benchmarking study were to collect comparative metrics to enable clarity regarding the differences and similarities across HTA agencies, to identify the processes and timing of processes in individual HTA agencies, and to enable comparisons to be made within agencies for quality assurance, as well as between agencies for performance improvement.

METHODS

The study was initiated by the Centre for Innovation in Regulatory Science (CIRS, London, UK) in 2012. The study protocol was designed based on the premise that notwithstanding the apparent variances among the HTA processes of different agencies, these processes are made up of a set of basic stages or building blocks that allow cross agency comparisons. These steps in the HTA process were identified and common milestones were defined for meaningful benchmarking. Our study was divided into three main phases (Figure 1).

Phase I—Identification of Appropriate HTA Agencies and Initiation of Collaboration

First, based on the information available in the public domain and on personal communication with individual HTA agencies, process maps for individual jurisdiction were developed to illustrate the relationship between national regulatory authorities, HTA organizations, and pricing and/or reimbursement decision-making bodies and to identify the appropriate HTA agencies to be benchmarked in this study (CIRS, 2018). Second, a call-for-interest proposal for a benchmarking study was developed and sent to eighteen HTA agencies using a purposive sampling method, based on their differences in size, the number of years in HTA experiences, and interest in collaboration. The first CIRS–HTA agency meeting was held on 25 June 2012 to discuss the domains of the questionnaire and relevant benchmarking metrics.

Phase II—The Development of the Questionnaire and its Use in the Pilot Phase

Based on the outcome from the first CIRS–HTA meeting and built on prior CIRS work and experience in benchmarking regulatory agencies (Hirako, McAuslane et al. 2007), the HTA benchmarking questionnaire was developed. Ten HTA agencies agreed to collaborate in the study to achieve an understanding of the different processes employed by each agency, highlighting areas of similarities and differences that were considered particularly important for benchmarking.

Participating agencies:

- AAZ—Agency for Quality and Accreditation in Health Care and Social Welfare, Croatia
- CADTH—Canadian Agency for Drugs and Technologies in Health, Canada
- CONITEC—National Committee for Technology Incorporation, Brazil
- INESSS—National Institute of Excellence in Health and Social Services, Canada, Quebec
- INFARMED—National Authority for Medicines and Health Products, Portugal
- KCE—Belgian Health Care Knowledge Centre, Belgium
- NICE—National Institute for Health and Care Excellence, UK England
- PBAC—Pharmaceutical Benefits Advisory Committee, Australia
- SMC—Scottish Medicines Consortium at NHS National Services, UK Scotland
- VASPVT—State Health Care Accreditation Agency at the Ministry of Health Lithuania

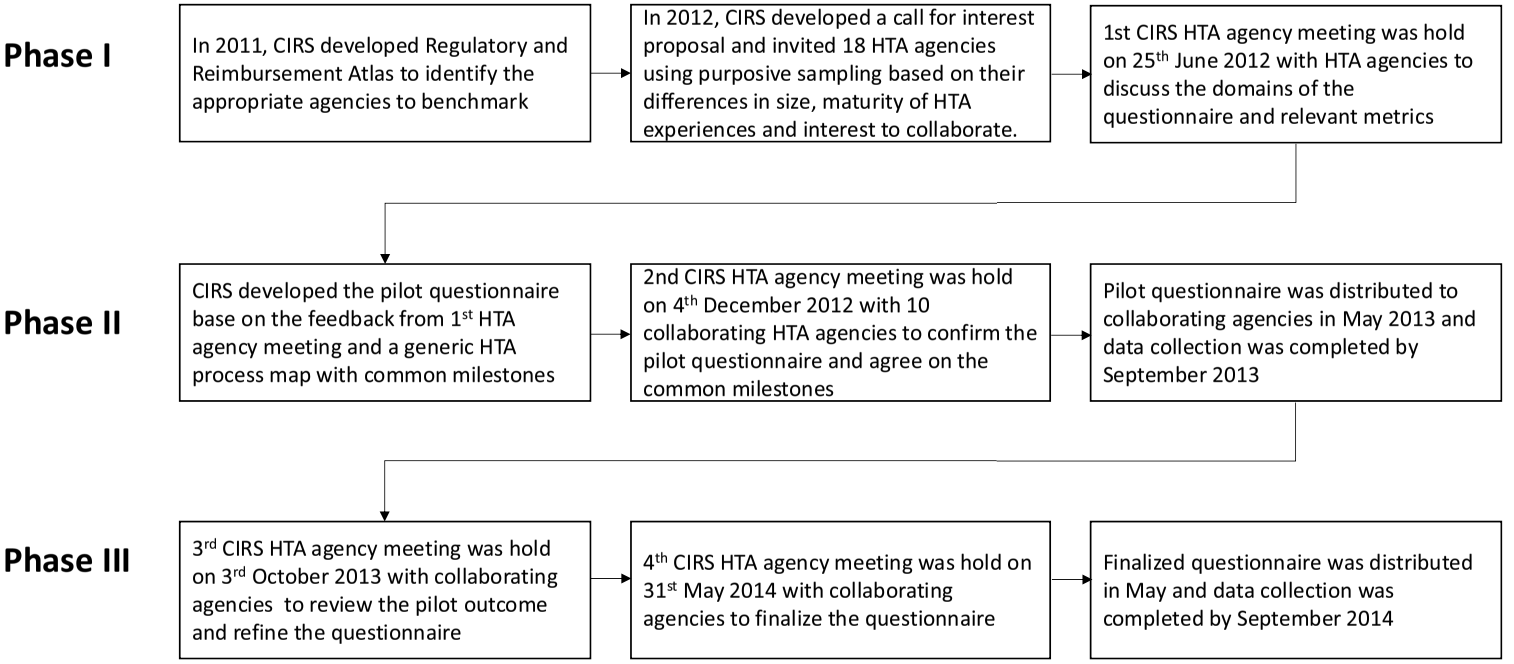

Figure 1. Phases of study development.

Collaborating HTA agencies were consulted through email and face-to-face discussions during the questionnaire development.

The questionnaire consisted of two main domains: information on agency organizational aspects and information on individual new medicine review timelines and outcomes. As part of the methodology, a generic process map was developed with common milestones. Although the review processes vary among collaborating HTA agencies, it was agreed by the agencies that individual steps in their review processes could be mapped to milestones common to all the agencies. Therefore, even though the sequence of each milestone during the review may differ, the defined metrics enabled comparison of individual systems and timelines among agencies.

Phase III—The Development of the Final Version of the Questionnaire and Data Collection for the Full Study

Feedback from the pilot study was discussed at the third CIRS–HTA meeting on 3 October 2013 and amendments were made to the questionnaire. The revised version of the questionnaire was sent to HTA agencies for their comments and feedback and the final version of the questionnaire was discussed at the fourth CIRS–HTA agency meeting on 31 May 2014. The final questionnaire retained the same structure as the original; that is, general information and individual product information.

The Excel questionnaires were distributed to ten HTA agencies for the fully study during May–September 2014. In the full study, we collected the information on all new active substances (NASs) that had undergone STA and received HTA recommendation in 2013. In general, HTA agencies provided data through completion of the Excel questionnaire; however, some parts of the questionnaire were pre-filled by the study authors based on the information available in the public domain to facilitate the data collection and the information was reviewed and verified by the HTA agencies.

In this paper, we provide full details of the benchmarking methodology. To demonstrate the feasibility of this benchmarking tool, we analysed metrics on timelines and agency characteristics. Timelines were chosen as a focus because of their interest to patients and other healthcare stakeholders as a marker of availability of new medicines. In addition, timelines have also been utilised by researchers as an overall indicator for agency performance; however, it is important that any time measures are contextualized in order to truly understand process efficiency. We calculated timelines based on the data directly provided or verified by HTA agencies. We have also focused on the subset of questions of budget and resources for agency comparison to provide the context of individual systems and processes necessary to interpret timeline results.

The analysis was based on results from five HTA agencies that were selected from the ten agencies that agreed to participate in the study based on the completeness of the milestone data provided, in order to assess their timelines during the assessment and appraisal phase. Because the focus of this paper is to demonstrate the validity

of the benchmarking tool rather than current specific agency performances and to preserve confidentiality, data were collected under the condition of individually anonymized reporting.

The median times of overall processes from HTA submission to recommendation were analysed to compare the performance across all agencies. In order to understand where time was spent during the process, the median time was further calculated for the common stages (assessment, appraisal, and appraisal to recommendation) at each agency, breaking down by agency time and company response time. The median time, 25th and 75th percentiles for each agency were calculated to show time variance. Finally, in order to explore the different approaches that may be employed by agencies, we further investigated the timeline for products with different HTA recommendations (positive, positive with restrictions, and negative), as well as for oncology versus non-oncology products.

RESULTS

A benchmarking tool was developed to systematically compare HTA agencies; the details of the questionnaire are provided in Table 1. The questionnaire included two main domains: general information domain and individual product domain.

The general information domain covered five main aspects (Scope and remit, Resource and budget, Appraisal/scientific committee, Transparency, and Review procedures and processes) containing fifty-one questions.

The individual product portion of the questionnaire consisted of four main aspects (Review timelines, Assessment/appraisal process, Outcome, and Scientific advice) containing thirty-five questions. In total, data for 109 HTA reviews from five HTA agencies were analysed to demonstrate the utility of the tool.

The characteristics of the participating HTA agencies are summarized in Table 2. The size of HTA agencies varied considerably; four agencies consisted of more than 100 full-time employees (FTEs) and one agency had less than 100 FTEs. The total number of FTEs assigned to HTA activities at the agencies varied from fourteen to eighty-eight, which amounts to less than 25 percent of total FTEs for two of the agencies, between 50 and 75 percent for two agencies and more than 75 percent for one agency. Total agency budgets ranged from less than 2 million USD to almost 115 million USD at the time of this study. Out of the five agencies, four indicated that they had experiences using external resources for HTA-related activities, among which three agencies have outsourced to universities or academic groups and four agencies have outsourced to individual independent contractors or consultancy companies. The frequency of outsourcing was not specified. The types of activities outsourced differed across agencies and may have included the development of the full HTA report, rapid HTA report, review of manufacturer's submissions, and educational activities. Median time taken from HTA submission to HTA recommendation (excluding company response time) varied between 99 and 862 days (Table 2).

Table 1. Questionnaire for HTA agency benchmarking study

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
Agency identifier	1. Please indicate the full name of the agency (free text prefilled) 2. Please indicate jurisdiction (free text prefilled)
Scope and remit	3. Please indicate the remit of the agency a. Drug technologies (yes/no) b. New Active Substances only (yes/no) c. Non-drug technologies (yes/no) d. Surgical interventions (yes/no) e. Health prevention programmes (yes/no) f. Medical devices (yes/no) g. Dental procedures (yes/no) h. Others (please specify) 4. Indicate the main activities that are covered by the agency a. Health policy (yes/no) b. Marketing authorisation/product licence (yes/no) c. Health Technology Assessment - original reports (yes/no) d. Health Technology Assessment - review submissions from the industry (yes/no) e. Health Technology Assessment-original reports AND submissions from industry (yes/no) f. Patient information (yes/no) g. Product safety (yes/no) h. Pricing (yes/no) i. Clinical trials advice (yes/no) j. Other, please specify (free text)
Type of agency	5. Indicate which of the following best describes this agency (yes/no) a. Independent from government b. Operates within administrative structure of the government 6. Date of establishment of the current agency (free text date) a. Date of establishment of single-technology review (free text date) i.e. Common Drug Review
Size of agency	7. Please provide information on internal staff numbers a. Total staff in the agency full-time employees (FTEs) (free text numbers) b. Number of full-time employees (FTEs) assigned to HTA activities (free text numbers) 8. Please provide information on agency assessors conducting specialised reviews a. Number of reviewers (FTEs) for industry submissions for New Active Substances (NASS) (free text numbers)

Table 1. (continued)

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
	b. Number of reviewers (FTEs) for industry submissions for Major Line Extensions (MLEs) (free text numbers) c. Number of reviewers (FTEs) for industry submissions for New Active Substances (NASs) AND Major Line Extensions (MLEs) in total (free text numbers) d. Number of reviewers (FTEs) for industry submissions for Devices (free text numbers) e. Number of reviewers (FTEs) for Industry submissions for other health technologies (free text numbers)

	Please indicate the professional background and numbers of the agency staff assigned to the review and assessment of industry submissions			
Question 9	Number Employed as assessors (Degree/Expertise)			
Question 9 table	Total	With PhD or PharmD	With MS	Other
Physicians				
Physicians with additional education/ expertise in health economics				
Physicians with additional education/ expertise in project management				
Statisticians				
Pharmacists				
Pharmacists with additional education/ expertise in health economics				
Pharmacists with additional education/ expertise in project management				
Health Economists				
Other scientists				
Project Managers				
Administrative staff				
Others				

9a) Please indicate the number of the administrative agency staff assigned to the review and assessment of industry submissions (as equivalent of FTEs)?

Table 1. (continued)

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
External resources	10. Does the agency outsource any HTA-related activities (yes/no) If YES please indicate to what external organisations: a. Universities/academic centres/academic groups (yes/no) b. Consultancy companies/consultancy groups (yes/no) c. Governmental agencies (yes/no) d. Individual independent contractors (yes/no) e. Hospitals/health service providers (yes/no) f. Others (please specify) 11. What types of HTA-related activities are outsourced? a. Full HTA reports (yes/no) b. Rapid HTA reports (yes/no) c. Critical review of manufacturer's submissions (yes/no) d. Educational activities related to HTA (yes/no) e. Others (yes/no) 12. If YES please specify what % of HTA-related activities budget is are designated for outsourced work (free text %)
Agency's budget	13. Please indicate whether the following data are in the public domain (yes/no) a. agency total budget (yes/no) b. agency total budget allocated to HTA activities (yes/no) 14. Please indicate agency total budget (local currency ;free text numbers) 15. Please indicate agency total budget allocated to HTA activities (local currency; free text numbers)
Fee structure (year 2013)	16. Are fees charged to sponsors for the review and assessment of applications for drugs (yes/no) If YES please provide the following information: a. Fee for review and assessment of NAS (local currency; free text numbers) b. Fee for review and assessment of generics (local currency; free text numbers) c. Fee for review and assessment of major line extension (local currency; free text numbers) d. Fee for review and assessment of other technologies please specify (local currency; free text numbers) 17. Does the agency charge a fee for scientific advice? (yes/no) If YES please provide the following information: a. Fee for scientific advice in local currency (free text numbers) 18. Please provide the following information in relation to the way the agency is funded a. Funded entirely by the statutory health insurance (yes/no) b. Self funded entirely from fees (yes/no)

Table 1. (continued)

Part I: General information on HTA organisations				
AGENCY INFORMATION	Question			
	c. Other please specify (free text) d. Partially funded from different sources (please give proportions of total budget below): i) % statutory health insurance (free text %) ii) Fees (free text %) iii) Other - please specify (free text %)			
Committee procedure	**19. If the appraisal procedure includes obtaining the information from Appraisal/Scientific Committee of internal and/or external experts please complete the following** a. Name of the Committee (free text) b. Number of Committee Members (free text numbers) c. Name of additional Committees if applicable (free text) d. Number of additional Committee Members (free text numbers) **20. Who nominates the members?** a. Ministry of Health (yes/no) b. Chair of the HTA organisation (yes/no) c. Other (please specify) **21. Briefly outline the committee members selection process (free text)**			
	Committee Members' professional discipline (free text)			
Question 22	Committee Members' professional discipline (Degree/Expertise)			
Question 22 table	Total	With PhD or PharmD	With MS	Other
Physicians				
Statisticians				
Pharmacists				
Health Economists				
Other scientists				
Project Managers				
Lay representatives / public members				
Others				
AGENCY INFORMATION	Question			
	23. Committee Members' years of experience/years in the Committee (numerical value) **Committee Members' years of experience/years in the Committee (Degree/Expertise)** Years of experience in the Committee *Less than 1 year*			

Table 1. (continued)

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
	Between 1-2 years *Between 3-5 years* *Between 6-10 years* *Over 11 years* *Total number of members in the Committee* 24. How frequently does the Committee meet? (multiple choice) a. Once per week b. Once per month c. Other (please specify) 25. Are the Committee meetings open to the following groups: a. Public (yes/no) b. Industry (yes/no) c. Patient groups (yes/no) d. Media (yes/no) e. Other (please specify) 26. For NAS and major line extensions (MLE) applications does the Committee review a. Once per week b. Once per month c. Other (please specify) 27. Is there defined voting procedure for the Committee? (yes/no) 28. Does the Committee review: a. The complete dossier (yes/no) b. Assessment reports from the reviewers (yes/no) c. The complete dossier AND assessment reports from the reviewers (yes/no) d. Other documents (please specify)
Transparency	29. What priority does your agency assign to being open and transparent in relationships with the public, professions and industry? (yes/no) a. High priority b. Medium priority c. Low priority d. Please comment (free text) 30. What are the main drivers for establishing transparency? Please indicate the top three incentives for assigning resources to activities that enhance the openness of the HTA system (yes/no) a. Political will b. Press and media attention c. Public attention

Table 1. (continued)

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
	d. Industry attention e. Patients/Patient Interest Group concerns f. Need to increase confidence in the system g. Other (please specify) **31. Please indicate which of the following information items about the assessment and appraisal processes are available to the public (yes/no)** a. Assessment and appraisal times b. Review documents c. Appraisal documents d. Executive summary documents e. HTA recommendation documents f. Conflict of interest disclosure documents of the Committee members g. Conflict of interest disclosure documents of HTA Agency management h. Conflict of interest disclosure documents of HTA Agency staff i. The Committee meeting dates j. Standard operational procedures (SOPs) followed for assessments/appraisals k. HTA guidelines l. The list of technologies being assessed and reviewed **32. If the agency publishes the list of technologies being assessed and reviewed, how often is it updated? (yes/no)** a. Daily b. Weekly c. Monthly d. Quarterly e. Once a year f. Less than once a year g. When key milestones are reached **33. Is the agency website available in English? (yes/no option)** **34. If NO - which local language(s) is the agency website available? (free text)** **35. Are companies able to follow the progress of their own applications? (yes/no)**
Transparency	**36. If YES please indicate the mechanisms available to industry (yes/no)** a. Electronic access to the status of application b. E-mail contact c. Telephone contact d. Meetings

Table 1. (continued)

Part I: General information on HTA organisations	
AGENCY INFORMATION	Question
	e. Other, please specify 37. Is there an electronic system for tracking applications? (yes/no) 38. If YES please indicate whether it has the following activities a. Tracing applications that are under review and identifying the stage in the process (yes/no) b. Signalling that target review dates have been exceeded (yes/no) c. Recording the terms of the HTA recommendation once issued (yes/no) d. Archiving information on applications in a way that can be searched (yes/no) 39. Is such system currently being developed (yes/no)? 40. If your answer to 37d is NO - are there plans to introduce such a system? (yes/no option) a. If so, please give target date for implementation (free text date)
Procedures and processes	41. Are there HTA guidelines available in the Agency?(yes/no) 42. Are there standard operational procedures available in the Agency? (yes/no) 43. Are there defined assessment and appraisal processes? (yes/no) 44. Is there any patient advocacy group engaged in the review process? (yes/no) 45. How are patients engaged in the review process? (yes/no) a. Not engaged b. Able to write submissions like any other stakeholder c. Defined patient representative group d. Participating in the decision making process (eg. seats on the board) 46. Are there criteria for priority setting? (yes/no) 47. Is there any topic selection process implemented in your organisation? (yes/no) 48. Are there explicit criteria for topic selection? (yes/no) 49. Does the agency give scientific advice to the industry? (yes/no) a. If yes, is advice available before submission to regulatory agency (yes/no) b. If yes, is advice available before submission to HTA organisation/agency (yes/no) c. If yes, is advice available after marketing authorisation (yes/no) 50. Are there any guidelines implemented concerning scientific advice? (yes/no) 51. Is scientific advice issued in parallel with the regulatory agency? (yes/no)

Table 1. (continued)

Part II: Information on individual products	
PRODUCT INFORMATION	Question
Product 1 - please provide product specific information in this section	
Product identifier and characteristics of the product	1. Drug INN (free text) 2. Drug ATC Class (free text) 3. Brand Name (free text) 4. Name of manufacturer (free text) 5. Indication approved by Regulatory Agency 6. Indication in question for HTA process 7. Innovation status (yes/no) a. First in class b. First in treatment c. First in indication d. Follow-on drug
Regulatory approval	8. Regulatory Agency approval date/Marketing Authorisation Approval date (Free text Date) (date that is applicable for jurisdiction in question)
Assessment, appraisal and decision-making phase on individual product	9. Submission date to the HTA Agency (Free text Date) (date that the agency records the submission) 10. Assessments performed in the Agency or used by the Agency (yes/no) a. Clinical analysis b. Economic analysis c. Budget impact analysis d. Subpopulations in label e. Other (please specify) (free text) 11. Patient advocacy or other groups solicited for consultation? (yes/no) 12. Patient advocacy or other group's consultation received? (yes/no) 13. If YES please provide name(s) of group(s) consulted (free text) 14. Date of the end of assessment phase (free text date) 15. Any time for clarification given to the industry during assessment phase? (yes/no) 16. Exact time for clarification given to the industry during assessment phase a. Date the questions were sent to the company (free text – dates) b. Date of the sponsor's response (free text – dates) 17. Procedure implemented to stop the time of the assessment phase if industry is asked for clarification/"stop the clock" procedure? (yes/no) 18. Starting date of the appraisal phase (free text date)

Table 1. (continued)

Part II: Information on individual products	
PRODUCT INFORMATION	Question
	19. Date of the end of the appraisal phase (free text date) 20. Any time for clarification given to the industry during appraisal phase? (yes/no) 21. Exact time for clarification given to the industry during appraisal phase a. Date the questions were sent to the company (free text – dates) b. Date of the sponsor's response (free text – dates) 22. Procedure implemented to stop the time of the appraisal phase if industry is asked for clarification/"stop the clock" procedure? (yes/no) 23. Date of final HTA recommendation (free text date) 24. Types of data used to develop HTA recommendation (yes/no) a. Systematic Review on safety/efficacy/effectiveness (yes/no) b. Meta-analysis (yes/no) c. Randomised Clinical Trials RCTs (yes/no) d. Prospective studies (yes/no) e. Registries (yes/no) f. Clinical guidelines (yes/no) g. Input from clinical professionals (yes/no) h. Evidence submission from manufacturer (yes/no) i. Cost minimasation analysis (yes/no) j. Cost effectiveness/utility analysis (yes/no) k. Cost benefit analysis (yes/no) l. Critique/review of manufacturer's pharmocoeconomic evaluation (yes/no) m. Input from patients (yes/no) 25. Please indicate if the HTA recommendation/conclusion was: a. Positive (yes/no) b. Positive with restrictions (eg. population, indication) (yes/no) c. Negative (yes/no) 26. Main reasons for approval, including restrictions (free text) 27. Main reasons for deny (free text) 28. Date of Minister of Health's/payer's/health insurance institution's final reimbursement/coverage decision if more than one, indicate date of first decision (free text date) 29. Please indicate if the MoH's/payer's/health insurance institution's final reimbursement/coverage decision was: a. Positive (yes/no) b. Positive with restrictions (eg. population, indication) (yes/no) c. Negative (yes/no)

Table 1. (continued)

Part II: Information on individual products	
PRODUCT INFORMATION	Question
	30. Was this drug subject to special or priority review (e.g. orphan drug, oncological drug)? (yes/no) a. If YES please provide details (free text) 31. Has scientific advice been given on this particular product? (yes/no) 32. If so please indicate the date of the scientific advice (free text date) 33. If so has scientific advice been followed by the sponsor? (yes/no) a. Fully b. Partially c. Not at all 34. Have there been any additional consultations required for this particular product? (yes/no) a. If YES - please specify (free text) 35. Has any pre-submission advice been given on this particular product? (yes/no) a. If YES - please specify (free text)
Comments	Comments relating to this Product

Detailed Timelines

To understand where time was spent in agency processes and enable cross agency comparison, a generic map was developed as part of the methodology to show the breakdown of HTA processes at individual agencies. Seven main stages were identified as common to HTA decision-making processes: receipt of data; HTA assessment; sponsor input during assessment; HTA appraisal; sponsor input during appraisal; appraisal to HTA recommendation; and coverage decision for the product. Common milestones for each stage during the processes were agreed by participating agencies.

Figure 2 presents the details of the generic map and uses two agencies as examples to show the breakdown of the timeline. The example agencies were selected based on their extreme values for median time from HTA submission to HTA recommendation (862 and 99 d for agencies A and E, respectively). Although the processes used by the selected agencies allowed companies to respond during the assessment and appraisal phase, the time differences were mainly attributed to agency time. The median time for HTA agencies during the assessment phase was 435 and 50 days for agencies A and E, respectively, and the median time for the appraisal phase also differed substantially, from 347 to 12 days for agencies A and E. These results need to be interpreted with caution as the different systems and processes between the agencies could influence the timelines,

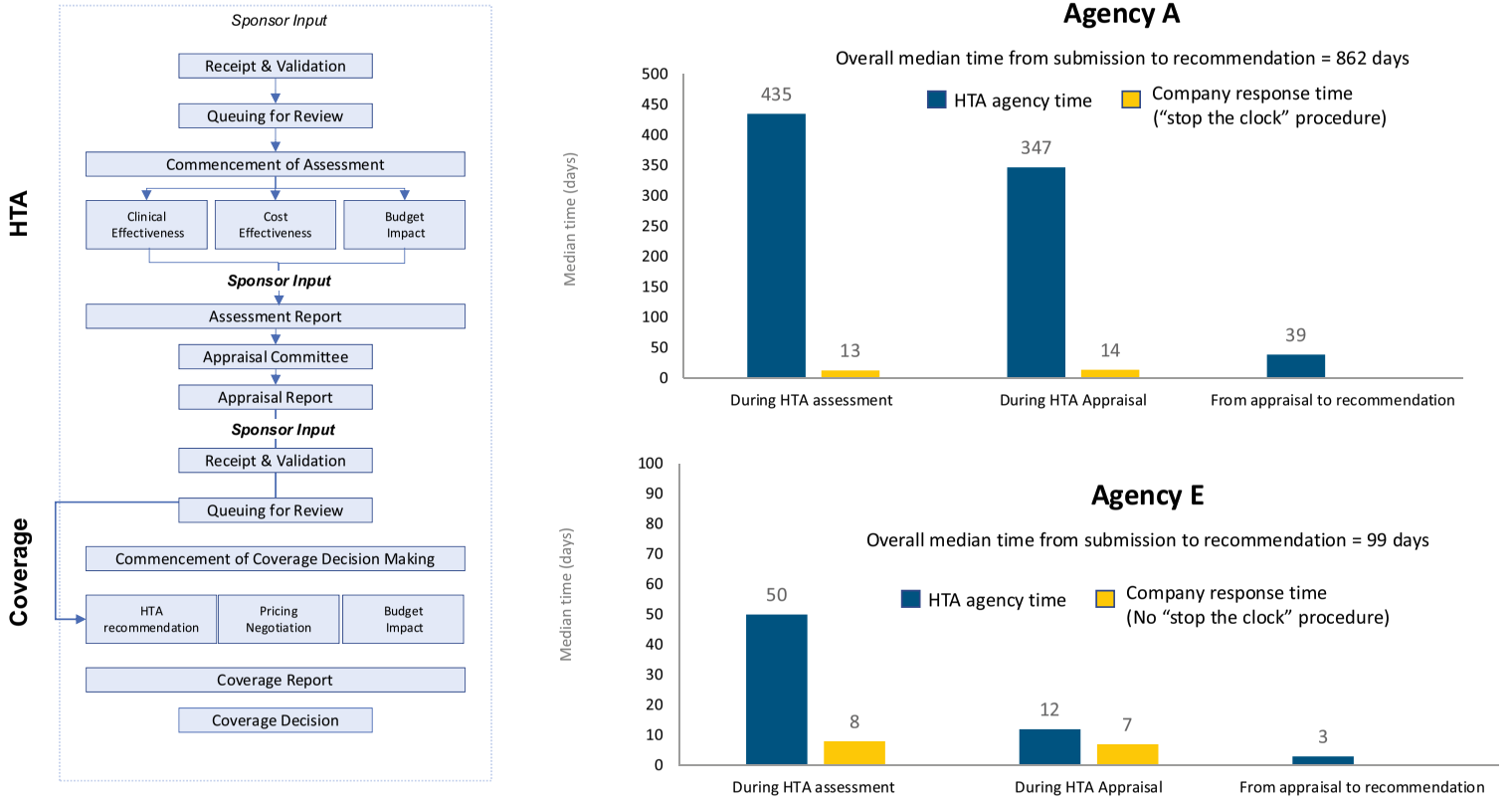

Figure 2. Comparison—where time is spent between HTA submission and final recommendation

as shown in Table 2. In Figure 3, the time between submission to the HTA agency and final recommendation is presented for individual products and also for oncology versus non-oncology products. Three agencies (E, D, and B) had consistent median times across oncology and non-oncology products, varying from 109 to 293 days for oncology products and from 99 to 247 days for non-oncology products. Agency C did not evaluate oncology products within the time period of the data collection.

For agency A, there was considerable difference between the median time for oncology versus non-oncology products (552 and 1,006 d, respectively) at that agency.

The timelines between HTA submission and HTA recommendation were analysed according to HTA outcome (positive, positive with restrictions, and negative). For agencies A and B, there were considerable differences in the median time by HTA outcomes: 767 and 975 days for positive and negative HTA outcomes respectively in case of agency A; 208, 260 and 315 days respectively for positive, positive with restrictions and negative HTA outcomes for agency B. For agencies C and D, the median times were very consistent across different HTA outcomes; however, there were no positive HTA outcomes included in this study for agency C. Agency E showed the shortest timelines (99 d for all products), the median time for negative HTA outcome was considerably longer (123 d) compared with positive and positive with restrictions HTA outcomes (95 and 96 d, respectively).

DISCUSSION

This study presents a benchmarking tool to compare HTA agencies and considers its potential for future use. Despite the variety of healthcare systems and HTA processes and outcomes, we propose that HTA processes can be mapped with common milestones identified and agreed, to understand and compare HTA agencies. HTA agencies have been compared by external groups (Nicod and Kanavos 2012, Kleijnen, Lipska et al. 2016); however, these analyses are often criticized by HTA agencies due to the lack of comparable bases. The methodology developed for this study could be used to provide comparative analysis across agencies by external stakeholders as well as within and across HTA agencies for their self-improvement.

Benchmarking HTA Agencies: Improving Timeliness and Transparency

Our study shows that participating HTA agencies can agree on common milestones during HTA processes, which enabled comparison of overall time, as well as where time was spent at each stage between HTA submission and recommendation. The generic process map and our study methodology can be taken further to support the design of procedures in newly established HTA agencies and the improvement of processes in existing HTA agencies.

Timelines of HTA processes are measurable but are not a measure themselves and should be always interpreted with a full understanding of the HTA processes. In his key principles of HTA, Drummond indicates that "HTA should be timely" which is considered

Table 2. Resources for HTA-related activities versus. median time of HTA process

Agencies		A	B	C	D	E
Main activities of the agency		Drug technologies Non-drug technologies Surgical interventions Health prevention programmes Medical devices	Drug technologies Non-drug technologies Surgical interventions Health prevention programmes Medical devices Dental procedures	Drug technologies Non-drug technologies Surgical interventions Health prevention programmes Medical devices Dental procedures	Drug technologies Non-drug technologies Surgical interventions Medical devices Dental procedures	Drug technologies
Remit		Health policy Marketing authorisation HTA review industry submissions Patient information Product safety Pricing	Health policy HTA – original reports and industry submissions Patient information	HTA – original reports and industry submissions Patient information	HTA – original reports and industry submissions Patient information Product safety	HTA- review industry submissions
Median time from HTA submission to recommendation		862 days	268 days	209 days	147 days	99 days
"Stop the clock"* procedure for company response		Yes	No	No	Yes	No
Patient advocacy solicited for consultation		No	Yes	Yes	Yes	Yes
Internal resources	Size of the agency	> 100 FTEs	> 100 FTEs	> 100 FTEs	> 100 FTEs	<100 FTEs
	Number of internal HTA FTEs	21	50.75	66	88	14.3

Table 2. (continued)

Agencies		A	B	C	D	E
External resources	Universities/ Academic centres/ academic groups	Yes	Yes	Yes	N/A	No
	Individual independent contractors	Yes	Yes	Yes	N/A	Yes
	Consultancy companies/ consultancy groups	No	No	Yes	N/A	No

* "Stop the clock" refers to the procedure in which the agency pauses activity to wait for a response from the manufacture for clarification or additional data

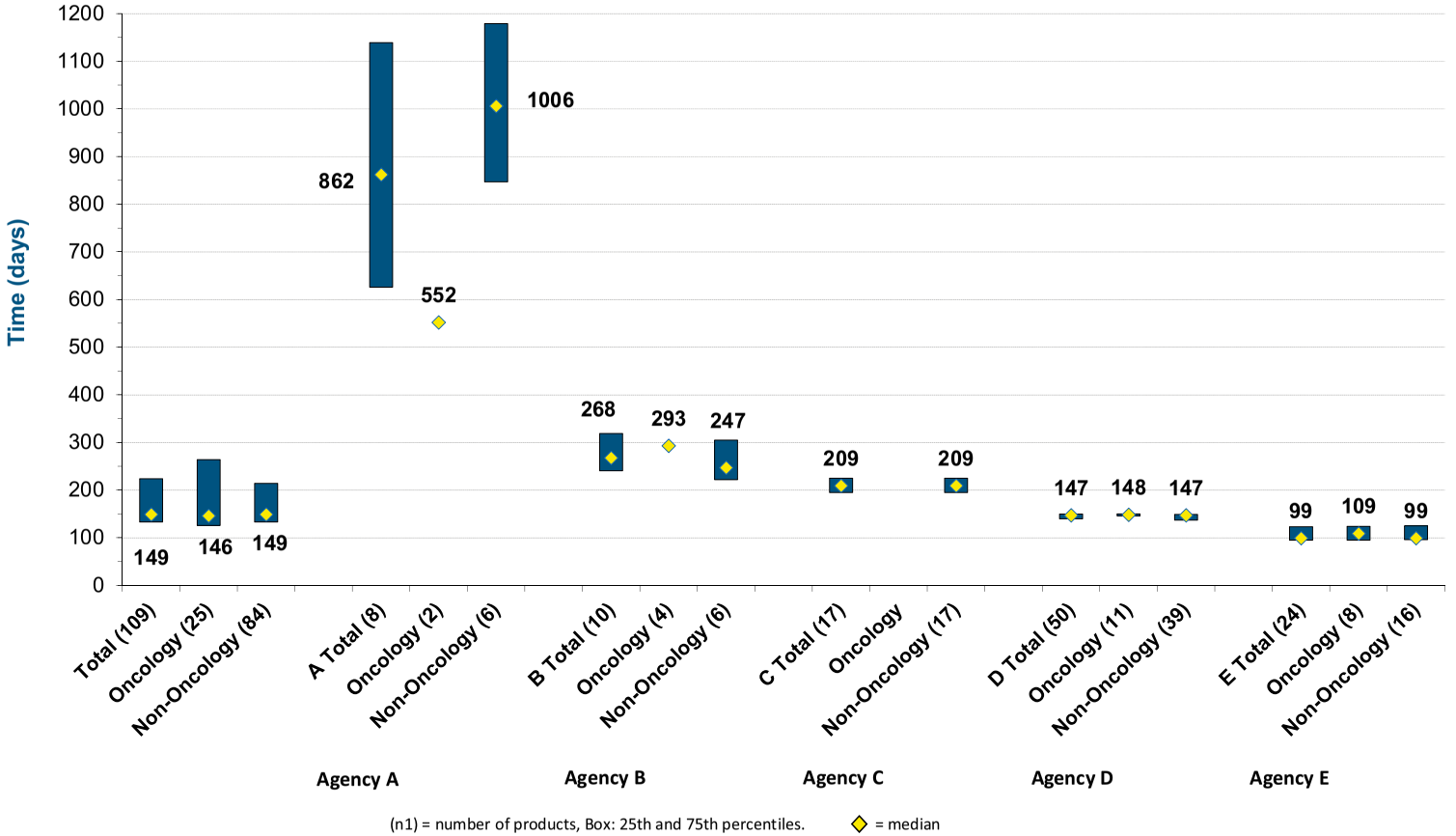

Figure 3. Time spent between submission to HTA agency and recommendation by HTA agency, analysed by oncology versus non-oncology and by HTA agency

to be the agreed principle within broader subgroup of key principles regarding the use of HTA in decision making (Drummond, Schwartz et al. 2008).

Because time is one indicator that can be measured precisely based on data provided by HTA agencies with common identified milestones, benchmarking HTA process time can create a valuable baseline to compare agencies. For HTA agencies, the results could facilitate internal performance improvement and the assessment of adherence to defined review target times for internal quality assurance, as well as improving the transparency of the HTA for external stakeholders in terms of where time was spent during the processes.

Benchmarking HTA Agencies: Understanding Organizational Context and Process

We emphasize in our study that to compare HTA agencies and measure and interpret timelines, an in-depth understanding of HTA processes across agencies and the numerous factor behind those processes is needed. Our study shows considerable differences among the median timelines from assessment through appraisal and final HTA recommendation for the five participating agencies. In the study, we collected fifty-one questions regarding the HTA organizational information to support interpretation of the timelines. The resources allocated for HTA activities are associated with review timelines: in the group of agencies analysed in our study only one agency has more than 75 percent of its resources dedicated to HTA activities, and this agency has the shortest median timelines. This was the only agency in the study where HTA processes constitute the core activities of the organization, whereas for the remaining four agencies, HTA activities are only part of broader scope of the organization's activities. This is particularly the case for two of the agencies, for which the percentage of FTEs dedicated to HTA activities is less than 25 percent and where the median timelines of the whole HTA process are the longest.

This interpretation needs to be regarded with caution as there are several other organizational factors that can impact timelines. First, different median timelines could be explained by the HTA processes in place in agencies; for example, extensive stakeholder involvement (including patients, clinicians, and pharmaceutical companies) in the processes, public consultation of draft documents or the appeal procedure available in case of negative HTA outcome (Rosenberg-Yunger, Thorsteinsdottir et al. 2012). Second, the frequency of appraisal committee meetings can also affect timelines, especially during the appraisal phase. In some organizations, committees meet several times per month and in some, several times per year. In this study, the frequency of committee meeting range is from twelve to twenty-one times per year. Third, delays can also be caused by pharmaceutical company strategy; for example, if a particular market is not a priority for a company, providing additional evidence or clarifications to an HTA agency could take longer.

This study shows that for three of the five studied agencies, the median time of overall processes were not affected by the HTA outcome whereas for the other two agencies,

the products that received a positive recommendation took the shortest time and the products that received a negative recommendation took the longest time. The results may indicate that for these two agencies, the HTA practice for assessing the products with negative outcome is different. For example, the longer timeline could be attributed to the involvement of stakeholders such as patient groups and clinicians, depending on the various mechanisms in place. Cai and colleagues investigated the time taken for products to receive the first HTA recommendation in six European jurisdictions (Cai, McAuslane et al. 2018), revealing that products that received a negative recommendation took longer to receive an HTA recommendation from the time of European Medicines Agency (EMA) approval. Although longer HTA timelines can delay patients' access to medicines, it is worth noting that time can be also spent on pharmaceutical company input such as additional evidence submission, comments and communication.

Has an International Standard or HTA Best Practice Already been Set and Implemented?

There has been an impressive number of internationally recognized initiatives to develop standards for best practice in HTA as well as practical HTA tools. Best practice in undertaking and reporting HTA has already been proposed by research groups in Europe over recent decades (Busse, Orvain et al. 2002). Also, some steps have been taken to establish internationally recognized good practices in HTA (Kristensen, Lampe et al. 2009). Consensus has been reached around the practical tools and methods in the field of HTA in Europe, including the HTA Core Model and rapid relative effectiveness assessments of new pharmaceuticals to be used for European collaboration (Kristensen, Lampe et al. 2009, Lampe, Makela et al. 2009, Kleijnen, George et al. 2012, Lampe, Pasternack et al. 2014, Kleijnen, Toenders et al. 2015). Continuous benchmarking of performance will be of great value to capture changes in the system. For example, in light of the EUnetHTA Joint Action 3 Work Package 4 joint production of HTA, for the products that underwent joint assessment, milestone metrics at individual HTA agencies could be collected using this methodology and used as a measure to assess the uptake time of EUnetHTA assessment in member states.

A recent report by the ISPOR HTA council suggested there was a lack of good practices in defining the organizational aspects of HTA and measuring the impact of HTA (Kristensen, Husereau et al. 2019). The implementation of HTA best practice into real healthcare system settings and thus the objective and reliable comparison of HTA agencies' outcomes and performance has yet to be resolved. This study uses quantitative metrics to measure agencies in terms of where time was spent at each stage of the HTA process, and the timeline can now be interpreted with qualitative information on agencies' process characteristics. This will facilitate a future study on setting a framework of good HTA practice.

Evidence from a regulatory agency benchmarking study showing a long queuing time in one agency led to an increase in resources at the agency to improve the submission

validation process (Hirako, McAuslane et al. 2007); similarly, HTA agencies could use benchmarking outcomes to improve processes by learning more effective and efficient ways to undertake reviews from other agencies.

STUDY LIMITATIONS

This study has some limitations that are worth noting. First, the number of agencies studied was small, as inclusion was based on data completeness. Second, the data sets used in the analyses were not up to date, as the results were intended to demonstrate the utility of the benchmarking tool, rather than assess the current performance of agencies. Another limitation of this study is the use of a trichotomous system of HTA recommendations (positive, positive with restrictions, and negative), which is a simplified categorization of HTA outcome. Further categorization has been used in research to provide more insight on different types of restrictions, but the detailed classification was used to investigate the divergences of decisions within a single HTA agency (O'Neill and Devlin 2010). To allow for comparison of HTA recommendations across agencies, the trichotomous classifications have been used in previous studies (Lipska, Hovels et al. 2013, Allen, Liberti et al. 2017, Allen, Walker et al. 2017).

The lack of assessment of the quality of industry submissions is another limitation of this study. Benchmarking is commonly associated with measuring quantitative metrics such as time, process, resource, and cost, but it is also possible to use qualitative measures in a systematic fashion to assess more difficult-to-measure parameters such as quality. However, although we consider that quality is an extremely important parameter, as the quality of an industry submission to an HTA agency can substantially impact timeliness of the HTA processes, it was considered to be outside of the scope of this research. Further studies to assess the quality of HTA submissions would be of benefit.

CONCLUSIONS

Our study shows that it is feasible to find consensus among participating HTA agencies regarding the common milestones of the HTA review process in order to map a jurisdiction-specific process against an agreed generic process. It is also possible to identify the detailed characteristics of each agency that enables these results to be interpreted in the appropriate context. Such benchmarking studies should be performed systematically and be based on the data provided directly by HTA agencies. Although a number of HTA agencies publish their recommendation date in the public domain, submission date to HTA agencies, and companies' responding time are not available. As one of the benefits of benchmarking HTA performance is to improve HTA transparency and predictability, and therefore we recommended that data on common milestones as well as target timelines be available in the public domain.

We observed that this HTA agency benchmarking tool has promising potential; however, timelines cannot be used as a single measure to compare or measure performance of HTA agencies but rather only in combination with an in-depth understanding of jurisdiction specific HTA processes.

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PART B

FOCUS ON PHARMACEUTICAL INDUSTRY

CHAPTER 3

COMPANIES' HTA STRATEGIES AND PRACTICES IN AUSTRALIA, CANADA, ENGLAND, FRANCE, GERMANY, ITALY AND SPAIN: AN INDUSTRY METRICS STUDY

Ting Wang, Neil McAuslane, Lawrence Liberti, Helga Gardarsdottir, Wim G Goettsch and Hubert GM Leufkens

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ABSTRACT

Background

Health technology assessment (HTA) has increased in importance in supporting payer decision making by assessing the relative effectiveness and cost effectiveness of new medicines. Thus, pharmaceutical companies need to address the HTA requirements early during development to improve reimbursement outcomes. Currently, there is a lack of research to assess the impact of HTA on development and jurisdictional outcome from companies' perspectives. This study aimed to assess companies' HTA strategy and characterise HTA practice in seven jurisdictions.

Methods

A multi-year, annual study collected information for individual products, focusing on development activities regarding inclusion of HTA requirements and selection of global comparators. The generation of local contextual information, submission strategies and predictability of HTA outcomes was examined jurisdictionally in Australia, Canada, England, France, Germany, Italy and Spain. The study questionnaire was built into a secure online data collection platform and data were provided annually by participating companies.

Results

Data for 169 compounds were provided by nine international companies between 2014 and 2018. HTA requirements were implemented in evidence generation plan for 63% of products during development. Global comparators were accepted by HTA bodies for more than half of studied products; Spain showed the highest acceptance rate (85%). Companies took advantages of parallel process in Australia and Canada to shorten product rollout time. Australia demonstrated general consistency in HTA review time, and England had the longest variation (interquartile range, 216 days). Requirements for additional information after submission occurred at all HTA bodies. Germany and Italy showed the highest percentage of products being reimbursed as per regulatory label (80% and 68% respectively). Canada was the most predictable jurisdiction, with the highest proportion of review outcome (90%) that met companies' expectations.

Conclusions

Companies are addressing HTA requirements during development for many products; however, they are challenged by varying requirements and practices and product success ultimately depends on how HTA organisations and payers assess added value in the context of the national healthcare systems. This ongoing study created a baseline to help capture fact-based changes for company HTA strategies and HTA body practices.

INTRODUCTION

Drug development is a long, costly and complex process (DiMasi et al., 2016) and in response to competitive pressure, pharmaceutical companies continue to improve research and development productivity to bring innovative medicines to market (Cohen, 2005; Smietana et al., 2015). There is also a growing interest from regulatory agencies and heath technology assessment (HTA) bodies to adapt flexible processes to expedite the availability of medicines to address critical healthcare needs (McAuslane and Liberti, 2019). Over the last decade, the number of medicines that have received regulatory authorisation has risen, and with 60 approvals in 2018, the US Food and Drug administration (FDA) had its highest number of approvals in the decade (Rodier et al., 2019). However, the success of these products for pharmaceutical companies remain to depend on how HTA organisations and payers will assess their added value in the overall context of the national healthcare systems (Sood and deVries, 2009).

HTA has increased in importance in supporting payer decision making by assessing the relative and cost-effectiveness of new medicines in comparison to existing technologies based on local context (Goodman and Ahn, 1999). One study showed that only a proportion of regulatory approvals received an initial positive HTA recommendation (Wang et al., 2019), which could result in price constraints, reimbursement restrictions by the payer and time delay to patient access, particularly as new products might become available in different jurisdictions at different times. Therefore, pharmaceutical companies need to address the expected HTA requirements during drug development in order to improve the HTA outcome and to maximise patient access and commercial success.

To this end, companies have implemented cross-functional collaborations within their organisations to bring clinical, regulatory, health economics and outcomes research (HEOR) and access teams together during the drug development process to ensure the generation of evidence that supports both regulatory approval and an HTA recommendation (van Nooten and Holstrom, 2012; Wang et al., 2018). Nevertheless, results of a recent stakeholder survey showed that companies were concerned about uncertainties regarding how best to incorporate HTA requirements early in development. Complexities included the variability in HTA requirements across jurisdictions, rapid changes in clinical practice and standard of care that could impact the choice of comparator and often highly divergent economic environments (Wang et al., 2018).

Researches have been undertaken to compare the processes and methodologies use by HTA bodies and their recommendations (Schwarzer and Siebert, 2009; Kristensen and Gerdhaus, 2010; Kleijnen and George, 2012; Nicod, 2012; Allen et al., 2014; Lipska et al., 2015; Salas-Vega et al., 2016; Nicod and Kanavos, 2017; Allen et al., 2017; Akehurst and Abadie, 2017; Angelis et al., 2018, Vreman et al., 2020). Table 1 summarises the feature of key HTA agencies studied by researchers. These studies have contributed to the awareness and identification of divergences in HTA recommendations and have reinforced the argument of the need to bring alignment across HTA bodies as an approach to improving patient access to new medicines on a global scale.

Works are in progress to promote better alignment of HTA. Early scientific advice programmes have been used as a platform at both national and international levels, for companies to gain insights on the evidence requirements from HTA bodies. A high level of agreement on the evidence generation between EMA and European HTA bodies have been observed during these advice meetings (Tafuri et al., 2016).

In Europe, a proposal for a "Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU" was published in 2018, suggesting joint work on HTA at Union-level (European Commission, 2018). This proposal was welcomed by pharmaceutical companies as a way to ensure consistency, transparency and synergies in clinical assessment by member state HTA bodies (European Federation of Pharmaceutical Industries and Associations, 2018). The European network for Health Technology Assessment (EUnetHTA) has developed the HTA core model as a standardised framework for the generation of HTA information (EUnetHTA, 2016). This methodological framework has been evaluated by companies and has been found to be useful in improving the efficiency of evidence generation (Gyldmark et al., 2018). In particular, the clinical domain of the core model has been found to be the main driver for HTA recommendations and the consistency that this model brings is expected to support the proposed joint assessment of the clinical value of new products at the European level (Giuliani et al., 2018).

Despite the continued refinement of HTA processes and methodologies, pharmaceutical companies continue to explore the most efficient internal practices that can be

Table 1. Summary of key features of HTA agencies

Jurisdiction	Regulatory approval	HTA assessment and appraisal	Main HTA criteria	Influence of HTA on drug pricing	Managed entry scheme
Australia	National	National	Clinical, Cost effectiveness	Indirectly as it has an impact on ICER	Yes
Canada	National	National and regional	Clinical, Cost effectiveness	Indirectly as it has an impact on ICER	Yes
England	Pan-European	National	Clinical, Cost effectiveness	Indirectly as it has an impact on ICER	Yes
France		National	Clinical	Yes, ASMR rating used for pricing negotiation	Yes
Germany		National	Clinical	Indirectly through the level of added benefit	No
Italy		National and regional	Clinical, budget impact	Yes	Yes
Spain		National and regional	Clinical, Budget impact	Yes	Yes

Allen et al., 2017;Angelis et al., 2018

implemented during the drug development process to ensure that the best data can be obtained to address jurisdictional HTA expectations, in order to support positive and timely reimbursement outcomes. Currently, there is a lack of research from the companies' perspective into the impact of HTA requirements on the drug development plan and subsequent jurisdictional submissions and assessments. This study aimed to characterise the practices of international pharmaceutical companies that address HTA requirements by collecting specific metrics and activities for new products from development to rollout at the jurisdictional level.

The objectives of this study were to:

- Identify companies' HTA practices during development and before jurisdictional submission;
- Capture rollout milestones that help provide an understanding of the companies' submission strategy and HTA bodies' consistency;
- Examine the predictability of reimbursement outcome.

METHODS

Development of the study questionnaire

A multi-year, annual metrics study was developed by the Centre for Innovation in Regulatory Science (CIRS) in partnership with pharmaceutical companies. The development of a study questionnaire evolved in three phases: First, an industry task force of interested senior executives from 7 multinational pharmaceutical companies guided the creation of the initial study proposal. A call for interest was then distributed to 15 multinational companies and 10 companies agreed to participate in the pilot study and took part in a questionnaire development process through a one-day industry discussion meeting. The meeting was held in March 2011 to agree on the methodology and to define the scope of the study, including the jurisdictions and products to be evaluated. The pilot study was conducted during July-September 2011 to collect information on three new active substances (NASs) from each company recently licenced in targeted jurisdictions. This phase identified the metrics to be collected to understand the impact of HTA requirements on the development programme, to assess the rollout timeline of products across jurisdictions and to provide participants with early insights.

Results of this study enabled the refinement of the methodology for next pilot study. The scope of 2012 pilot was expanded to include both recently licenced products and projects currently under pivotal trial development. The inclusion of development projects captured current HTA strategies for drug development and enabled continuous data collection in future studies when the projects become licenced. These pilot studies led to the finalisation of the annual study questionnaire, which has been in use from 2013 onward.

Structure of the study questionnaire

The final study questionnaire was organised into two sections and collected metrics on drug development and jurisdictional roll out. The structure and the rationale of the questionnaire are listed in Table 2.

Product and jurisdiction inclusion criteria

The scope of products in the study covers both projects under development and licenced products. Information for both NASs and major line extensions (MLEs) that met the criteria were collected. The inclusion criterion for the development projects were pivotal trials beginning within 1 year from the data collection year. The inclusion criterion for the licenced products were market authorisation or HTA recommendation in a target jurisdiction within 1 year from the data collection year. There is no restriction on the therapeutic area, all compounds fit the above criteria have been included in the study.

Exclusion criteria were: generics; vaccines; development of a marketed active substance without any change to formulation or indication/disease state; changes to labelling for reasons other than those relating to new indications/disease states or new formulations; changes to manufacturing and control methods; applications where a completely new dossier was submitted from a new company for the same active substance and the same indication(s) as already approved for another company; and applications from a new or additional name, or a change of name for an existing compound.

The key jurisdictions included in the study were Australia, Canada, England, France, Germany, Italy, and Spain. Jurisdictions were selected by study participants based on the importance of the market to companies and the maturity of the HTA systems. For Canada, Italy and Spain, data on HTA were collected at the national level, the regional adoption of national HTA decisions was out of scope of this study.

Milestone definitions

"First worldwide regulatory submission" was defined as the date a product was submitted to the first regulatory agency for market authorisation anywhere in the world. "Regulatory submission gap" was calculated as the time taken from first worldwide regulatory submission to the submission to local regulatory agency. "Regulatory review time" was defined as the time taken from the submission of the dossier to the approval by the specific regulatory agency (EMA review time was defined as the date of application submission to the date of the European Union (EU) Commission decision). "HTA submission gap" was defined as the time taken from the date of local regulatory approval to the date of the first submission to the jurisdictional HTA body. "HTA review time" was defined as the time taken from the first submission of the value dossier to the date of the first HTA recommendation in that jurisdiction, HTA review time for re-submissions was not included in this analysis.

Table 2. Structure of the questionnaire

Sections	Key topics	Rationale	Example questions
Drug development section 10 questions (28 metrics) *Current data collection for development projects; retrospective data collection for licensed products*	Compound characteristic and development milestones	Basic characteristics of compound were collected to facilitate tracking the success of the project over the long term and identify different HTA review trends by product type	Active substance type: Please select if the product is new active substance or major line extension
			Therapeutic area: Provide the first two levels of the WHO Anatomical Therapeutic Chemical (ATC) classification system (enables partitioning of the data by indication)
		Key milestones from development phase were collected in order to determine the relative length of development and whether inclusion of HTA considerations or timing of HTA advice influences development time or decision making	Pivotal trial date: Provide the development milestone of first pivotal dose for the respective indication
	HTA scientific advice	The collection of data on scientific advice meetings during drug development and the impact of these meetings on trial design are important elements in development decision making	When and from whom were companies seeking scientific advice?
			Did the advice change the evidence programme?
	HTA-related considerations	A key element of the development survey is to determine which HTA technical requirements are currently being included in pivotal trials and the extent of their implementation or non-implementation	Which HTA technical requirements have been incorporated into global development? For example, HTA accepted primary endpoint
			Were active comparators/ interventions included in drug development?
Jurisdictional section 9 questions (34 metrics) Jurisdictions included:	Local submission strategy	To identify if additional clinical evidence specific to the requirements of the individual jurisdiction were generated and whether any of the local jurisdictions were consulted by the company prior to submission	Was additional local contextual information (in terms of local population and local standards of care) generated prior to submission?
			When and from whom were companies seeking pre-submission advice?

Table 2. (continued)

Sections	Key topics	Rationale	Example questions
Australia, Canada, England, France, Germany, Italy, and Spain *Data collection for recently licensed products*	HTA review characteristics	To review the evidentiary package submitted to the jurisdiction, as well as explore specifically the issue of inclusion of comparators into the evidentiary package. To assess the expectation in terms of reimbursement outcome for each jurisdiction and used to identify jurisdictions that are or are not predictable	Were the comparators in the global evidence package accepted by the local HTA agency? Were additional comparator(s) required? What type of additional comparator(s) were required?
	Review milestones HTA appraisal/ reimbursement outcome	The dates for product submission to respective agencies and the dates of agency decisions will be used to compare the timeliness and the consistency of different agencies Compare the recommendations of the key HTA/ decision-making agency in each jurisdiction, as well as the final reimbursement outcome.	First HTA submission and recommendation date Final coverage decision date Reimbursement label to the regulatory approval label population Post-marketing studies requirements
	Reason for success and outstanding issues	To ascertain reasons for success for each product and to identify issues of concern that were raised, irrespective of recommendation outcome, by the HTA agency.	Provide information on the outstanding technical issues raised by agency during the HTA decision-making process

Data processing and analysis

The study questionnaire was built into a secure online data collection platform developed by CIRS, and data were provided by company participants during second and third quarter each year. Data collection was completed by the third quarter each year and the data were exported into an Excel file and analysed using descriptive statistics. For each analysis reported in this paper, the cohort of products included in the calculation was based on the completeness of data provision. To maintain confidentiality, only aggregated results were reported and any data that identified an individual product or a specific company were excluded from the analysis.

In the timeline analysis, median time in days was calculated for products rolled out to each jurisdiction; the range of HTA review time was also explored using a box plot to show the variation between 25th and 75th percentiles; product characteristics such as NAS type and main therapeutic area were applied to stratify analysis results.

Jurisdictional predictability was studied based on variation of HTA review time and level of expectation in HTA recommendation. The HTA review time measured the time taken from submission to first HTA recommendation, regardless the outcome of the recommendation. The review time variation of each jurisdiction was analysed by the interquartile range of HTA review time for all products assessed in the jurisdiction. The expectation of HTA recommendation was subjective measure of companies' view, companies were asked to rate if the recommendation was expected or not, regardless of the outcome of the recommendation. The level of expectation in HTA recommendation was calculated based on the number of products for each jurisdiction that achieved the company's expectation among all products assessed in that jurisdiction.

RESULTS

In this paper, we excluded data from the pilots and focused on information provided by companies that participated between 2014 and 2018. A total of 169 compounds were collected from 9 international companies during this period, of which 66% were NASs. More than half of the compounds (53%) in the database were oncology products, which were consistent with the top therapeutic areas identified in the current development pipeline and recently approved products (Albrecht, B, 2018). The jurisdictional information was analysed based on licenced products and the timing of first worldwide regulatory submission for those products ranged from November 2006 to August 2017. For each analysis in this paper, the number of products assessed at jurisdictions varied due to the availability of data for that question, the number of products and companies were stated in each figure.

Evidence requirements during drug development and rollout

For 65 of 104 licenced products (63%), HTA requirements were considered and implemented in the evidence generation plan, which showed a good level of incorporation

of HTA expectations during development. However, practices varied between companies, ranging from 37% to 100% of the developed products, showing different strategies among the participating companies.

The most commonly included technical HTA requirements among the 65 products were safety measures (92%), HTA acceptable secondary endpoints (89%), patient selection criteria (88%), study design elements (88%), HTA acceptable primary endpoints (86%) and trial duration (85%). Non-technical requirements were also embedded, including addressing the place of the new therapy in treatment pathways (75%), addressing unmet medical need (71%), and providing a cost-effectiveness evaluation (65%). We followed up the comparators included in the global development plan by companies and investigated the acceptance of the comparator choice by HTA bodies during roll out.

For more than half of the submissions, the choice of the comparator was fully accepted at target HTA bodies, with Spain and Canada showing the highest acceptance rate (Figure 1). In some cases, HTA bodies also partially accepted the global comparator choices, and requested additional comparators to their assessment. This was seen mostly in Australia (33% of submissions) and England (26% of submissions). HTA bodies that conducted benefit assessment (e.g. in France and Germany) showed the highest proportion of comparator rejections, 12% and 27% of total submissions, respectively. For submissions where the global comparators were not accepted, additional comparators were required by the HTA bodies. In most cases (77%) comparators based on the local standard of care for this indication were requested, and 23% of cases recommended the use of the least costly therapy as the comparator.

In this study, eight products were reviewed in all seven target jurisdictions, however, their reimbursement status varied across all jurisdictions. Four of the eight products had their global comparators accepted (full or partially) across all seven jurisdictions, nevertheless in the case of the other four products, the comparator choices were not accepted by one or two HTA bodies.

In addition to the evidentiary package based on the global development plan, we observed that companies in this study generated local contextualised information before submission to meet the specific requirement of an HTA body. A high proportion of submissions to England (90%) incorporated local contextual information (in terms of local population and local standard of care), followed by Germany (82%), Italy (80%), Spain (79%), France (72%), Canada (63%) and Australia (61%).

The study revealed that after the dossiers were submitted, HTA bodies still required additional evidence to be provided by the companies to support the assessment. Figure 2 showed the proportion of submissions at the local level for which additional evidence was required by HTA bodies. England showed the highest frequency of requesting additional evidence from companies, with 63% requests being for a locally relevant comparator; this was followed by Germany, with 56% requested being sub-group analysis. We further analysed the details of the evidentiary requests across all HTA bodies: 53 of 120

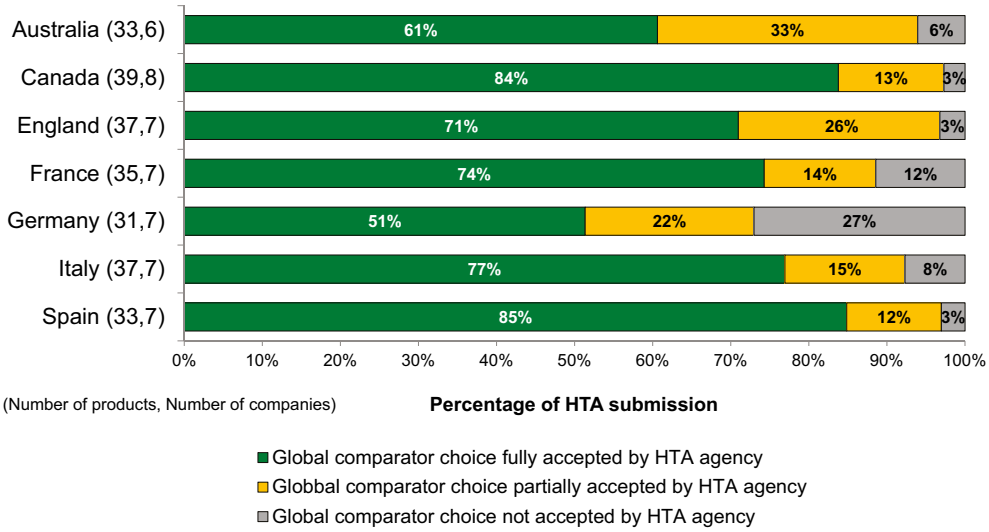

Figure1. Acceptability of companies' selection of comparators in global clinical trials.

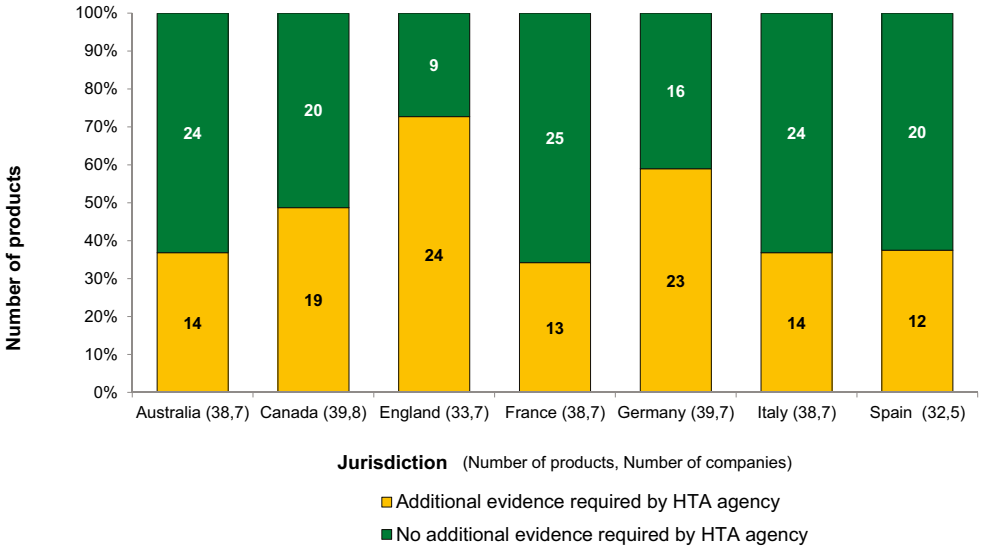

Figure 2. Proportion of companies' submissions where additional evidence were requested.

requests (44%) were related to the use of a locally relevant comparator, 35% were for a sub-group analysis, 26% were for a locally relevant economic analysis, 24% were to contextualise the evidence to the local population, 21% were for the use of a different analysis methodology, 13% were related to the use of a network meta-analysis, and 10% were requests for trial data in the local population.

Companies' submission strategy to regulatory agencies and HTA bodies

Products that received HTA recommendation in targeted jurisdictions were analysed for their rollout time, that is, the time taken from first regulatory submission to the HTA decision in each local jurisdiction. Companies were likely to submit to Europe for market authorisation first across the target jurisdictions, followed by Australia and Canada, with median delays of 81 and 73 days, respectively.

In Australia and Canada, companies can submit the dossier to the respective HTA body before the market authorisation is granted; the median overlap between the regulatory and HTA process was 107 days in Australia and 30 days in Canada. There was a variation from the EMA approval to the HTA submissions in Europe; the median time gap was 7 days in England, 23 days in Italy, 29 days in France, 42 days in Germany and 49 days in Spain. Companies sought advice from agencies before HTA submission, the study showed that Germany has the highest proportion of pre-submission advice among its total submissions (73%), followed by Australia (69%), France (35%) and Canada (23%). Information on pre-advice in other jurisdictions was limited.

The time from HTA submission to recommendation varied across the targeted European jurisdictions, ranging from 155 days in France to 375 days in Italy. Figure 3 illustrates the median time and 25th to 75th percentile of HTA review for products provided by companies in each jurisdiction. Australia demonstrated general consistency in HTA review time, with interquartile range (IR) being 9 days. England had the longest variation for HTA reviews (IR, 216 days), followed by Spain and Italy (IR, 161 days and 144 day respectively). Canada and Germany showed similar variation in the review process with IR being 97 days and 89 days.

We further stratified the HTA median review time by product types. For companies that submitted oncology products for HTA review, the median time taken to receive HTA decision was longer in Spain, England and Italy compared with overall median time; there were no differences in median time to receive HTA decision for oncology products in Australia, France and Germany. The biggest divergence in HTA review time for oncology products was observed in Spain, where it was 51 days longer than the overall median. Interestingly, Spain also showed the biggest difference in median HTA review time for NASs compared with overall products, which was 56 days longer. In England and Italy, NASs products were reviewed faster (40 days and 6 days respectively) compared with the overall median.

Companies' predictability of HTA success and restriction on reimbursement

Predictability of HTA outcome plays an important role in market access planning for companies. In this study, participating companies were asked if the outcome of the HTA recommendation for each of their products had achieved the companies' expectation prior to submission. France was identified as the least predictable jurisdiction, based on the outcome of the initial HTA recommendation (55% of total submissions), followed by Italy (58%) and Germany (70%). In comparison, Canada showed the highest proportion of products (90%) that met companies' initial expectation regarding HTA outcome.

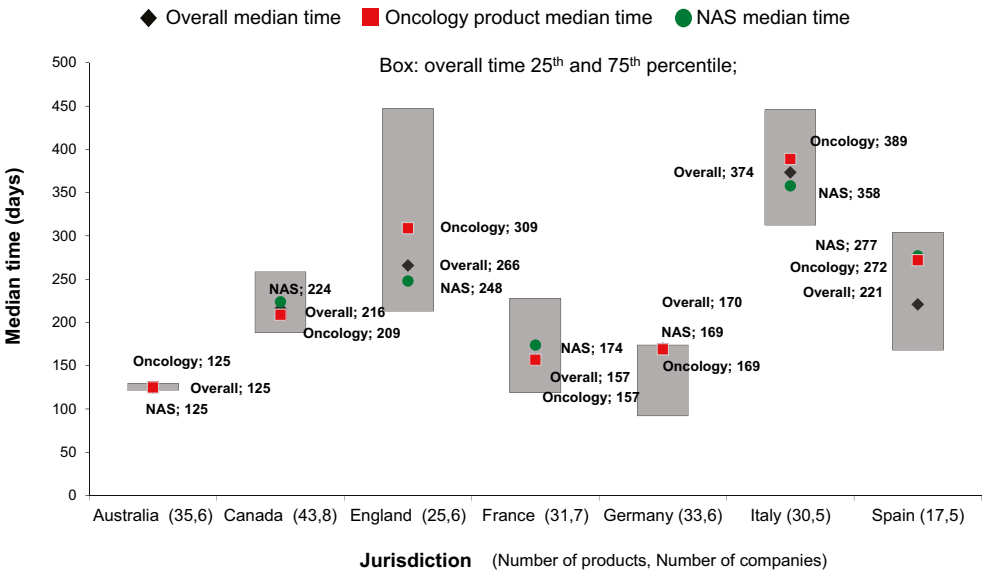

Figure 3. HTA review time for products provided by participating companies.

In relation to the reimbursement outcome, we assessed the reimbursed indication by comparing it with the authorised label use (Figure 4). Germany and Italy showed the largest proportion of products reimbursed as per regulatory label, while Australia applied the highest percentage of label limitations (72%) to its submissions. In Germany, four products were reviewed as "no added benefit" and were subsequently withdrawn by the companies. The four products were categorised as "not reimbursed". No product in this study received the same initial reimbursement outcome across all jurisdictions.

For products for which the companies indicated that they had an expected HTA outcome, the majority (93%) were reimbursed fully or with restriction to label population. Meanwhile, for products that were not reimbursed or severely restricted of use, 70% of their HTA outcomes were viewed as "unexpected" by companies. In this study, 55 reimbursement decisions were granted with staged entry to market, which was mostly used in Australia (38% of reimbursement decisions), Italy (32% of reimbursement decisions) and Canada (25% of reimbursement decisions). The most utilised mechanisms were "risk-sharing plan required for reimbursement" (47%) and "managed entry scheme" (35%).

DISCUSSION

A clear understanding of how HTA requirements are embedded in drug development and addressed in jurisdictional submissions is imperative for companies to ensure better predictability of an HTA outcome. This study collected HTA related metrics for individual products from companies, the results provided a snapshot of companies' current

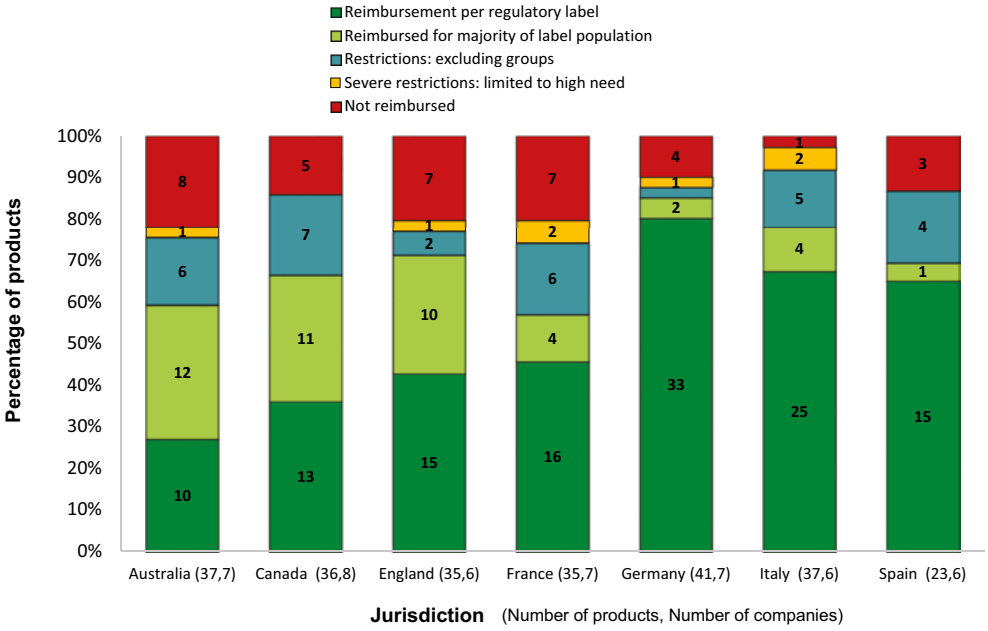

Figure 4. Reimbursement decisions for products provided by participating companies

practices in terms of including HTA requirements in evidence generation plan, submission strategy to HTA bodies and their predictability of HTA success. The results also reflected the divergences of HTA systems from companies' perspective and provided practical implications for companies to improve the understanding and readiness for jurisdictional HTA submission.

Companies' practice in generating HTA-relevant evidence during development and rollout

First, this study evaluated the acceptance of comparator choice by HTA bodies. Clinical trials provide an important evidence base for regulatory and HTA assessments. It is important for companies to choose the right active comparator in the development phase to ensure the scientific validity of trial designs and to be able to prove the value proposition of new products. Our results revealed a good level of acceptance on comparator amongst the HTA bodies studied, reflecting that companies were generally making the right development decisions. A survey conducted in 2017 among HTA bodies in Europe confirmed that the efficacy and safety profile were the most important criteria for comparator choice, along with identifying the comparator that was likely to be replaced by the assessed technology (Kristensen, 2017). However, companies in our study were challenged in Germany with a 27% rejection rate on the global active comparator choice. This may be because the added benefit of new medicines was assessed on subsets

of the population by Institut für Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) (Kaiser et al., 2015); therefore, additional comparators were utilised to identify benefits in the subgroups. A better understanding of the rationale for comparator selection by different HTA bodies is, therefore, needed. The choice of comparators has been a key discussion component at EMA-HTA parallel advice meetings; divergences were observed in the advice provided across different HTA bodies, and the potential solution of using indirect comparison was recognised (Tafuri, Pagnini et al. 2016).

Second, this study evaluated the companies' preparation before the HTA submission at the jurisdictional level. Local evidence generation related to comparisons to the local population and local standard of care was seen often in submissions to England and Germany. This suggested that the local company affiliates in these jurisdictions were actively preparing for the HTA submission, translating the global evidence package to the local context. Conversely, the highest proportion of HTA submissions requiring additional evidence were in England and Germany, which showed a divergence between companies' and HTA bodies' perspectives. In Germany, the most requested information after the HTA submission was a subgroup analysis. This issue has been recognised by other researchers and a more comprehensive discussion between companies and HTA bodies was suggested regarding the meaningfulness of subgroup analysis (Rasch and Dintsios, 2015). It has been recognised that a minimum set of evidence requirements could be prepared for HTA submission across Europe (Oyebode et al., 2015); however, to move forward with a centralised HTA assessment in Europe, it is crucial to understand the additional evidence required among HTA bodies, why these requests diverge across the jurisdictions, and the ultimately added value of extra evidence generation.

HTA submission strategies and rollout timelines

Timely recommendations for drug reimbursement by HTA bodies is critical to ensure patient access to new medicines. Researchers continuously monitor HTA timelines as an indicator of drug availability (Wang et al., 2019; Zamora et al., 2019); however, because HTA submission dates are not generally publicly available, these studies have been based on milestones collected from the public domain and have only measured the overall time from regulatory approval to the HTA recommendation. As the milestone metrics in this study were provided directly by companies and included the HTA submission dates, our rollout analysis was able to illustrate the full picture of regulatory and HTA pathways in the key jurisdictions.

In Australia, a parallel review process has been available since 2011 for companies to submit HTA dossiers prior to receiving market authorisation. Although the process allows companies to submit HTA dossier to the Pharmaceutical Benefits Advisory Committee (PBAC) as soon as the regulatory application to the Therapeutic Goods Administration (TGA) is accepted for review, but HTA decisions cannot be made until the TGA delegate report is finalised for approval (PBS, 2018). Our data showed that companies generally

submitted a median of 107 days prior to the TGA regulatory approval and consequently, Australia was typically the first country in which companies received an initial HTA recommendation within the studied jurisdictions. The parallel process has also been available in Canada since 2012; it differs from the Australian system in that submission to the Canadian Agency for Drugs and Technology in Health (CADTH) should occur within 90 days before the date of anticipated notification of compliance (NOC) from Health Canada. In our study, companies tended to submit the HTA dossier approximately 1 month prior to the regulatory approval in Canada. From 2 April 2018, the deadline for CADTH submission was extended from 90 to 180 days before the anticipated NOC (CADTH, 2020). It is expected that the impact of this extension on companies' submission strategies will be reflected in future results from this continuing study.

The submission gap from EMA approval to submission to European HTA bodies can be attributed to both company submission strategies and HTA system settings. In England, companies are likely to generate local contextual evidence prior to the HTA submission and the submission gap showed in our study was only 1 week (median). This may be because National Institute for Health and Care Excellence (NICE) conducts scoping exercises before a product has received a market authorisation and before an appraisal topic is referred to NICE by the Department of Health (NICE, 2009).

In Germany, the HTA process starts within 3 months from regulatory approval by law, and the HTA assessment is to be completed within 6 months from submissions (Gemeinsamer Bundesausschuss,2020). In our study, the submission gap was a median 42 days (1.4 months) in Germany, and HTA review time was a median 170 days (5.7 months), showing good compliance with these defined timelines.

In general, HTA submissions were conducted across all the studied European HTA bodies within 2 months of EMA approval, showing that it is possible for companies to submit the HTA dossiers in a timely manner. This supports the case that companies can be ready to submit their value dossiers quickly should a centralised HTA platform come into play in the near future.

The variation in HTA review timelines can be explained by the different review procedures used and the nature of company interactions during the review. The median HTA review time in Australia was consistently 4 months, which reflected the frequency of the PBAC Committee meeting; the timeline did not differ for NASs and MLEs, or by therapeutic areas, and this consistency confirmed that HTA in Australia was procedurally predictable.

Company-HTA body interactions during assessment such as providing additional evidence and clarifications on questions can contribute to longer HTA review time. A number of HTA bodies applied a stop-the-clock mechanism during the HTA process (Kristensen, 2017), for example, in England, NICE will allow a clock stop for certain products. In our study England showed the most variation in review time, which was also in line with the high proportion of requests for additional evidence. Despite that the observation that Germany requested additional evidence for a high proportion

of its submissions, the review time was within 6 months, in compliance with the law. Certain HTA bodies employed a clock-stop mechanism while companies were preparing a response; we did not characterise whether the clock-stop was applied by the studied HTA bodies. Companies also sought pre-submission advice from HTA agencies, such activities are intended to improve the quality of the dossier submitted and potentially reduce the need for clarification during the assessment. Further research is needed to assess the link between pre-submission advice and company-HTA interaction during the assessment.

In England, the HTA review of oncology products took longer than the median NICE review time; in the case that NICE appraisal concluded that there was insufficient evidence to support a recommendation, products could be reimbursed through cancer drug fund (National Institute for Health and Clinical Excellence, 2020).

Practical implications for companies

HTA bodies are continuously improving their procedures and methodologies to ensure quality decision making that enables timely patient access to medicines of value. Research has been carried out to identify attributes that underpin a good HTA submission and review (Mazumder et al., 2015; Wang, 2015). A recent literature review summarised the areas in which good HTA practices have been identified, including the identification and interpretation of evidence, priority setting, framing, scoping principles, and HTA implementation. This research also pointed out areas in which good practices were currently lacking, including defining the organisational aspects of HTA, the use of deliberative processes and measuring the impact of HTA (Kristensen et al., 2019). However, there was no systematic and continuous measure of HTA submission and review practice. Our study collected metrics on individual products from companies and provided unique insights regarding HTA bodies' review practices by characterising timeliness, transparency and predictability at key jurisdictions.

Australia showed the greatest predictability regarding HTA review time and outcome expectation; the consistent review time of 125 days was associated with the frequency of the PBAC Committee meeting (Pharmaceutical Benefits Advisory Committee, 2017). Moreover, companies have taken advantages of the parallel process in Australia with a median 107-day overlap between regulatory and HTA review, which resulted in shortening the overall rollout time. However, Australia was the country to most often not reimburse medicines as per regulatory label in this study. CADTH, which was the second most consistent HTA body in terms of review time, also showed a high level of acceptance of active comparators used in global clinical trials. Whilst companies need to be aware of additional evidence requirements by CADTH during the review process, which affected half of its submissions in this study; most of the CADTH recommendations met the expectations of companies, reflecting a good understanding and predictability of the system. Medicines were also likely to be reimbursed with limitations compared with the approved regulatory label in Canada.

In England, NICE does not appraise all new medicines approved by EMA; however, the topic selection was transparent, with its rationale, process and decisions published on the NICE website. As part of the topic selection, NICE scoping activity includes a draft scoping report and scoping workshop to identify information related to the medicine before EMA approval. The scoping step was viewed by NICE as a critical step to ensure a successful appraisal (Kaltenthaler et al., 2011) and this efficient process was reflected in our results in terms of the short gap between EMA approval and NICE submission time, as well as a high number of submissions with local contextual information generated before NICE submission. Nevertheless, NICE had the widest variation in review time compared with all studied HTA bodies, reflecting the NICE process which involves stakeholders and public comments on draft guidance before the finalisation of recommendation (National Institute for Health and Clinical Excellence, 2009)

France showed the quickest median HTA review time among all European jurisdictions in this study. However, the speed of decision was compromised by a less predictable outcome, with 45% of applications submitted to Haute Autorité de Santé (*HAS*) receiving an unexpected benefit rating. A 12% rejection rate of global comparator choice in France also demonstrated the needs for further communication between companies and the HTA body during the development stage to facilitate the local submission and improve the predictability of the outcome.

The German HTA system was consistent in terms of submission gap and review time and complied with the timeframe of 3 months and 6 months respectively as defined in law. The outcome of Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) benefit assessment was associated with the price negotiation between companies and the National Association of Statutory Health Insurance Funds (Spitzenverband Bund der Krankenkassen, GKV-SV); therefore, the reimbursed labels of products in our study were mostly in line with regulatory approval. To achieve better G-BA outcome for a favourable reimbursement price, companies need to have a better understanding of the evidentiary requirements in Germany, in particular, regarding active comparator choice and sub-group analysis.

Italy stood out among all studied jurisdictions with the longest HTA review time. Despite the fact that companies submitted dossiers for HTA review just 23 days after EMA approval, it took more than 1 year for products to gain an HTA recommendation in Italy. The duration of the review time may be attributed to the process of price negotiation and access restrictions. AIFA implemented extensive use of outcomes-based managed entry agreements (Angelis et al., 2018), and a 2019 study by Villa et al showed that the managed entry agreement and product monitoring registry were the main determinants for price negotiation, that led to reduction from the proposed price by industry to the final negotiated price (Villa et al., 2019). In our study, although results showed that 80% of evidence packages submitted for HTA review in Italy included local contextual information and 77% used the comparator choice accepted by HTA, HTA

outcomes were still unexpected for 42% of total Italian HTA reviews in this study, and more than one third of HTA recommendations required staged entry to market.

Spain had the highest acceptance rate of comparator choices (97%) and also good predictability of HTA outcome (77% of total submissions). Companies were prepared for the HTA submission in Spain, with 79% of dossiers including local contextual information, however, this preparation may have led to a submission gap after EMA approval, which was the longest in Spain among all studied European jurisdictions.

STRENGTH OF THE STUDY

Although there is an increasing number of studies to compare the HTA process and subsequent outcomes for new medicines, specific metrics to inform company decision making around HTA requirements are limited. This annual metrics study has been developed by CIRS in partnership with multinational companies. This collaborative approach represents the first effort among industry to collect HTA-related metrics by following individual products from development through to an initial reimbursement decision. The results provide unique insights into both companies' practices regarding HTA during development and reflected the timeliness, predictability and requirements of HTA systems in studied jurisdictions.

LIMITATION OF THE STUDY

This study collected information from nine participating multinational companies, therefore the results were viewed through the lens offered by these companies rather than the whole industry. However, we believe these companies were representative of international companies and their practices were a good indicator of other companies' HTA approaches. Caution needs to be taken when interpreting the jurisdictional results, as these were not a reflection of the overall performance of the studied HTA bodies.

For each product, not all metrics in the questionnaire were provided, due to practical limitations of access. Therefore, the completeness of datasets for each question differed, and resulted in small divergences in the size of datasets used for specific analyses in the study. Another limitation is the type of products provided by company, where oncology products made up to 53% of the database in this study. As regulatory and HTA agencies have been increasing the transparency of their decision making, information such as regulatory public assessment reports and HTA recommendation reports have been made available on the public domain. Aligning the information from the public domain and the company-provided data will enhance the completeness of the database and enable further research questions to be addressed.

CONCLUSIONS

This CIRS-industry study is the first consolidated effort to collect metrics to assess the companies' practice to address HTA requirement during development and rollout.

The results demonstrated that companies have been actively including HTA requirements during development and generated local contextual information for jurisdictional HTA review. Companies utilised parallel regulatory/HTA review processes in Australia and Canada, while timing of HTA submission after EMA approval varies in European jurisdictions. The collection of jurisdictional evidence requirements, predictability of HTA outcome and reimbursement decisions provided insights into different approaches of HTA bodies. This ongoing study will create a baseline to help address fact-based changes for both companies' HTA strategies and the practices of the studied HTA bodies. As the HTA landscape is evolving, these study results will support future convergence of evidentiary requirements across HTA bodies and more aligned process between regulatory and HTA agencies to expedite patient access.

LIST OF ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technology in Health
CIRS	Centre for Innovation in Regulatory Science
EU	European Union
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GKV-SV	Spitzenverband Bund der Krankenkassen
HAS	Haute Autorité de Santé
HEOR	health economics and outcomes research
HTA	health technology assessment
IQ	interquartile range
IQWiG	Institutfür Qualität und Wirtschaftlichkeit im Gesundheitswesen
MLEs	major line extensions
NASs	new active substances
NICE	National Institute for Health and Care Excellence
NOC	notice of compliance
PBAC	Pharmaceutical Benefits Advisory Committee
TGA	Therapeutic Goods Administration

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CHAPTER 4

BUILDING HTA INSIGHTS INTO THE DRUG DEVELOPMENT PLAN: CURRENT APPROACHES TO SEEKING EARLY SCIENTIFIC ADVICE FROM HTA AGENCIES

Ting Wang, Neil McAuslane, Helga Gardarsdottir,
Wim G Goettsch and Hubert GM Leufkens

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ABSTRACT

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

INTRODUCTION

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 (Hofer, Jakobsson et al. 2015). 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 (van Nooten, Holmstrom et al. 2012). 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 (Grueger 2015).

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 (Maignen, Osipenko et al. 2014, Wiebe, Schmitter et al. 2016). 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 and, more recently, in Canada (Ofori-Asenso, Hallgreen et al. 2020, CADTH 2021). 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 formalised as EMA-EUnetHTA parallel consultation in 2017 (Elvidge 2014). 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 formalised in 2017 as the EUnetHTA Multi-HTA Early Dialogue (ED) program (EUnetHTA, 2021). 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 Excellence (NICE) launched a program to provide simultaneous early HTA advice (CADTH, 2021).

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 (Henshall, Mardhani-Bayne et al. 2011, Fronsdal, Pichler et al. 2012). Tafuri and colleagues analysed the meeting minutes of EMA-EUnetHTA parallel consultations and identified a high level of overall agreement among agencies in the advice (Tafuri, Pagnini et al. 2016). 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 (Dintsios and Schlenkrich 2018, Khan and Carter 2019).

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:

1. assess company approaches to gaining HTA insights during drug development through stakeholder interactions;

2. identify company practices to seeking formal scientific advice from HTA agencies, including when to seek advice, from whom, and on what topics; and

3. investigate the impact of HTA scientific advice on the drug development plan.

METHODS

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 (Wang, McAuslane et al. 2020).

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 (Wang, McAuslane et al. 2020). 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 authorisation of a product. 'Global clinical development' was defined as any clinical trial conducted as part of a multinational drug development program.

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 analysed 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, reflecting their research intensity (Cristel 2019).

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 (Figure 1).

Overall, advice from a single HTA agency was the most utilised 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:

1. internal reasons, including well-conducted internal payer research, internal expertise and established knowledge in the therapeutic area, and different priorities among pipelines; and
2. 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 (Figure 2). Of these,

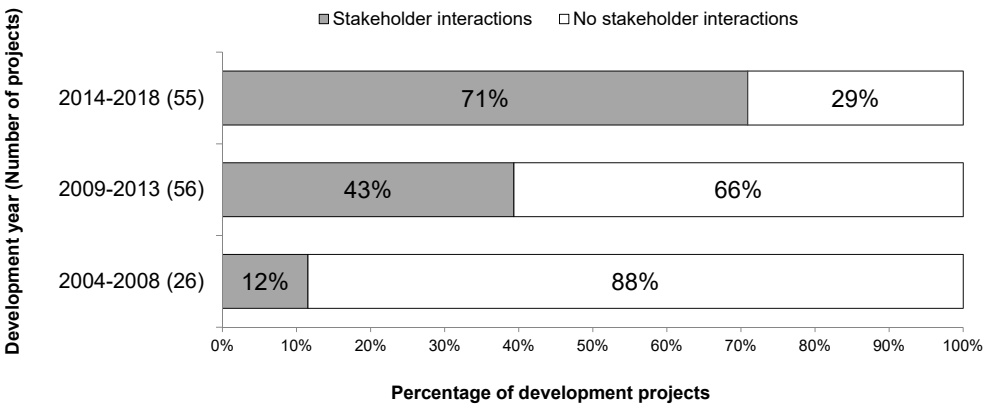
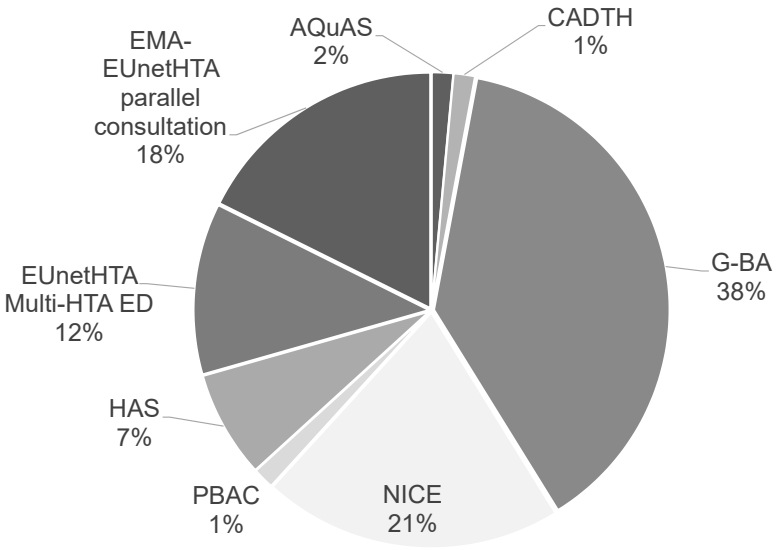


Figure 1. Stakeholder interactions providing insights from Health Technology Assessments (HTAs) for inclusion in development plans



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

Figure 2. Scientific advice meeting according to the Health Technology Assessment (HTA) agency involved (N = 68)

35 products were NASs (76%), and 11 products were MLEs (24%). For each product, companies could use more than one scientific 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 (Figure. 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

Table 1. Questions discussed at the HTA advice meetings

Topic of questions discussed	Type of the HTA advice meetings (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)

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/effective-ness evaluation, trial design, and patient selection.

To identify the trend of advice over time, we analysed 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 (Figure 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).

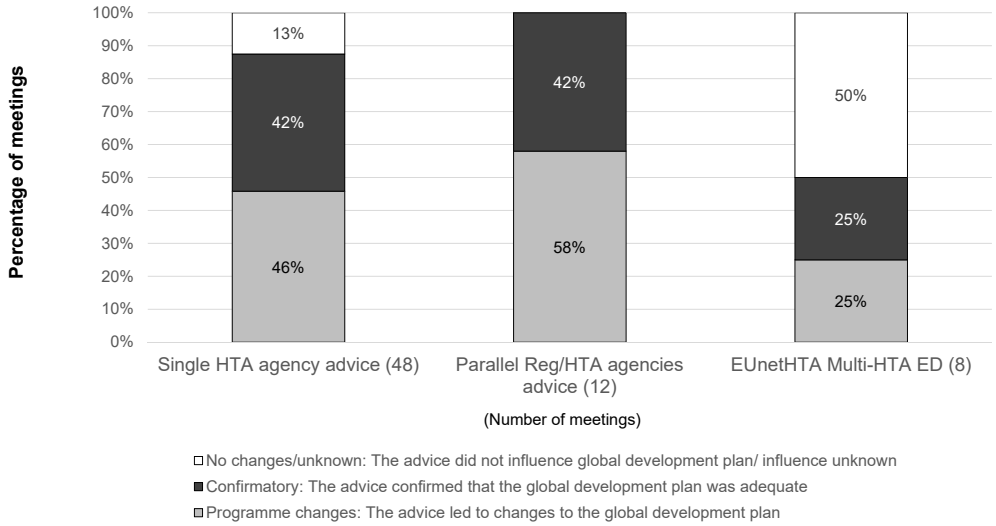


Figure 3. Impact of Health Technology Assessment (HTA) advice on the development plan. Abbreviations: ED, Early Dialogue; EUnetHTA, European Network for Health Technology Assessment

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 (Nielsen, Lauritsen et al. 2009, Wonder, Backhouse et al. 2013, Balaisyte, Joos et al. 2018, Wang, McAuslane et al.

2018, Khan and Carter 2019). 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 (Wiebe, Schmitter et al. 2016). 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 (Allen, Liberti et al. 2017). 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 (Maignen, Osipenko et al. 2014, Tafuri, Pagnini et al. 2016, Wiebe, Schmitter et al. 2016). 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 (Balaisyte, Joos et al. 2018). NICE evaluated the timing of all their advice meetings, and 61% were in Phase II of development (Maignen, Osipenko et al. 2014). 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 (Dintsios and Schlenkrich 2018). 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 (Wang, McAuslane et al. 2018). 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 post licensing evidence generation (PLEG) at early advice meetings. PLEG is a continuum of evidence development for a pharmaceutical product after market authorisation. 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 (Moseley, Vamvakas et al. 2020).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 perspective, the value of HTA advice will be ideally reflected through a favorable HTA recommendation (Khan and Carter 2019). 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 (Maignen and Kusel 2020).

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 (Tafuri, Lucas et al. 2018). 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 (Wang, McAuslane et al. 2016).

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 (NICE, 2021). 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 (NICE, 2021).

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 (Ermisch, Bucsics et al. 2016). 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 (van Lente, Dawson et Al. 2020, Hughes-Wilson 2014). 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 (Khan and Carter 2019). 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.

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CHAPTER 5

CHALLENGES AND OPPORTUNITIES FOR COMPANIES TO BUILD HTA/PAYER PERSPECTIVES INTO DRUG DEVELOPMENT THROUGH THE USE OF A DYNAMIC TARGET PRODUCT PROFILE

Ting Wang, Neil McAuslane, Wim G Goettsch,
Hubert GM Leufkens, Marie L De Bruin

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ABSTRACT

Background

The target product profile (TPP) outlines the desired profile of a target product aimed at a particular disease and is used by companies to plan clinical development. Considering the increasing importance of health technology assessment (HTA) in informing reimbursement decisions, a robust TPP needs to be built to address HTA needs, to guide an integrated evidence generation plan that will support HTA submissions. This study assessed current practices and experiences of companies in building HTA considerations into TPP development.

Methods

An opinion survey was designed and conducted in 2019, as a cross-sectional questionnaire consisting of multiple-choice questions. The questionnaire provided a qualitative assessment of companies' strategies and experiences in building HTA considerations into the TPP. Eligible survey participants were the senior management of Global HTA/Market Access Departments at 18 top international pharmaceutical companies.

Results

11 companies responded to the survey. All companies included HTA requirements in TPP development, but the timing and process varied. The key focus of HTA input related to health problems and treatment pathways, clinical efficacy/effectiveness, and safety. Variance of HTA methods and different value frameworks were identified as a challenge for development plans. Stakeholder engagement, such as HTA scientific advice, was used to pressure test the TPP.

Conclusion

This research provides insight into current practice and potential opportunities for value-based drug development. It demonstrates the evolution of the TPP to encompass HTA requirements and suggests that the TPP could have a role as an iterative communication tool for use with HTA agencies to enhance an integrated evidence generation plan.

INTRODUCTION

Healthcare systems have been moving towards a value-driven approach. With an aging population and rising healthcare costs, it is vital for decision makers to ascertain where to spend and on whom to spend based on available healthcare budget (Porter, 2009). With the purpose to inform decision making in order to promote an equitable, efficient and value-based health system, health technology assessment (HTA) has emerged and evolved as a multidisciplinary process that uses explicit methods to determine the value of a health technology (O'Rourke et al., 2020). HTA agencies evaluate a (new) health technology such as a medicine based on its relative clinical effectiveness, and/or cost effectiveness to assess if this product provides the best value for money (Rutledge, 2010). However, a range of different methods utilized by HTA agencies may have led to divergent HTA recommendations for pricing and reimbursement, which has resulted in inequitable patient access to new technologies in different jurisdictions (Nicod, 2017). Several studies focusing on the disparity of HTA recommendations have been conducted in the past decade; these have called for improvement of HTA methodology, as well as better collaboration and communication among HTA agencies (Nicod and Kanavos, 2012, Nicod, 2017, Nicod et al., 2016, Kleijnen et al., 2012). The European Network for HTA (EUnetHTA) was set up in 2006 to facilitate HTA collaboration in Europe. A key product of EUnetHTA was the development of the "HTA core model", a methodological framework to enable international collaboration in producing HTA and efficient sharing of information (Kristensen et al., 2009). The EUnetHTA core model defined a standardized set of HTA questions and contained the following nine domains: current use, technical, safety, clinical effectiveness, cost & economic evaluation, ethical analysis, organizational aspects, patient & social aspects, and legal aspects (European Network for Health Technology Assessment (EUnetHTA), 2016). This value framework has been adapted for production of relative effectiveness assessment (REA) (Kleijnen et al., 2012) for new medicines among European jurisdictions; a recent study evaluating the REA confirmed its benefit in addressing the heterogeneity across HTA agencies and potentially standardizing data requirements (Chassagnol et al., 2020).

In current practice, the submission to HTA agencies for pricing and reimbursement recommendations follows shortly after the regulatory approval; except in Australia and Canada, where companies can submit the HTA dossier during the regulatory review to streamline the timing of the two decision-making processes. Therefore, at the time of the regulatory review and HTA assessment, regulators and HTA agencies use similar data, which are generated from global clinical trials. As a result, companies need to consider not only regulatory requirements during development but also generating evidence that addresses HTA needs. Companies have been refining their internal structures and development strategies to incorporate HTA perspectives into clinical development (Wang et al., 2020). HTA agencies have also started engaging with companies during development to provide early scientific advice. Early scientific advice can either be

provided by a single HTA agency, a consortium of multi-HTA agencies, or jointly with a regulator (Wang et al., 2016). Despite efforts by companies and agencies to improve their process and communicate early during development, a key question that remains for companies is how to adapt the requirements from different HTA agencies into a global development plan.

In addition to the HTA evaluation, various value frameworks have emerged in the recent years to assess the value of a new technology. A number of US-oriented value assessment frameworks that are disease-focused have been developed to measure and communicate the value of a new medicine for decision making, such as the American College of Cardiology and the American Heart Association (ACC-AHA) value framework; the Conceptual Framework to Assess the Value of Cancer Treatment Options, developed by the American Society of Clinical Oncology (ASCO); the Institute for Clinical and Economic Review (ICER) Value Framework; the National Comprehensive Cancer Network (NCCN) Evidence Blocks; and the Patient-Perspective Value Framework (PPVF) (Garrison et al., 2018). Notably, ICER has grown its influence over the years to inform payer decisions on funding a new technology (Pizzi, 2016). Hence, companies need to navigate different types of value frameworks during development and run a few scenarios to help understand the value proposition of their products and to ensure the development plan is capturing value-adding components (Neumann et al., 2018).

An essential tool used by companies in the context of planning the clinical development is the target product profile (TPP). The TPP outlines the desired 'profile' or characteristics of a target product that is aimed at a particular disease or diseases. There is no defined template for a TPP, however, it is generally structured as a synopsis of its intended labelling. The TPP states the intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics (WHO, 2022). The TPP has been used as an effective communication tool with regulators during drug development and is associated with more efficient regulatory review times (Breder et al., 2017, Tyndall et al., 2017). Many regulatory agencies issue guidance to companies on the development of TPPs (US Food and Drug Administration (FDA), 2007, European Medicines Agency, 2009). The WHO has also developed TPP documents to inform companies and healthcare decision makers on R&D and public health priorities (WHO, 2022). Considering the increasing importance of HTA and other value frameworks in the reimbursement decision, a robust TPP needs to be built to address HTA/payer perspectives, in order to guide an integrated evidence generation plan to aid companies in their development and marketing strategies (Sax et al., 2015). Consequently, companies need to create a dynamic TPP that has a clearly stated value proposition for a new technology. This involves understanding the current standard of care and potential reimbursement environment, navigating through different HTA systems and value frameworks on the evidentiary requirements, and ensuring the right health outcome data is collected during the clinical development phase.

Currently, the concept of the TPP is not commonly used in the context of downstream decision making by HTA agencies. Nevertheless, the TPP has become essential in

the upstream decision making by companies and serves as a roadmap for a product's development and HTA/payer strategy. This study is therefore designed to assess the current practices and experiences of companies in building HTA/payer perspectives into the development plan through the TPP. Specifically, the objectives were to (1) evaluate the challenges faced by companies from different HTA agencies, (2) identify companies' practices of TPP development that address HTA/payer perspectives, (3) explore companies' stakeholder engagement strategies during development to test the value proposition.

METHODS

This study was developed by building on previous Centre for Innovation in Regulatory Science (CIRS) research, which collected quantitative data from pharmaceutical companies on individual products to assess the impact of HTA during drug development and roll out (Wang et al., 2020).

Study design

This research was designed in the form of an opinion survey to provide a qualitative assessment of companies' strategies and experiences in building HTA/payer considerations early into development through the TPP. A pilot questionnaire was developed in September 2019 and reviewed by potential responders from two invited pharmaceutical companies in October 2019. Feedback was provided on the clarity of the questions and was used to finalize the survey on 31st October 2019.

Eligible participants were international pharmaceutical companies with large R&D budgets (2019 budget >1 billion USD), which reflected their innovativeness and value-based medicine development approach. 18 companies were selected based on this purposive sampling, as well as being members of CIRS to ensure the timeliness of the study and maximize the response rate. Questionnaires were sent to the senior management of Global HTA/Market Access Departments at these companies via email on 7th November 2019, and they were asked to complete and return the survey by 28th November 2019. Feedback from both the company's Global HTA Department and local HTA affiliates were gathered and provided as a consolidated survey response to CIRS.

Structure of the study questionnaire

The survey was designed as a cross-sectional questionnaire consisting of eight multiple-choice, closed questions and one open question (see Appendix). It was organized into three sections: company challenges and solutions for key markets (questions regarding outstanding issues raised by HTA/payers and potential solutions); current practices of companies to build value into the TPP (questions regarding the timing of TPP development, cross-function involvement and HTA/payer perspectives included in the TPP); and company strategies for testing the value proposition during development (questions regarding stakeholder engagement and utilization of relevant value frameworks). A free-text

comment option was provided for each question to allow for further clarification. The selection of the HTA agencies in this study was based on the importance of the related market to companies. For the US, where there is no initialized HTA organization, ICER was assessed as a comparator to the HTA agencies and represented an independent value assessment body.

Data processing and analysis

The responses were manually tabulated into a Microsoft Excel file and analyzed using descriptive analysis. Analysis was conducted inductively, data were expressed as absolute number of respondents for each analysis, and ranking was applied where suitable. Free text comments were reviewed and analyzed using the constant comparative method, which involved comparing and contrasting concepts to inform relationships between phrases expressed by the study participants to identify emerging themes (Boeije, 2012). To protect the confidentiality of the individual companies, only aggregated results were presented in this paper.

RESULTS

11 out of the 18 pharmaceutical companies responded the survey (61% response rate). Nine of the 11 respondents were in the top 25 companies by R&D expenditure in 2019 (Christel, 2019), reflecting the research intensity of the companies and the innovativeness of their development pipelines.

Understanding key HTA/payer challenges

Firstly, the study assessed the challenges that companies have experienced from key HTA bodies in Australia, Canada, England, France, Germany, Italy, the Netherlands, and ICER in the US. For each jurisdiction, the respondents were asked to rate three issues frequently raised by the agencies that impact market access decisions. Not all companies provided data for each jurisdiction; results were expressed as the absolute number of responders rating each issue (Table 1).

In Australia, Canada and England, the most frequently raised issues on the evidence of a new medicine were "not cost-effective," and "lack of longer-term outcomes". In Germany and France, where the HTA recommendation is mainly based on added therapeutic value, the outstanding issues centered around comparators, such as insufficient improvement over comparator, comparator choice being unacceptable, the validity of the endpoint and lack of longer-term outcomes or follow-up. In comparison, there was a diversity of issues experienced by companies with ICER in the US.

Building HTA/payer perspectives into TPP development

All participating companies had a TPP to guide the evidence generation plan during drug development. The timing of the initiation of TPP development and the inclusion of HTA/

Table 1. Outstanding issues that companies have been challenged by HTA/payer on the evidence of a new medicine

Outstanding issues by area (n= number of companies rated this issue)		Germany (IQWIG/G-BA) n = 9	England (NICE) n = 9	France (HAS) n = 8	Australia (PBAC) n = 8	Canada (CADTH) n = 8	US (ICER) n = 7	Italy (AIFA) n = 5	Netherlands (ZIN) n = 4
Health Problem and treatment pathway	Inappropriate patient identification	1	1						
	Inferior place in treatment pathway	1							
Cost Effectiveness	Not cost-effective/Unacceptable price vs. comparator		7		8	7	3	3	4
	Budget impact	1	1	1	2	1	1	2	2
Clinical Efficacy/ Effectiveness	Invalid endpoints	4	1	1	1	2	2	2	
	Comparator not accepted	5	2	2		1	1	2	
	Insufficient efficacy / improvement over comparator	3	3	6	3	4	2	3	2
	Length of trial deemed too short/Lack of longer-term outcomes or follow-up	6	5	3	4	5	3	1	1
	Interpretation of external validity of registration trials does not meet local conditions	1	1						
	Inappropriate sub-group selection	1	2	2	3	2	2	1	1
Cost effectiveness/ Clinical effectiveness	Uncertainty in indirect comparison		1	1	1		2		
Safety	Insufficient safety evidence		1	1	2		1	1	
Patients and Social aspects	Insufficient societal benefit								1

payer perspectives varied among companies (Figure 1). Three companies initiated the TPP during pre-clinical development, while most companies started developing the TPP during Phase I development (5 of 11). HTA/payer perspectives were built into the development plan and were mostly incorporated in the TPP during Phase II (6 of 11). When comparing whether the HTA/payer perspective was included in the TPP since its inception, there was a mix in practices: five companies incorporated HTA/payer perspectives at the beginning of TPP development, whereas six companies included it later. In particular, the companies that started TPP development during the pre-clinical phase did not build in HTA/payer perspectives until Phase I development had started.

We further assessed the specific components included in the TPP that reflect HTA/payer perspectives (Figure 2). The results showed that companies focused on three main areas: health problem and treatment pathway, clinical efficacy/effectiveness, and safety. More specifically, the components always included in the TPP were on target population (100% companies), safety (91%), magnitude of clinical effect (91%), differentiation from the standard of care or competitors (91%), the clinical endpoint or surrogate endpoint (91%), epidemiology and burden of disease (82%) and unmet medical needs (82%). In addition, hospitalization was rated as a key component (64%) in the TPP development, but this was only considered when necessary to address HTA/payer needs on an ad hoc basis.

The development of a TPP involved multiple functions within a company, however, the process to consolidate the input from different functions was not always systematic. Five companies had a fully integrated approach where TPP decisions were based on

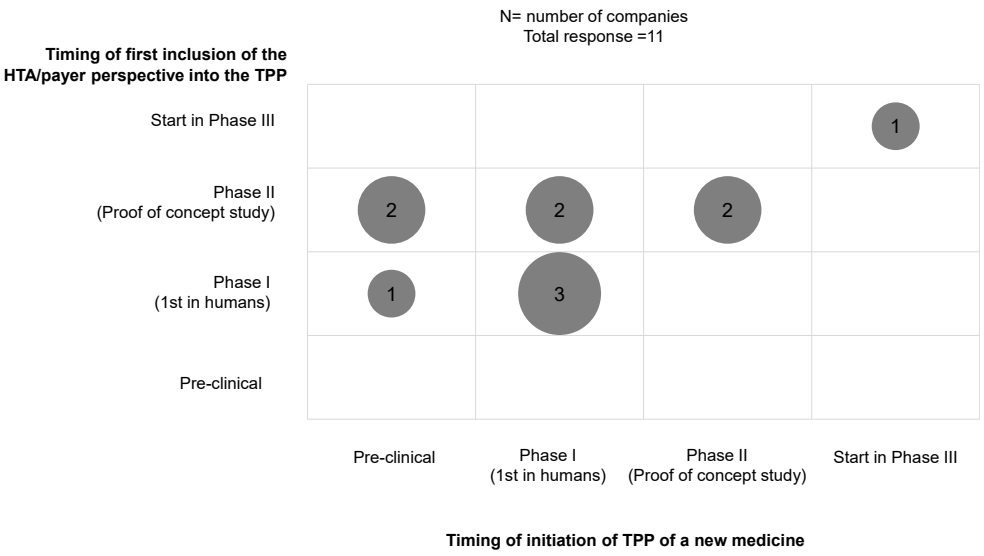

Figure 1. Timing of the initiation of TPP development and inclusion of HTA/payer perspectives

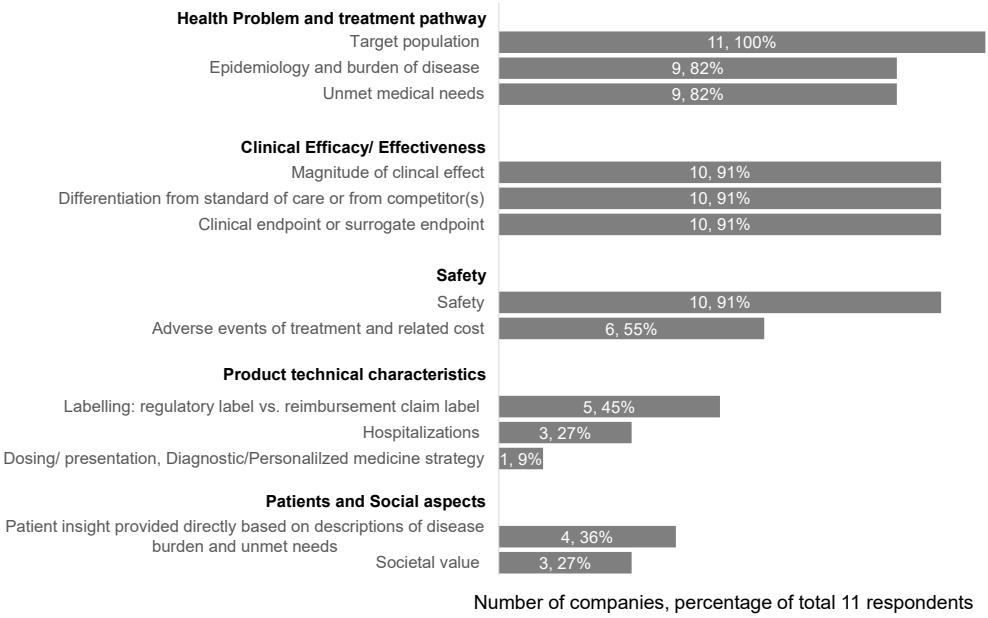

Figure 2. Components included in the TPP that reflect HTA/Payer perspective

consensus across functions, while six companies had a partially integrated process that tended to prioritize regulatory perspectives over HTA/payer perspectives or made the TPP decisions on an ad hoc basis. Clinical, regulatory, health economics and outcomes research (HEOR) and pricing and reimbursement functions were most frequently reported to be involved in TPP development (Figure 3). Two companies reported the participation of a health policy group, and two companies reported the engagement of a patient advocacy group/representative in TPP development; the involvement of these functions was fully integrated.

Testing value propositions with internal and external stakeholders

To optimize the TPP of a new medicine, stakeholder engagement was used to "pressure test" the value proposition of the new drug (Figure 4). The survey results showed various internal and external engagement methods utilized by companies, including formal advice from agencies (parallel regulatory-HTA, single HTA, and multiple HTA advice), internal payer research, external payer advisory groups, consultations with therapeutic heads, and patient advisory boards. All companies studied in the survey had experience of internal and external stakeholder engagement. Formal agency advice was usually sought during phase II or pre-phase III, and other types of input tended to occur later in development or on an ad hoc basis.

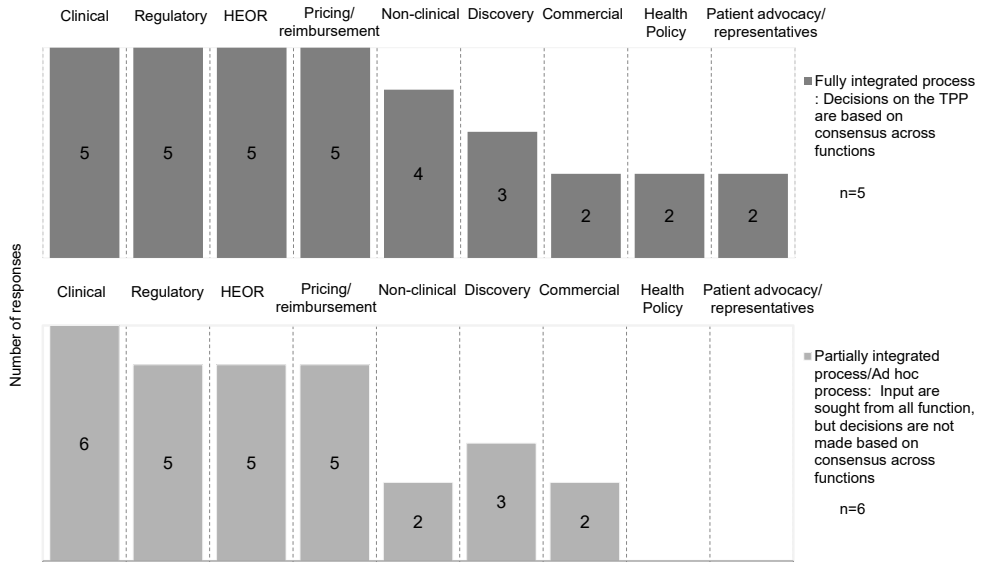

Figure 3. Cross function involvement in the development of TPP

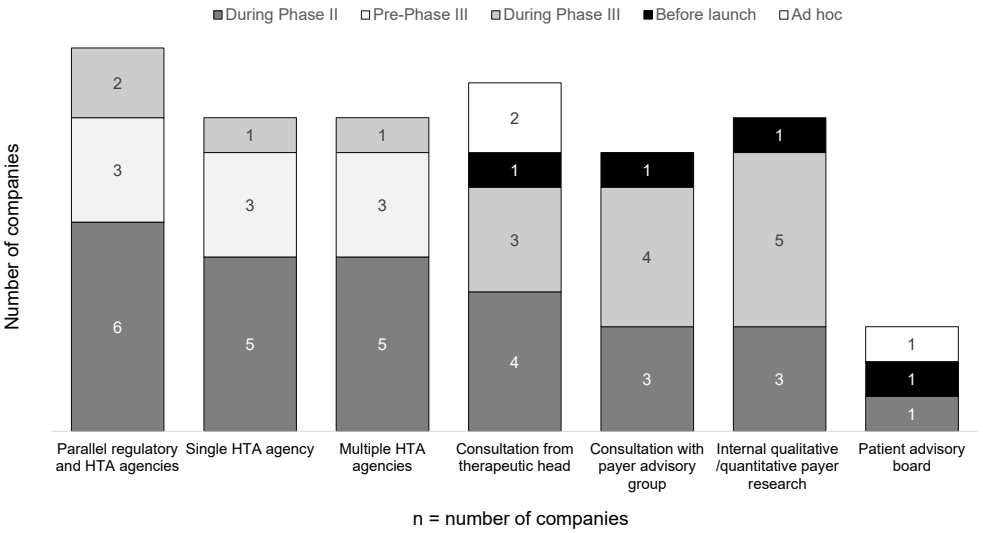

Figure 4. Stakeholder engagement strategy to test the value proposition

The majority (10 of 11) of companies also assessed the proposed evidence generation plan for a new medicine against a current value framework in the relevant therapeutic area. The most utilized framework was ICER (60% of responders), followed by PPVF (50%), the European Society for Medical Oncology (ESMO) framework (40%), ASCO (40%), NCCN (40%), ACC/AHA (30%) and EUnetHTA Core Model (20%).

Thematic analysis identified a number of key challenges and potential solutions for building value propositions early into development plans to meet the needs of different jurisdictions (Table 2). These building blocks will be supported by companies' evolvement of increasing internal awareness of HTA, prioritizing resources, and better alignment internally across multi-functional teams.

DISCUSSION

The TPP is a projection of the expected safety, efficacy/effectiveness and value proposition of a new product and supports companies' decision-making regarding technology design, strategic evidence generation and future marketing strategy. This paper examined the current experiences of pharmaceutical companies in addressing HTA/payer needs through the development of the TPP; the results collected from 11 participating companies provided a unique insight into current operational practice and potential opportunities for value-based drug development.

TPP development that underpins companies' internal HTA/payer strategy

The TPP is developed during early stages of drug development and is typically structured in the format of regulatory labelling; the TPP has been used frequently in communication with regulatory agencies to support market authorization (Tyndall et al., 2017). Our study showed an evolution of TPP development to encompass HTA/payer requirements. All the responding companies indicated that HTA/payer perspectives were included in the TPP. However, we observed a mix of practices in the timing of development of a TPP, with half of respondents starting the TPP development with HTA/payer needs in mind,

Table 2. the key challenges and potential solution for building the value proposition sufficiently early into the development programme to meet the needs of the different jurisdictions

Practical challenges	Potential solutions
Limited HTA resource during early development	Raise awareness of the need of HTA resource in early development
Uncertainty in the clinical outcome	Iterative value proposition based on clinical outcome
Internal alignment cross functions	Better understanding of impact of HTA requirements on development to provide incentives for early alignment
Divergent stakeholder's need and priorities	Recognize the impact and make explicit tradeoffs/choices
Stakeholder interaction not early enough	Clear strategy and resource for early advice that can be utilized for development
Treatment / reimbursement landscape change	Scenario planning and good competitor intelligence

and the other half including HTA/payer requirements after the TPP was established. Therefore, while the TPP can be established as early as before clinical development, the incorporation of HTA/payer requirements was built in at a later stage, mostly during phase II development. The variation in practice may be related to the involvement of HTA/market access teams in internal cross-functional processes.

Good levels of engagement of clinical, regulatory, HEOR, and pricing and reimbursement teams were observed in TPP development in our study. However, the internal decision-making process was not always fully integrated. Our finding is consistent with one of our earlier studies, which recognized that input from HEOR teams was sought during development, but final decisions were prioritized based on the regulatory requirements (Wang et al., 2018). Respondents recommended ways to improve the internal process, such as raising awareness of the impact and requirements of HTA and prioritizing resources to address HTA needs. A more aligned process with systematic internal decision making will facilitate efficient development of the TPP, and at the same time, a systematically developed TPP can also help to align objectives across different company functions and accelerate development timelines (Lambert, 2010). Two companies also engaged with patient advocacy group/representative in TPP development. With the increasing focus on patient-centered drug development, it would be interesting to assess how patient groups will be further participating in TPP development (Crawford et al., 2017, Kluetz and Bhatnagar, 2021).

Nevertheless, when examining the specific HTA/payer requirements incorporated in the TPP, only 36% respondents stated that "patient insight provided directly based on description of disease burden and unmet needs" was included. HTA/payer considerations included in the TPP concentrated on elements that support the clinical effectiveness evaluation: target population, magnitude of clinical effect, clinical endpoint or surrogate endpoint, safety and differentiation from standard of care. The unmet medical need from the HTA/payer perspective was also included in the TPP by most companies (9 out of 11). Yet, a recent study explored the definition of unmet medical need and concluded that its quantification depended on different stakeholders and their decision context. Therefore, there was a need to align the perspectives on unmet medical need and its measures within the broader value framework for decision making (Vreman et al., 2019). Further development on this topic will be helpful for companies to enhance the TPP with a clear understanding and articulation of unmet medical need.

Dynamic TPP development to address external stakeholder needs

Comparing to the focus on clinical effectiveness in the TPP, our study showed the outstanding issues raised by HTA agencies were mostly "not cost-effective and "unacceptable prices" in Australia, Canada, England, the Netherlands and ICER in the US. "Lack of longer-term outcomes" and "insufficient improvement over comparators" were reported to be frequent challenges in Germany and France. The outstanding challenges

were related to the varying requirements from HTA agencies and how they assess added value in the context of their national healthcare system (Wang et al., 2020). An industry survey pointed out that evidence that supported value proposition at the global level will provide the direction of strategy and key value messages, but then the information must be adapted to the local context, considering variations in standards of care and treatment practices across different markets (Kooreman et al., 2014). In addition, economic value is assessed within the context of national healthcare resources, therefore, jurisdictional pricing and reimbursement strategy will need to be built at the national level (Lucioni and Jommi, 2017). Our study showed that companies have a good understanding of challenges raised by HTA agencies, and the thematic analysis in Table 1 listed the areas of outstanding issues. The learning from jurisdictional experiences will help to improve understanding of HTA/payer needs during development, and an improved TPP during development will in turn facilitate a better evidence generation plan and increase the likelihood of future commercial success. Future studies could concentrate on the impact of the inclusion of the HTA perspective during development on jurisdictional patient access; further indicators can be built based on the value elements included in development, comparing to the added value assessed by HTA agencies. This will be enhanced by the transparency, consistency, and predictability of the HTA decision-making process. In particular, pharmaceutical companies have emphasized transparency as the key principle of value frameworks: transparency in the method and transparency in the types of data and models used (Angelis et al., 2020, Eddy et al., 2012).

HTA agencies have been improving their methodologies and process to ensure a robust and efficient approach to assess the value of a new technology (The National Institute for Health and Care Excellence (NICE)). Initiatives are also underway to refine value frameworks; the Professional Society for Health Economics and Outcomes Research (ISPOR) Special Task Force developed a value flower containing 12 elements of value assessment, which expanded beyond traditional clinical and cost evaluation and included elements such as "value of hope" (Lakdawalla et al., 2018). Nevertheless, it is not practical to encompass all value elements or HTA requirements during development. The 2017 HTA International (HTAi) Policy Forum discussed the development of value frameworks used by HTA agencies and third-party organizations and called for agreement and refinement of the core components of value frameworks (Oortwijn et al., 2017).

As companies are creating the TPP prior to Phase II, it will take approximately 4-7 years before the product receives regulatory approval and undergoes subsequent HTA assessment, at which point the evidence requirements and reimbursement environment may have changed. It has been suggested by a company to focus on a core list of elements such as avoidable uncertainty during development and make changes to adapt to HTA needs (Facey et al., 2015). An iterative process leads to the creation of a dynamic TPP document, which will be initially developed focusing on a core list of evidentiary

requirements and then be updated as new outcomes are generated from the clinical trial and as the treatment landscape changes.

Ensuring TPP development through stakeholder interactions

A key strategy to test the value proposition of a product is stakeholder engagement. This survey showed that internal activities such as qualitative or quantitative payer research and consultation with the therapeutic head were mostly used, while external advice meetings with HTA agencies and payer advisory groups were frequently sought. Most companies in the study stated that they assessed the proposed evidence generation plan for a new medicine against a current value framework in the relevant therapeutic area. The most utilized value framework was ICER, followed by the PPVF, ESMO and ASCO frameworks. A study by Wild and colleagues showed that testing the product profile with value attributes will help to identify different scenarios and understand perceived product value (Wild and Mukku, 2011). The EUnetHTA HTA Core Model has also been utilized by companies; it has been viewed as a useful framework to standardize the domain of HTA questions and understand the common terminology (Gyldmark et al., 2018). In addition, one company has developed internal access evidence generation tools based on the HTA Core Model, which has a direct impact on drafting the TPP (Ducournau et al., 2019).

There has been a proliferation of early HTA advice programs in recent years, available at both national and international levels. Our survey showed that the most frequently used format was parallel regulatory-HTA advice. Recent experiences of these advice meetings have been positive, with the benefit of aligning perspectives among different stakeholders and offering opportunities to shape the development plan (Maignen and Kusel, 2020, Tafuri et al., 2016, Vlachaki et al., 2017, Wang et al., 2022). It was acknowledged that although the role, function and remit of regulatory and HTA agencies are different and should remain distinct, more interactions and alignment between the agencies will be helpful to ensure more efficient drug development. Potential interactions between regulatory and HTA agencies have been suggested to converge clinical requirements, align national review and reimbursement process, and increase transparency and trust between stakeholders (Centre for Innovation in Regulatory Science (CIRS), 2021). A previous study also suggested that payers should be involved in TPP development, which can facilitate evidence generation and understanding of payer related issues and unmet medical needs (Fatoye et al., 2019). Nevertheless, the advice provided by HTA agencies is non-binding and the treatment and reimbursement landscape may change by the time the product reaches market access; therefore, internal activities are also critical to enable good competitor intelligence and scenario planning.

Companies participated in early scientific advice meetings where HTA agencies generally used a briefing book to summarize the key characteristics of a product, and the key questions to be discussed at the meeting. Although the TPP has been frequently used in early advice meetings with regulators (Tyndall et al., 2017), it was unknown how

the TPP has facilitated the development of the briefing book for HTA advice, and how the advice taken from HTA agencies has been built into the dynamic TPP. As a development tool, it would be useful for the TPP to be used not only internally by companies, but also as an iterative communication tool with regulators, HTA, payers and patient groups to enhance an integrated evidence generation plan.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our findings should be interpreted in light of this study's strengths and limitations. This paper is based on a perception survey from 11 participating companies therefore the results reflect the view of those companies from purposeful sampling. However, the participants represent international companies that are focusing on development of innovative medicine, therefore are a good marker of HTA practices. For each question in the survey, not all of the participants responded due to their experiences and perceptions; analyses were therefore shown with both absolute numbers and percentages. In addition, the HTA perspectives in the paper were assessed from companies' positions. Further study on the topic could be explored from HTA/payer perspectives to provide a balanced view on how best to build HTA into a sufficient development and roll out process.

CONCLUSIONS

The TPP has been used as a blueprint to guide companies on their development plan for a new medicine. In this study, all participating companies have included HTA/payer perspectives in TPP development. However, there were practical divergencies in terms of the timing of the inclusion, the cross-functional process and the key requirements included. It showed that companies were at different levels of utilizing the TPP in drug development to address future HTA/payer needs. Considering the variance of HTA methods and different value frameworks used in assessing the value of a new technology, a dynamic TPP is essential to facilitate evidence generation plans by focusing on a core list of components, which can be pressure tested through early scientific advice with agencies, payer research and internal assessment against relevant value frameworks. Building on this paper, further research could explore the wider application of the TPP, such as in supporting communication with HTA agencies or payers.

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ABBREVIATIONS

ACC	American College of Cardiology;
AHA	American Heart Association;
AIFA	Agenzia Italiana del Farmaco;
ASCO	American Society of Clinical Oncology;
CADTH	Canadian Agency for Drugs and Technology in Health;
CIRS	Center for Innovation in Regulatory Science;
ESMO	European Society for Medical Oncology;
EUnetHTA	European network for Health Technology Assessment;
G-BA	Gemeinsamer Bundesausschuss;
HAS	Haute Autorité de Santé;
HEOR	health economics and outcomes research;
HTA	health technology assessment;
ICER	The Institute for Clinical and Economic Review;
IQWiG	Institutfür Qualität und Wirtschaftlichkeit im Gesundheitswesen;
NICE	National Institute for Health and Care Excellence;
NCCN	National Comprehensive Cancer Network;
PBAC	Pharmaceutical Benefits Advisory Committee;
PPVF	Avalere/Faster Cures Patient-Perspective Value Framework;
TPP	target product profile;
ZIN	Zorginstituut Nederland.

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APPENDIX: STUDY SURVEY

Section A: Incorporating value proposition into the development of TPP (Target Product Profiles)

1. Please choose one option by putting an X for the following questions

When does your company first start the development of TPP of a new medicine? Select one by putting an X	When does your company first include the HTA/payer perspective into the TPP to demonstrate the value proposition? Select one by putting an X
• Global project frame	• Global project frame
• Pre-clinical development	• Pre-clinical development
• Phase I (1st in humans)	• Phase I (1st in humans)
• Phase II (PoC study)	• Phase II (PoC study)
• Start in Phase IIb	• Start in Phase IIb
• Start in Phase III	• Start in Phase III
• Before regulatory submission	• Before regulatory submission

2. Which functions within your company are involved in the process of building the TPP for a new medicine? Select all applicable options by putting an X.
   - ❑ Discovery
   - ❑ Non-clinical
   - ❑ Clinical
   - ❑ Regulatory
   - ❑ HEOR
   - ❑ Pricing and reimbursement
   - ❑ Healthcare Policy
   - ❑ Patient advocacy group/patient representatives
   - ❑ Others, please specify _____

3. Is there a systematic process to consolidate input from different functions into the development of the TPP?
   - ❑ Yes, fully integrated process : Decisions on the TPP are based on consensus across functions
   - ❑ Yes, partially integrated process: Input is sought from all functions, but regulatory perspective is prioritized over HTA/payer perspectives
   - ❑ No: Decisions are made on an ad hoc basis
   - ❑ Others, please specify _____

4. What are the elements that your company includes in the TPP that reflect HTA/payer perspectives?

Elements in the TPP that reflect HTA/payer perspectives	Included in TPP all the time	Considered but only included on an ad hoc basis
Unmet medical needs	❑	❑
Epidemiology and burden of disease	❑	❑
Target population	❑	❑
Differentiation from standard of care or from competitor(s)	❑	❑
Clinical endpoint or surrogate endpoint	❑	❑
Magnitude of clinical effect	❑	❑
Safety	❑	❑
Hospitalizations	❑	❑
Adverse events of treatment and related cost	❑	❑
Labelling: regulatory label vs. reimbursement claim label	❑	❑
Patient insight provided directly based on descriptions of disease and treatment burden and unmet needs	❑	❑
Societal value		
Others :Please specify perspectives?	❑	❑

Section B: "Pressure testing" the value proposition of a new medicine

5. **What is your company's strategy for testing the value proposition of a new medicine during development?** Select all applicable options by putting an X.

Strategy	Timing of interaction *(please provide the phase of drug development)*
• Seek early scientific advice from a single HTA agency	
• Seek early scientific advice from multiple HTA agencies	
• Seek early scientific advice from parallel Regulatory and HTA agencies	
• Consultation with payer advisory group	
• Consultation from therapeutic head	
• Internal qualitative /quantitative payer research	
• Patient advisory boards	
• Others, please specify	

6. Does your company assess the proposed evidence generation plan for a new medicine against any value framework in the relevant therapeutic area?

Value assessment framework	Select all applicable options by putting an X.
The European Society for Medical Oncology (ESMO)	❑
The Institute for Clinical and Economic Review (ICER)	❑
The American College of Cardiology/American Heart Association (ACC/AHA) frameworks	❑
The American Society of Clinical Oncology (ASCO)	❑
The National Comprehensive Cancer Network (NCCN) framework	❑
The Avalere/FasterCures Patient-Perspective Value Framework (PPVF)	❑
Others, Please specify	❑

Section C: Value interpretation during roll-out at key jurisdictions

7. What are the top 3 outstanding issues that your company has been challenged by HTA/payers on the evidence of a new medicine?

   Please select top 3 issues for each jurisdiction from the list on below

   a. *Invalid endpoints*
   b. *Comparator not accepted*
   c. *Insufficient improvement over comparator*
   d. *Insufficient efficacy*
   e. *Insufficient safety evidence*
   f. *Length of trial deemed too short*
   g. *Lack of longer term outcomes or follow-up*
   h. *Interpretation of external validity of registration trials does not meet local conditions*
   i. *Inappropriate patient identification*
   j. *Inappropriate sub-group selection*
   k. *Inferior place in treatment pathway*
   l. *Not cost-effective*
   m. *Unacceptable price vs. comparator*
   n. *Budget impact*
   o. *Insufficient societal benefit*
   p. *Others (please specify in the table below)*

Jurisdictional HTA	Top 3 outstanding issues that were frequently raised by HTA that have an impact on the market access(*Please select relevant letters from the list above)*
Australia (PBAC)	
Canada (CADTH)	
England (NICE)	
France (HAS)	
Germany (IQWIG/G-BA)	
Italy (AIFA)	
Netherlands (ZIN)	
US (ICER)	

8. What were the key internal barriers for building the value proposition sufficiently early into the development programme to meet the needs of the different jurisdictions?

   Please list the top three challenges and potential solutions

Challenges	Solutions
1.	1.
2.	2.
3.	3.

9. Do you have any comments you would like to provide with regard to this topic that you believe would be of value to discuss at the upcoming CIRS Technical forum? Please specify.

PART C

MULTI-STAKEHOLDER INTERACTIONS

CHAPTER 6

BUILDING SYNERGY BETWEEN REGULATORY AND HTA BEYOND PROCESS AND PROCEDURES – CAN WE EFFECTIVELY ALIGN THE EVIDENTIARY REQUIREMENTS? A SURVEY OF STAKEHOLDER PERCEPTIONS

Ting Wang, Neil McAuslane, Lawrence Liberti,
Hubert GM Leufkens and Anke Hövels

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ABSTRACT

Objectives

To evaluate the current practice of companies and agencies in order to assess the changes made in aligning regulatory and HTA stakeholders; to identify areas of commonality of evidentiary requirements that could occur; to identify strategic issues and trends of regulatory and HTA synergy.

Methods

Two separate questionnaires were developed to assess stakeholders' perceptions on regulatory and HTA alignment, one for pharmaceutical companies and another one for regulatory and HTA agencies. The responses were analysed using descriptive statistics.

Results

Seven regulatory and 8 HTA agencies from Australia, Canada, and Europe and 19 international companies developing innovative medicine responded to the survey. This study provided a snapshot of the current regulatory and HTA landscape; changes made over the past five years were reflected in three main areas: there is an increasing interaction between regulator and HTA agencies; current conditional regulatory approvals are not always linked with flexible HTA approaches; companies are more supportive of joint scientific advice. Four types of evidentiary requirements were identified as building blocks for better alignment: acceptable primary endpoints; inclusion of an active comparator; use of patient-reported outcomes; choice and use of surrogate endpoint.

Conclusions

The study showed that the gap between regulatory and HTA requirements has narrowed over the past five years. All respondents supported synergy between regulatory and HTA stakeholders, and the study provided several recommendations on how to further improve evidentiary alignment including the provision of joint scientific advice, which was rated as a key strategy by both agencies and companies.

INTRODUCTION

The pathway for bringing a new medicine to market is dependent on two sequential processes: achieving market authorisation from the regulatory agency and reimbursement from a payer (Eichler, Thomson et al. 2015). The current healthcare environment is evolving rapidly: faced with an increasing pressure to control spiraling healthcare costs (Dierk Beyer 2007), payers need to make decisions on the reimbursement of medicines to maximize public health outcomes within limited health budgets. As a result, an important stakeholder has emerged – the health technology assessment (HTA) agency that aims to provide recommendations on reimbursement based on the value of a new medicine (Kristensen 2009). The role of HTA agencies as advisors to the reimbursement decision maker is crucial for application of funding by the healthcare system, in particular within a single payer system (Claxton, Sculpher et al. 2002). Consequently, drug developers seeking to deliver new medicines need to coordinate a development program to generate evidence that meets the needs of both regulatory and HTA agencies.

Pharmaceutical companies have already started to adjust their internal structures and development strategies to meet the goal of demonstrating the efficacy, safety and cost-effectiveness of a new medicine (van Nooten, Holmstrom et al. 2012). However, challenges remain in developing evidence that meets the requirements of both regulatory and HTA agencies at the point of launch. The fundamental reasons for these challenges are twofold. First, a regulatory agency focuses on the benefit and risk balance of a medicine, which is based on results from clinical trials provided under ideal circumstances, whilst an HTA agency focuses on effectiveness evaluation of an intervention under the general circumstance of clinical practice. Second, HTA evaluation compares a new medicine against one or more existing treatments. The comparative nature of HTA requires an active comparator trial to demonstrate the value of new medicine, while few regulatory approvals are based on the superiority of a new medicine over active comparators (Eichler, Bloechl-Daum et al. 2010). In addition, HTA evaluates the clinical effects and cost over time. Finally, the basic regulatory requirements have been established and standardized via the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines. In contrast, HTA evaluates medicines in local clinical context; therefore, the scientific requirements of HTA agencies vary according to local standards of care. This variability introduces uncertainty into drug development decisions and can result in a potential mismatch of regulatory and HTA outcomes.

Numerous studies have assessed the association between regulatory and HTA outcomes across European countries, where significant divergences in the HTA recommendations were identified for medicines approved via the European Medicines Agency (EMA) centralized procedure (Nicod and Kanavos 2012, Lipska, Hovels et al. 2013, Mathes, Jacobs et al. 2013, Grepstad and Kanavos 2015), resulting in inequitable patient access across countries in Europe. In addition, in response to the increasing demand for new medicines to address unmet medical need, regulatory agencies have developed flexible

pathways to speed the review process, including mechanisms such as accelerated and conditional approvals. However, there seems to be no association between these flexible regulatory pathways and HTA decisions (Lipska, Hoekman et al. 2015). This disconnect between regulatory approval and HTA recommendation for products to address unmet medical need may, amongst other outcomes, leads to false hope from patients in need.

Over the past decade, a number of initiatives have been established to address the disparities of regulatory and HTA requirements. These include tripartite discussions among pharmaceutical companies, regulators, and HTA agencies have been launched as a platform to receive parallel scientific advice on drug development plans (Wonder, Backhouse et al. 2013, Tafuri, Pagnini et al. 2016); collaboration between EMA and European HTA agencies to improve European Public Assessment Reports (EPARs) in support of the HTA assessment of relative effectiveness (Berntgen, Gourvil et al. 2014); and regional policy-level initiatives such as the establishment of the European Network for Health Technology Assessment (EUnetHTA) facilitate the reduction of duplication of effort (Kristensen, Chamova et al. 2006, Nielsen, Lauritsen et al. 2009). In addition research-level initiatives are being conducted to understand decision-making processes and to determine if divergent decisions between regulatory and HTA agencies are due primarily to differences in the evidentiary requirements or other factors (Salas-Vega, Bertling et al. 2016). Despite the growing interest in this area of regulatory and HTA alignment, no studies have assessed the impact of activities focused on improving dialogue and efficiency. Therefore, it is timely to assess the current landscape for the alignment of regulatory and HTA requirements.

The objectives of this study were to evaluate the current practice and procedures of companies and agencies in order to assess the changes made in aligning the stakeholders; to identify areas of commonality of evidentiary requirements as building blocks of achieving alignment; to identify the strategic issues and trends for synergy between regulatory and HTA agencies.

METHODS

Design and participants

Two questionnaires were developed with the same aim to assess the perceptions from stakeholders, one for pharmaceutical companies and another one for regulatory and HTA agencies on key topics related to alignment. A pilot industry survey was completed by two companies and a pilot agency survey was completed by one regulatory and one HTA agencies to evaluate the clarity and validity of proposed questions. Feedback was received from the four sources and supported finalization of the questionnaires. Questions were answered by tick box responses to statements or by using a scale ranging from 1 to 5 (representing strongly agree to strongly disagree), Free-text comments were optional for each question. The industry and agency questionnaires contained analogous questions where appropriate. Both were organized into three sections: Overview of current practice

and procedure; Evidence and technical requirements; Strategic issues and trends of synergy between regulatory and HTA.

The finalized industry questionnaire was sent to senior management at 25 international pharmaceutical companies, requesting one response from each company's Regulatory Affairs department and one response from the Health Economics, Outcomes and Research (HEOR) (or equivalent) department. The companies selected were international companies that develop innovative medicines. The finalized agency questionnaires were sent to contacts holding senior positions within 34 agencies (16 regulatory agencies and 18 HTA agencies) in Australia, Canada, and Europe. Questionnaires were sent via email during July and August 2016; the responses were collected by September 2016.

Data collection and processing

Company responses represented a consensus opinion within their department (Regulatory Affairs or HEOR). Agencies responded to the survey as individuals, and the views expressed were those of the respective individuals rather than the general view of the agency. The responses were analysed using descriptive statistics. Free-text comments were reviewed and manually grouped into key themes according to high concordance responses.

RESULTS

Characteristics of study participants

Twenty-nine responses were received from 19 companies including responses from the regulatory departments of 13 companies, the HEOR departments of 12 companies and joint department responses from 4 companies. These respondents represented a mix of expertise from major companies, and 14 participating companies were categorized as being among the "top 20 companies based on R&D investments" in 2014 (EvaluatePharma®, 2015). Eighteen of the 34 agencies responded to the survey request, of these, three expressed interests but were not able to complete the survey by the deadline, and 15 agencies provided detailed feedback.

The agencies that participated represented key stakeholders from a mix of geographical locations: Regulatory agencies included Australia's Therapeutic Goods Administration (TGA), Health Canada, EMA, Irish Medicines Board (IMB), Sweden's Medical Products Agency (MPA), Swissmedic, Netherlands' Medicines Evaluation Board (MEB); HTA agencies included Australia's Pharmaceutical Benefits Advisory Committee (PBAC), the Canadian Agency for Drugs and Technology in Health (CADTH), Quebec, Canada's Institut national d'excellence en santé et en services sociaux (INESSS), England's National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), Poland's Agencja Oceny Technologii Medycznych I Tarryfikacji (AOTM), Sweden's Tandvårds-Och Läkemedelsförmånsverket (TLV) and Basque, Spain's Servicio de Evaluación de Tecnologías Sanitarias (OSTEBA).

Part I: Current practice and procedures

We first looked at the companies' approaches to addressing regulatory and HTA requirements during development (Figure 1). There were mixed views regarding the transparency of HTA requirements, with 10 company respondents agreeing these were transparent and 11 stating that they were not. A clear divergence was observed between the responses from regulatory departments and those from HEOR departments. All company respondents felt that there was an increasing need to include HTA requirements earlier in development, with the aim to develop products that are approvable as well as reimbursable. However, this approach requires efficient coordination across regulatory and HEOR departments in the development decision-making process. Only 5 respondents confirmed their company had an integrated approach for the two groups working together and generated evidence based on aligned input. Twenty-three respondents reported that the interactions between the regulatory and HEOR department took place on an ad hoc basis, and although HEOR input was sought during development, the final decision regarding evidence generation prioritized regulatory requirements.

Several barriers to integrated decision making during development were observed: internal structure and strategy issues included resource constraints, lack of appropriate infrastructure, lack of awareness of HTA requirements, and development plans being driven by the US market. External uncertainty issues included variation in HTA requirements to be considered and incorporated, rapid changes of clinical practice and standard of care, as well as divergent economic considerations among different markets.

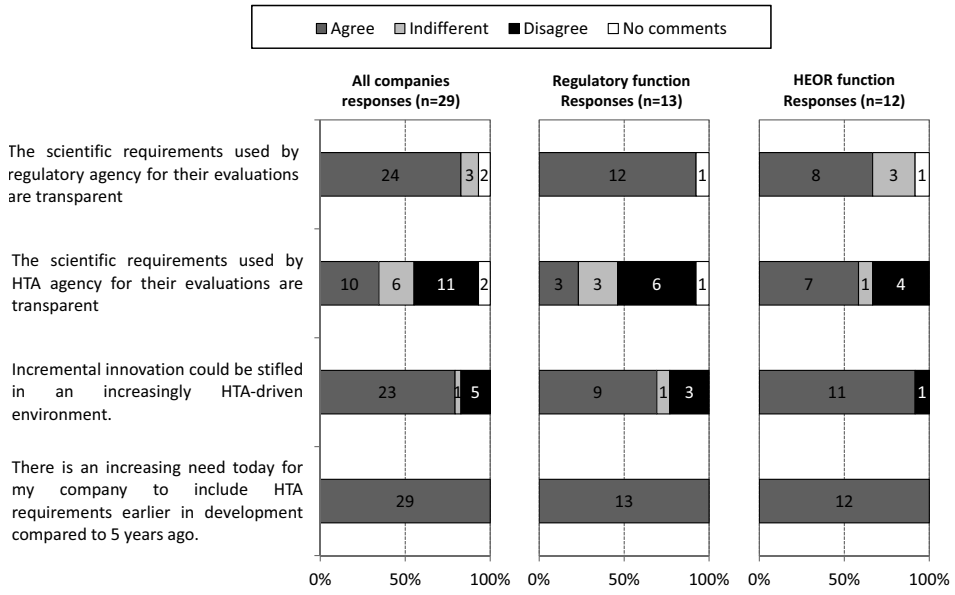

Figure 1. Company respondents' views on the regulatory and HTA requirements. HEOR, Health Economics, Outcomes and Research; HTA, health technology assessment.

All 29 company respondents provided suggestions to overcome both internal and external barriers, including further communication and training for R&D and regulatory departments in order to raise awareness of the HTA environment, prioritizing assets that would benefit the most from aligned input from regulatory and HEOR teams, establishing a project team to coordinate across departments to ensure early interactions and using more consistent decision-making processes. Finally, respondents suggested that seeking early HTA scientific advice would be valuable to improving internal awareness of the importance of HTA, as well as to understanding the external requirements to be included in the development plan.

We further asked the agencies to comment on their current practice in terms of interactions with peer agencies in the same jurisdiction. Interactions between regulatory and HTA agencies were observed across different stages of the product life cycle. Three HTA (TLV, NICE and Osteba) and four regulatory agencies (EMA, IMB, MEB and MPA) that participated in the survey currently provide joint scientific advice to companies during drug development. Two HTA agencies (CADTH and PBAC) accept a submission while the medicines are still under review by the respective regulatory agencies. NICE can also start its process prior to EMA authorisation, however it is not a formal parallel procedure. Information sharing between regulatory and HTA agencies during the post-authorisation period occurred in four HTA and four regulatory agencies. The collaboration between regulatory and HTA agencies was mainly driven by the increasing demand for faster patient access to new medicines (Figure 2). Regulatory agencies also indicated that

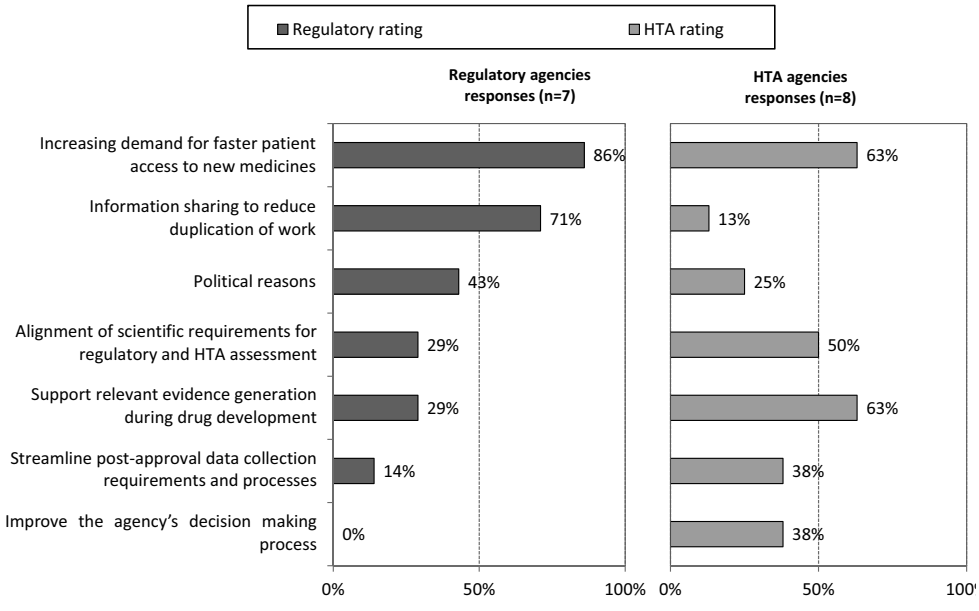

Figure. 2. Main drivers for regulatory and HTA agency collaboration. HTA, health technology assessment.

information sharing to reduce duplication of work was a key driver, and HTA agencies were keen to support relevant evidence generation during drug development.

Nevertheless, barriers to regulatory and HTA agencies working together were identified, including organizational issues resource limitations, working culture challenges legislative issues and importantly, divergences in assessment methodology and evidentiary requirements. The details are listed in the Supplementary Table 2.

Part II: Divergences observed and potential alignment of evidentiary requirements

Company respondents indicated that the two main areas where regulatory and HTA divergences have been observed related to products for which there was a high level of clinical uncertainty; for example, oncology products, orphan drugs, and products receiving conditional and accelerated approval. Furthermore, economic concerns from high-cost and high-budget-impact medicines contributed to divergences.

Both companies and agencies were asked to review a list of evidentiary requirements and identify the areas where divergences have been observed and potential alignment could occur. The results are detailed in the Supplementary Table 1. The areas where divergences were frequently perceived among all three stakeholders were: acceptable primary endpoints; inclusion of an active comparator arm in the trial; choice and use of surrogate endpoints. Areas of evidentiary requirements where commonality could occur were also evaluated. Overall companies were more positive is their perceptions of potential evidentiary alignments than regulators or HTAs. For example, companies were positive about the alignment of health-related quality of life measures (82% of respondents). In contrast, only 57% of regulatory respondents and 50% of HTA respondents agreed for that requirement (Table 1).

In considering the criteria for choice of a surrogate endpoint, companies and regulatory agencies revealed similar views. However, the most disparity in viewpoints in this area occurred between respondents from companies and HTA agencies. Most company respondents (93%) suggested that they would choose a surrogate endpoint that was previously used by an HTA agency. Surprisingly, HTA agency respondents indicated a low acceptance (25%) of this approach and specified rather that surrogate endpoints need to be clinically relevant and related to local context and would therefore be considered on a case-by-case basis rather than be based on precedent choice (Figure 3). All company respondents commented that ideally, regulatory and HTA agencies should work together to develop a joint list of acceptable and validated biomarkers and surrogate endpoints.

Part III: Strategic issues and trends of synergy between regulatory and HTA agencies

Early scientific advice was suggested by companies as a key strategy for drug development. Company respondents were positive about their joint scientific advice experiences. However, two thirds of the respondents revealed that early scientific advice

Table 1. Top areas where potential alignment across regulatory and HTA requirements could occur

Evidentiary requirements	Companies (n=28)	Regulatory agencies (n=7)	HTA agencies (n=8)
Acceptable primary endpoints	86%	86%	75%
Inclusion of an active comparator arm in the trial	86%	71%	75%
Use of patient reported outcomes (PROs)	86%	71%	75%
Health related quality of life measures	82%	57%	50%
Choice of and use of surrogate endpoints	79%	86%	75%
Criteria considered in choice of comparator: therapeutic	79%	86%	63%
Use of subgroup analyses	75%	71%	63%
Inclusion and choice of secondary efficacy parameters	75%	100%	63%
Definition of unmet medical need	75%	86%	63%
Use of biomarkers to monitor patient outcomes	75%	86%	63%

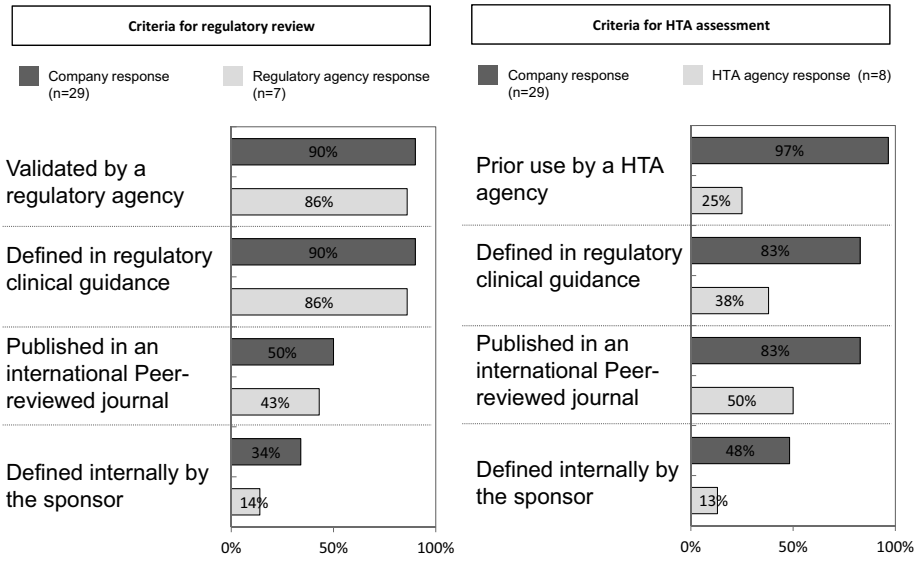

Figure 3. Key criteria considered for the choice of a surrogate end point. HTA, health technology assessment.

had not yet reached its full potential to align regulatory and HTA requirements. Company respondents pointed out that the input from the current joint advice meetings were more regulatory focused and advice received was diverse rather than an aligned view from both stakeholders.

Agencies recognized that joint scientific advice would be of great value, especially for conditional approvals. Benefits include clearer strategies for earlier and controlled released of new medicines, commitment by all stakeholders for post-marketing evidence

development, and maximizing the ongoing post-approval assessment of new medicines. For agency respondents, joint scientific advice would add value to the development plan in the areas of use of patient-reported outcomes, agreeing on acceptable primary endpoints, defining unmet medical need, agreeing on health-related quality of life measures, analysis methodology, choice and use of surrogate endpoints. However, four areas where regulatory and HTA agencies hold important different opinions were defining the size of the trial (100% regulatory rating vs 50% HTA rating), use of subgroup analyses (100% regulatory rating vs 63% HTA rating), pharmacological criteria considered in the choice of comparator (43% regulatory rating vs 88% HTA rating); and potential needs for diagnostics (0% regulatory rating vs 63% HTA rating), suggesting uncertainty of joint advice outcomes regarding these requirements.

Five HTA agency respondents indicated that conditional reimbursement schemes could be applied to products that have received regulatory conditional approvals; but companies reported that conditional approvals were not currently aligned with conditional reimbursement. Most company respondents (17 of 27) and HTA agencies (5 of 7) stated that the HTA processes currently used to assess conditional approvals were no different to standard approvals. However, company respondents pointed out that the HTA recommendations was different as a result of higher level of scrutiny for conditional approvals by HTA agencies. The majority of regulatory (57%) and HTA (75%) respondents indicated that joint scientific advice discussions on selection of compounds for accelerated assessment would be beneficial in achieving mutual understanding of an unmet medical need and identifying compounds that would offer clear value for healthcare systems.

Regarding the future trends, the majority of company and regulatory agencies respondents suggested that HTA agencies should seek to rely on regulatory public assessment reports in order to minimize duplication of work, whereas HTA agencies held a more tempered view on this approach. Regulatory agencies being involved in the assessment of cost effectiveness of new medicines was indicated as a possibility by both HTA agency and company respondents; however, all regulatory agency respondents disagreed with this option (Figure 4).

DISCUSSION

The two sequential processes of regulatory and reimbursement decision making have resulted in a degree of uncertainty regarding patient access to new medicines. HTA requirements for relative and cost-effectiveness are often referred to as the "fourth hurdle of market access" (Rawlins 2012). Over the past decade, interest has risen in the growing body of research comparing regulatory and HTA decisions, stimulating calls for more effective alignment between the two bodies (Nicod and Kanavos 2012, Allen, Lipska et al. 2014, Grepstad and Kanavos 2015, Lipska, Hoekman et al. 2015). A stakeholder survey conducted in 2012 by Liberti and colleagues was the first effort to explore the stakeholder

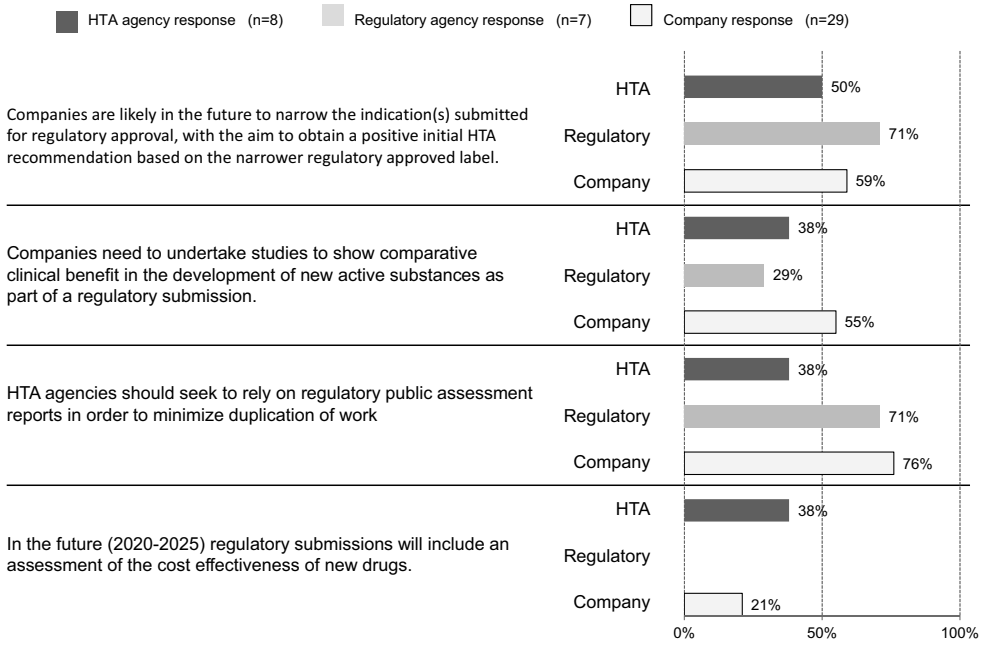

Figure 4. Perceptions regarding future trends in regulatory HTA collaboration. HTA, health technology assessment.

perceptions of regulatory and HTA interactions (Liberti, Pichler et al. 2012). Our study assessed the current practices and perceptions of companies and agencies regarding the synergy of regulatory and HTA activities and the changes in this area to date. Compared with the 2012 study, our study respondents perceived that the gap between regulatory and HTA stakeholders has narrowed, and all companies and agencies that responded to our survey supported synergy of regulatory and HTA. The current environment was reflected in three main areas in this study: 1) there is increasing interaction between regulator and HTA agencies; 2) current conditional regulatory approvals are not always linked with flexible HTA approaches; company respondents pointed out that the HTA recommendations was different as a result of higher level of scrutiny for conditional approvals by HTA agencies; 3) companies show more willingness and support of joint scientific advice.

Agency respondents recognized increasing interactions between regulatory and HTA agencies within their jurisdictions, driven mainly by the increasing demand for faster patient access to new medicines. Collaboration between the two stakeholders within their jurisdiction were observed in the study, mostly related to providing joint scientific advice to companies during development and early submission to HTA agencies during the regulatory review process. Although coordinated data collection post-authorisation was perceived as being of great value by respondents, in particular for products that

were approved under conditional or accelerated pathways, the level of collaboration during post-authorisation was confined to inter-agency information sharing. A number of international platforms facilitate the collaboration between regulatory and HTA agencies, such as the HTAi interest group HTA-Regulatory Interactions & Conditional Coverage (RICC), and EUnetHTA.

The increasing overlap in activities between agencies was mirrored in the more integrated approach between regulatory and HEOR departments within companies. This encouraging development in companies may be related to the increasing awareness and understanding of HTA requirements through knowledge and capacity building, as well as to learning from interactions with HTA agencies through early scientific advice. However, as regulatory division respondents rated transparency of HTA requirements lower than those from HEOR divisions, it showed that more internal education may improve the understanding of regulatory and HTA evidentiary requirements across functions.

Conditional approvals are granted to allow early access to medicines such as anti-cancer drugs that fulfil an unmet medical need. The 2012 study raised an open question as how the conditional approvals were associated with HTA decisions for faster patient access (Liberti, Pichler et al. 2012). Our survey showed that companies felt that the processes that HTA agencies currently use were no different to those used for standard approvals. Although conditional reimbursement schemes existed in certain HTA systems, these were not believed to be aligned with conditional approvals. This is supported by the findings by Desjardins and associates and Lipska and colleagues where no association was found between the type of EMA approvals and HTA decisions within selected EU countries (Desjardins and Conti 2015, Lipska, Hoekman et al. 2015). These results raised questions regarding the benefit of conditional approvals as an early access route to patients. It is therefore important for regulatory and HTA agencies to work in a more aligned way on the process of reviewing conditional approvals. For countries where there is no current conditional approval (for example, Australia, at the time of this study), a collaborative approach may be worth considering when setting up a formal procedure for applying for flexible regulatory routes.

Further to understanding the process and procedures, company respondents pointed out that the evidentiary requirements from HTA agencies on conditional approvals showed the biggest divergence compared with regulatory requirements. As conditional regulatory approvals are normally granted based on less comprehensive data compared with standard approvals, companies experienced a higher level of scrutiny by HTA agencies for products approved through these pathways. This divergence leads to the challenge for companies to find the right balance between timely access and optimal reimbursement, and to generate a data package that will be acceptable to both regulatory and HTA agencies as soon as possible.

These results were supported by the study from Liberti and colleagues in which HTA agencies were seen as being less committed to flexible approaches than were regulators and recommended that that one of the building blocks to a successful flexible regulatory

pathway is a streamlined approach to align regulatory and HTA requirements (Liberti, Stolk et al. 2015). Our survey respondents suggested that the requirements not only need to be aligned at the initial approval stage, but also during post-authorisation to best fulfill the follow-up evidentiary requirements of regulators and HTA agencies. A recent study by Rouf and associates assessed the post-authorisation data request from EMA and the German HTA body G-BA (Ruof, Staab et al. 2016), and found that G-BA made additional requests with less clear instructions compared with those made by EMA.

Joint scientific advice has been suggested by survey respondents as a platform for input from regulators and HTA agencies regarding the evidence generated during development and post-authorisation. The 2012 survey results showed a reluctance from companies to seek joint advice due to uncertainty about its benefits (Liberti, Pichler et al. 2012). Changes to this perception were observed in our study and all company respondents agreed that their joint scientific advice experiences have been helpful. However, the respondents still felt that the current advice meetings did not reach their full potential and issues raised in this regard included more focus on regulatory questions rather than a balanced input, diverse advice across agencies, and the unbinding nature of advice, which resulted in uncertainty regarding outcome. A previous study also showed similar opinions for joint advice meetings regarding a predominantly regulatory focus as well as the perception that joint advice meetings could be better utilised to reach a more aligned and better outcome (Wang, McAuslane et al, 2016).

Questions discussed during joint scientific advice meetings are prepared by companies and normally submitted prior to the meeting in a briefing book or structured template (Elvidge 2014). Therefore, preparing the right questions to be addressed is crucial for maximizing the benefit of joint advice. In our survey results, the type of topics identified as being of most value included the use of patient-reported outcomes, acceptable primary endpoints, health-related quality of life measures, analysis methodology, and surrogate endpoints.

Because our survey results suggested that HTA agencies are less likely to rely on precedents in the choice of surrogate endpoints, it is critical for companies to understand HTA requirements for acceptance of these endpoints during early interaction. A recent study by Tafuri and colleagues reviewing EMA and HTA agencies' parallel scientific advice meeting minutes also demonstrated the need to discuss the choice of surrogate endpoint, as some HTA agencies requested demonstration of a correlation of the surrogate endpoint with clinical outcomes and quality of life (Tafuri, Pagnini et al. 2016). Tafuri and colleagues also found disagreement amongst HTA agencies regarding the choice of comparator. The definition of unmet medical need was also viewed as one of the important topics to be discussed during joint advice meetings, particularly regarding the selection of products for conditional or accelerated regulatory routes of review. In fact, in 2015, EMA issued guidance that recommended companies seek joint scientific advice with HTA agencies for products intended for conditional approval.

LIMITATION

While our research is international in nature, we excluded jurisdictions with maturing HTA systems due to their different capacity levels and focused on jurisdictions with mature HTA agencies, including Australia, Canada and selected European countries that utilize cost-effective assessment in the HTA review. Therefore, respondents in the survey represented jurisdictions with regulatory and HTA agency interaction experience, potentially leading to more positive perspectives regarding awareness of and readiness for alignment.

CONCLUSION

Based on the findings of this study, recommendations are suggested to continuously improve synergy (Table 2).

This study identifies the current practice and perceptions from stakeholders and showed progress made in this area. In addition, we explored the stakeholders' perceptions

Table 2. Recommendations to improve synergy between regulatory and HTA stakeholders

Category	Area	Recommendations to improve synergy between regulatory and HTA stakeholders
Practice	Company internal practice	• Seek early scientific advice with HTA agencies • Raise awareness of access environment outside US • Increase skills and capabilities of staff • Establish a project/brand team with aligned input from regulatory and HEOR functions • Prioritise assets that will benefit the most from aligned approach
	Agency practice	• Understand the advantages of alignment and use political will to promote interaction • Alignment of timelines/review process between regulatory and HTA • Rolling review of valid new evidence and better understanding of uncertainties • Continuous joint scientific advice and early dialogue to improve mutual understanding
Evidentiary requirements	Area for alignment	• Focus on unmet medical need • acceptable primary endpoints, • Inclusion of an active comparator arm in the trial, • Choice and use of surrogate endpoints
	Strategy	• Focus alignment of evidence generation on efficacy/effectiveness • Align on minimum thresholds for clinical trials • Align where appropriate and acknowledge national differences

Table 2. (continued)

Category	Area	Recommendations to improve synergy between regulatory and HTA stakeholders
Future trend	Opportunities	• Utilise real-world evidence to support relative effectiveness assessment • Achieve aligned views on endpoint and outcome • Enable adequate and effective data collection • Continues evolvement of joint advice process • Information sharing on patient input • Improve transparency in decision making • Joint evaluation or share assessment of clinical context • Aligned post-marketing evidence generation • Establishment of joint registry

of where alignment of requirements could occur as building blocks to better alignment. The next step of this research will be to investigate the synchronization of regulatory and HTA decisions by assessing the respective review times and access outcomes, to help quantify the changes made to patient access.

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APPENDIX: SUPPLEMENTARY DATA

Supplementary table 1. Areas where divergences have been observed between regulatory and HTA as well as potential area for alignment (n= number of responses)

N= number of respondents that rated "Yes" Total number of respondents Company = 28 Regulator =7 HTA =8	Divergence has been observed between regulatory and HTA			Potential for regulatory and HTA alignment		
Clinical trial development	**Company**	**Regulator**	**HTA**	**Company**	**Regulator**	**HTA**
Ethical considerations	8	0	5	12	1	5
Patient selection	23	6	6	18	6	6
Size of trial	15	6	3	18	5	6
Inclusion of an active comparator arm in the trial	25	6	8	24	5	6
Acceptable primary endpoints	26	6	7	24	6	6
Choice of and use of surrogate endpoints	24	6	7	22	6	6
Inclusion and choice of secondary efficacy parameters	21	6	5	21	7	5
Validation of biomarkers	10	2	3	15	3	4
Use of biomarkers for patient selection (inclusion/exclusion)	16	4	2	18	6	6
Use of biomarkers to monitor patient outcomes	18	4	3	21	6	5
Re-analysis of results based on biomarker stratification of the patient population	14	2	3	14	2	4
Use of patient reported outcomes (PROs)	22	6	7	24	5	6
Analysis methodology	18	3	6	19	5	5
Use of subgroup analyses	22	6	6	21	5	5
The specification of the non-inferiority margin	8	3	4	11	4	4
Acceptability of foreign data	16	2	1	13	2	4
Dosage levels	10	2	2	12	4	4
Safety evidence	13	4	5	17	4	4
Health related quality of life measures	23	4	8	23	4	4
Criteria considered in choice of comparator	**Company**	**Regulator**	**HTA**	**Company**	**Regulator**	**HTA**
Pharmacologic	17	2	4	17	4	4
Therapeutic	24	4	6	22	6	5

Supplementary table 1. (continued)

N= number of respondents that rated "Yes" Total number of respondents Company = 28 Regulator =7 HTA =8	Divergence has been observed between regulatory and HTA			Potential for regulatory and HTA alignment		
Clinical trial development	Company	Regulator	HTA	Company	Regulator	HTA
Economic	15	2	5	9	1	3
Clinical pathway	15	3	5	17	4	3
Potential needs for diagnostics	11	1	3	13	1	5
Selection of compounds for accelerated assessment	15	2	7	14	5	5
Determination of benefit-risk of the new medicine	20	4	3	18	4	2
The amount of incremental innovation required to be considered non-inferior to an existing therapy	14	3	4	16	4	2

Supplementary table 2. Barriers identified to regulatory and HTA agencies collaboration

Barriers	Details
Organisational issues	• Different goals and objectives/ priorities • Different mandate and remit • Centralised regulatory agency vs. divergent HTA systems in Europe • Different expertise and professional groups • Operational complexity
Resource limitation	• Limited agency resource • There may be waste of HTA resources by reviewing a drug early if the product is not approved by regulatory agency
Working culture challenge	• Concern on confidentiality of data • Lack of trust • May lead to unclear responsibilities from both agencies • No willingness to share
Concern regarding financial capability	• Reimbursement of high-cost drug with weak evidence of effectiveness • Tension between medical need and financial capabilities
Legislative issues	• Political barriers • Different legal frameworks • Healthcare system structure is different, issues in Europe are different from US
Divergence of evidentiary requirements	• Remaining divergence of evidentiary requirements • Different emphasis on comparator between regulatory and HTA • Different assessment methodology • Need to identify areas where convergence is possible and where there are limits

CHAPTER 7

REGULATORY, HTA AND COMPANY INTERACTIONS: THE CURRENT LANDSCAPE AND FUTURE ECOSYSTEM FOR DRUG DEVELOPMENT, REVIEW AND REIMBURSEMENT

Ting Wang, Neil McAuslane, Wim G Goettsch,
Hubert GM Leufkens, Marie L De Bruin

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ABSTRACT

Background:

Regulatory-HTA, multi-HTA and multi-regulatory interactions, have evolved at both product and policy levels, spanning nationally and across jurisdictions. There is a need to assess the current and future landscape of interactions between company, regulatory and HTA stakeholders, address challenges and identify potential solutions for improvement.

Objectives

Identify the current landscape of interactions within and across regulatory and HTA, as well as companies' experiences in engaging in these activities; Assess the added value of these interactions as well as divergences and limitations; Explore the future ecosystem for interactions across stakeholders.

Method

3 separate questionnaires were developed for companies, regulators and HTA agencies respectively, to assess their experiences and perceptions. The responses were analysed using descriptive statistics then discussed at a multi-stakeholder workshop. Key outcomes from the surveys and workshop breakout groups were reported.

Results

7 regulators and 7 HTA agencies responded to the survey, from a mix of locations. The results showed more formal collaboration between regulators compared to HTA agencies. All 9 companies had experiences of taking early scientific advice but indicated they need to prioritize for future interactions. Four key interaction principles were proposed: keep the remit and functions of regulator and HTA separate; align process; converge evidence requirements when scientifically justifiable; and increase transparency to build trust.

Conclusions

This research brought together regulators, HTA agencies and companies to examine how they interact with one another, propose measures of value and make recommendations on future evolvement to enable better evidence generation and improve regulatory and HTA decision making.

INTRODUCTION

The process of bringing new medicines to markets involves multiple stakeholders: pharmaceutical companies, regulators and health technology assessment (HTA)/payer agencies. Although the ultimate aim of these stakeholders is to provide innovative medicine to patients in a timely manner, their agendas may not fully align: regulators aim to improve their pathway to provide a flexible mechanism for faster market authorisation; HTA agencies and payers are under pressure to recommend reimbursement for new medicines within the constraint of the healthcare budget; and companies in turn will need to generate evidence during development to ensure the product is approvable as well as reimbursable (Honig 2011, Liberti, McAuslane et al. 2020, Wang, McAuslane et al. 2020). Realizing the challenges and potential delay in patient access, stakeholders have started to work collaboratively to improve the efficiency of the decision-making process.

Over the last decade, regulatory and HTA interactions, as well as multi-HTA and multi-regulatory interactions, have evolved in thinking and mutual activities; this has occurred at a product level as well as at a policy level, and spanned both national and cross-jurisdictional systems. Regulators have a long history of collaboration. Since its initiation in the 1990s, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been bringing together regulators and companies to develop harmonized guidelines that help to ensure that evidence submitted to regulators is presented in a consistent manner (ICH, 2022).). For maturing regulatory agencies, reliance models have been put in place to facilitate the efficiency of the review process (Duran, Canas et al. 2021, Keyter, Salek et al. 2021). For mature regulatory agencies, collaborative initiatives have been set up, such as the Project Orbis for concurrent submission and review of oncology products (FDA, 2022) and the Access Consortium for medium-sized agencies to reduce duplication and align regulatory requirements (TGA, 2021). For HTA agencies, networks have been established to enable capacity building and shared learning, such as HTA international (HTAi) and The International Network of Agencies for Health Technology Assessment (INATHTA) at the global level, and HTAsiaLink and Health Technology Assessment Network of the Americas (RedETSA) at the regional level (Longson 2014, Schuller and Soderholm Werko 2017, Teerawattananon, Luz et al. 2018). Within Europe, the European Network for Health Technology Assessment (EUnetHTA) has been established to create an effective and sustainable network for HTA (Nielsen, Lauritsen et al. 2009, Luhnen, Ormstad et al. 2021). In addition to interactions among agencies, agencies also actively engage with companies to provide scientific advice to facilitate evidence generation during development; this advice comes either from the regulator, HTA agency or jointly from both stakeholders (Katsnelson 2004, Seldrup 2011, Wonder, Backhouse et al. 2013, Wang, McAuslane et al. 2022). More recently, it has been suggested that scientific advice should expand from development to post-licensing evidence generation (PLEG) for life-cycle data collection (Moseley, Vamvakas et al. 2020).

Responding to the fruition of various stakeholder interactions, research has been undertaken to assess the learnings of these activities. Most studies focused on early scientific advice in terms of processes, discussion content and potential impact (Seldrup 2011, Maignen, Osipenko et al. 2014, Tafuri, Pagnini et al. 2016, Wang, McAuslane et al. 2022). A recent study by Ofori-Asenso et al. examined the interactions between regulatory and HTA agencies and identified areas for further collaboration, such as early tripartite advice, parallel submission, adaptive licensing and PLEG (Ofori-Asenso, Hallgreen et al. 2020). More recently, these channels of communication and the networks for interactions have been tested by the COVID-19 pandemic, illuminating both challenges and opportunities as new and repurposed medicines are developed and their assessment accelerated (PharmacoEcon_Outcomes 2020, Soumyanarayanan, Choong et al. 2021). Therefore, there is a need to identify not only the current but also the future landscape of interactions within and across the key stakeholders (companies, regulators and HTA agencies), address challenges and examine potential solutions for the evolvement of these interactions. This paper is based on the outcomes of a multi-stakeholder survey and workshop with the aim of identifying the current landscape and future ecosystem of stakeholder interactions to support drug development and patient access.

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OBJECTIVES AND METHODS

Survey

CIRS conducted a multi-stakeholder survey in February 2021 with the main objectives to:

- Identify the current landscape of interactions within and across regulatory and HTA agencies, as well as companies' experiences in engaging in these activities.
- Assess the added value of these interactions from each stakeholder's perspective and how to measure the success
- Explore what the future ecosystem could be for interactions across stakeholders.

Three separate questionnaires were developed for companies, regulators and HTA agencies respectively (Annex 1). The pilot surveys were developed in January 2021 by the first author and were reviewed by all the co-authors with the purpose to validate the clarity, format and applicability of the surveys. Feedback provided by co-authors was used to refine the wording of questions and to finalize the surveys on 3rd February 2021. The questionnaires were distributed via email on 4th February 2021 to invited participants, who were asked to complete the questionnaire by 25th February 2021. A reminder email was sent on 22nd February 2021 for returning the survey. The agency surveys were sent to CIRS contacts holding senior positions within 17 regulatory agencies and 15 HTA agencies in Australia, Canada, Europe and Asia. The agencies selected were either considered major international regulators and HTA agencies, or had been invited to the workshop. The agency surveys were made up of 4 multiple-choice, closed questions and 3 open-ended questions. The surveys focused on 3 sections: assessing

the current experiences with the different stakeholders on interactions; identifying the characteristics of an effective interaction model; and recommending an effective model for future interaction. The company questionnaire was sent to senior management at 19 international pharmaceutical companies, which were selected using purposive sampling based on the membership of CIRS to ensure timeliness of the study and to maximize the response rate. The company survey consisted of 6 multiple-choice, closed questions and 3 open-ended questions that focused on current interactions between stakeholders. The survey was composed of 4 sections: effective models of stakeholder interactions; convergence through interactions; focus on 2030 and what would an ideal ecosystem be for interactions; and ensuring interactions between different stakeholders are adding value. The company, regulator and HTA agency questionnaires contained analogous questions where appropriate. A free-text comment option was provided for each question to allow further clarification or comments.

Workshop

A multi-stakeholder workshop was held virtually on 10-11th March 2021 on the topic of "Regulatory, HTA and payer interactions and collaborations: optimizing their use and outcome success" (CIRS, 2021). The objectives of the workshop included:

- Identify through case studies the key areas, types of interactions and collaborations between stakeholders that are effective, as well as the challenges and opportunities.
- Understand the value-add these interactions and collaborations bring to enabling improved decision making by the stakeholders as well as how to address divergences and limitations.
- Make recommendations on what can be learnt across jurisdictions from the current initiatives so as to inform the future evolution of stakeholder interactions and collaborations and how they can enable better evidence generation as well as improved outcomes for patient access.

92 senior representatives from regulatory agencies, industry, payers, HTA bodies, patient organizations, healthcare, and academia participated in the workshop (the list of participating organizations is provided as Annex 2). The results from the survey were presented at the meeting, followed by keynote speakers, case studies and panel discussion. Participants were then arranged into four breakout groups, pre-assigned with a diversity of stakeholders to ensure a balance of each perspective and were selected randomly. The breakout topics were aligned with the survey topics and each breakout group was led by a chairperson selected by CIRS based on their expertise. A rapporteur for each group was also selected to document the discussion and present a summary of the discussion back to all workshop participants. This paper focused on the discussion output from the breakout groups.

Data processing and analysis

The responses from the survey were tabulated into an Excel file manually and analysed using descriptive statistics. Data were calculated as the absolute number of responses if respondents were less than 10, and percentage of total responses if respondents were 10 or more; ranking was applied where suitable. The first author conducted content analysis for free text comments and open questions to identify key themes, before employing the constant comparative method. The results were reviewed by the second author to verify the phases and themes expressed by the study participants. The results for the breakout discussions were summarized by the first author based on the rapporteur presentations, as well as meeting recordings.

RESULTS

Survey results

Representatives of 7 (41 percent response rate) regulatory agencies and 7 HTA agencies (47 percent response rate) responded to the survey, which included key stakeholders from a mix of geographical locations. The regulatory agencies were Health Canada, the European Medicines Agency (EMA), Sweden's Medical Products Agency (MPA), Switzerland's Swissmedic, the Netherlands' Medicines Evaluation Board (MEB), Singapore's Health Sciences Authority (HSA) and China's Center for Drug Evaluation (CDE). The responding HTA agencies were Australia's Pharmaceutical Benefits Advisory Committee (PBAC), the Canadian Agency for Drugs and Technology in Health (CADTH), England's National Institute for Health and Care Excellence (NICE), Sweden's Tandvårds-Och Läkemedelsförmånsverket (TLV), China's National Health Development Research Center, Singapore's Agency for Care Effectiveness (ACE), and Thailand's Health Intervention and Technology Assessment Program (HITAP). 9 out of the 19 pharmaceutical companies completed the survey (47 percent response rate). These companies were in the top 25 companies by R&D expenditure in 2019 (Michael, C., 2019), reflecting the research intensity of the companies and the innovativeness of their development pipelines.

Agencies' experiences and perception of value of stakeholder interactions

All participating agencies indicated that they have interactions with other agencies. For regulatory-regulatory interactions, the top areas of interactions were formal work sharing during review, regulatory strengthening through workshops and training and informal exchange of knowledge and information. Respondents saw value in reducing duplication of work and providing an opportunity for capacity building, enabling more efficient drug development and support for post-approval activities. For HTA-HTA interactions, the top areas of interaction focused on HTA methodology/framework, HTA capacity building and informal exchange of knowledge and information. These interactions were reported as being useful to improve understanding of the divergences in evidence requirements and to validate agency internal thinking. (Figure 1). Two European HTA respondents were experienced in joint assessment through EUnetHTA.

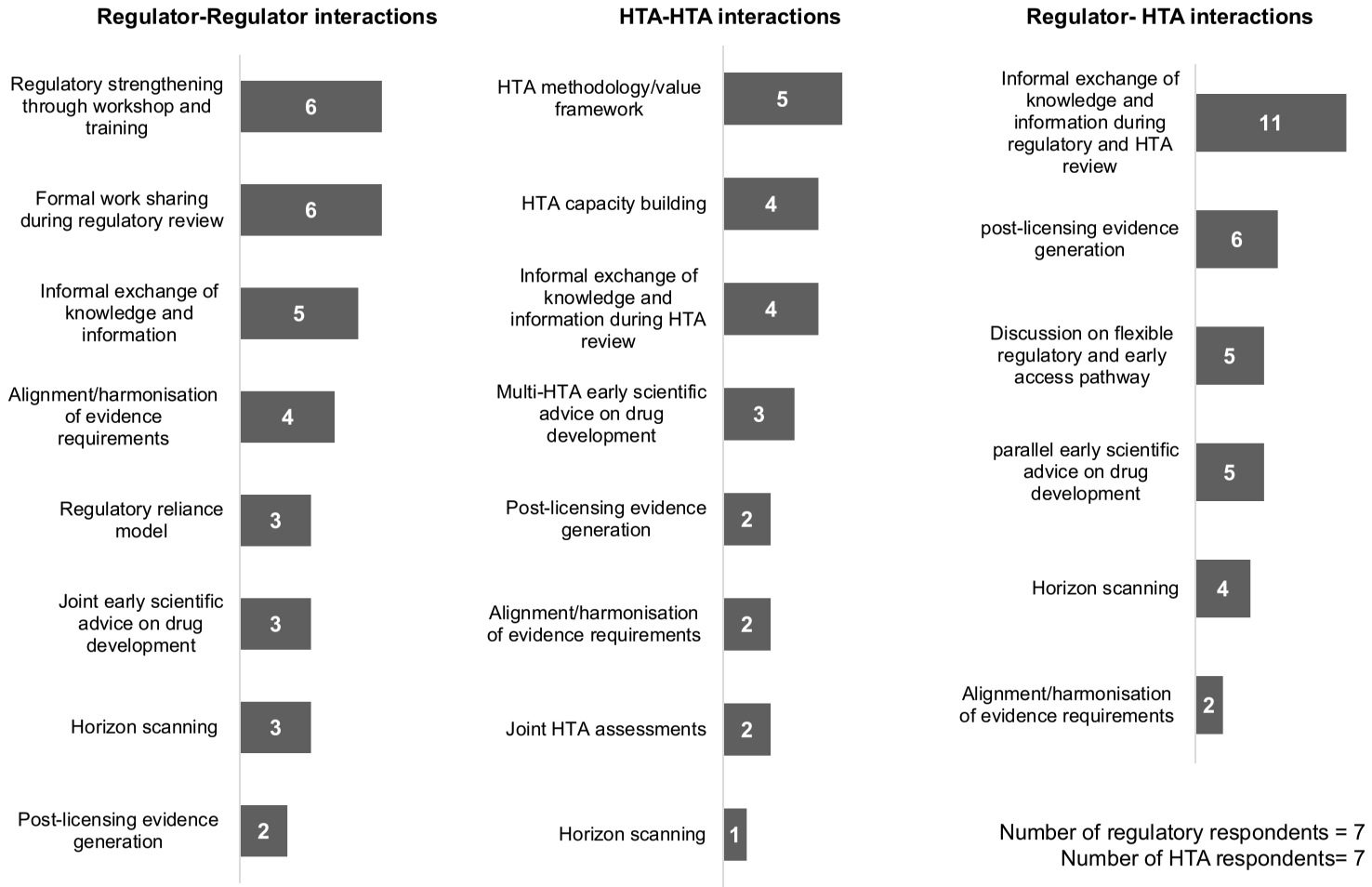

Figure 1. Overview of the current interactions between agencies

For cross-stakeholder interactions, the top areas of regulatory-HTA interaction were exchange of knowledge and information during regulatory and HTA review (85 percent of total respondents) and PLEG (46 percent of total respondents). Only 2 of 14 agencies reported on alignment/harmonization of evidence requirements. Regulatory-HTA interactions were seen to have fewer practical advantages but provided the opportunity to learn about the complexity of different systems. Both regulators and HTA agencies reported having interactions with payers to facilitate informal exchange of knowledge and information. HTA-payer interactions primarily focused on the implementation of HTA recommendations, discussion on pricing and budget impact, as well as discussion on conditional reimbursement/managed entry schemes.

Companies' experiences and perceptions of value of stakeholder interactions

All 9 companies reported having experiences in seeking early scientific advice with a regulator, HTA agency or through parallel regulatory-HTA advice. 5 companies had experience with multi-HTA joint advice and 4 with joint multi-regulator advice. Advice on PLEG plans tended to be more common with regulators than with HTA agencies (5 vs. 2 companies). Companies indicated that this interaction should be prioritized for products responding to unmet medical need, or new technologies such as cell/gene therapies. Companies also had interactions through public-private-partnerships such as Get-Real-Initiatives to facilitate alignment of evidence requirements (8 respondents), as well as input into evidence standards at the policy level (7 respondents).

6 companies reported that external interactions were a priority and that there were plans for future engagement, while 3 companies had agreed this in principle, but subject to the resource available to support these interactions. 6 companies indicated that the "success of interaction is measured subjectively" with a partially developed set of indicators, while 3 companies did not have any indicator in place to measure external interaction. All companies responded on the key areas that potential success indicators could be built on at both the product and therapy level (Figure 2). At the policy level, the value of stakeholder interactions could be measured by "input into guideline development", promoting "good HTA review practice", supporting "HTA capacity building" and "Regulatory strengthening".

Effective model of current interaction between regulators, HTA agencies and companies

Respondents noted that interactions were effective if the outcome aligned with the aim of the activities. ICH was rated by both companies and agencies as an effective model to support harmonization of technical requirements. EUnetHTA early scientific advice was voted as an effective collaboration to support evidence generation. Access Consortium and Orbis projects were selected as an effective way of formal regulatory work sharing, while the Medicines Evaluation Board (MEB) and the Zorginstituut Nederland (ZIN) parallel

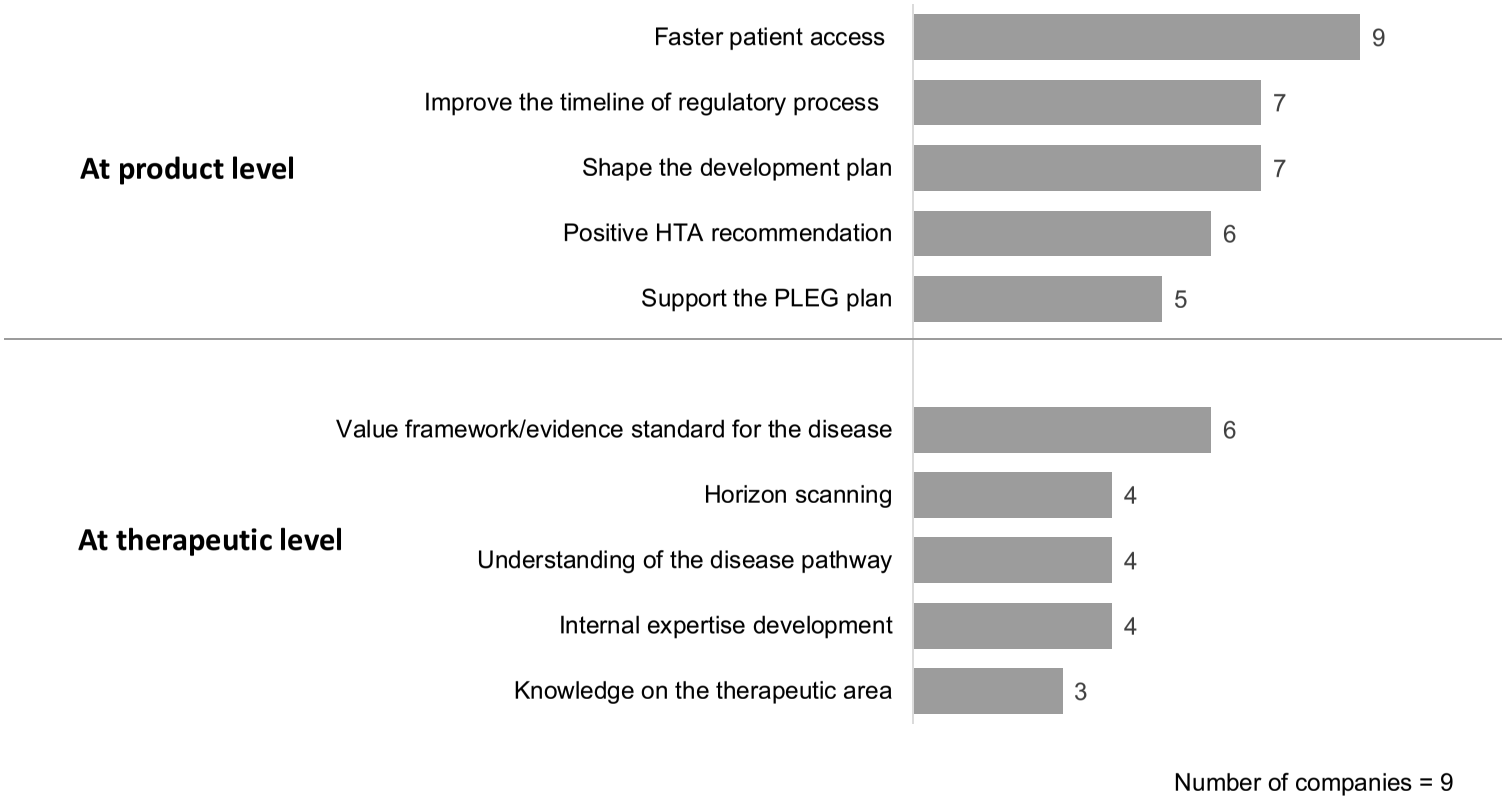

Figure 2. Companies' perspectives on the indicator to measure the value of stakeholder interactions

process in the Netherlands and the Innovative Licensing and Access Pathway in UK were viewed as good models to align regulatory and HTA process. With regards to improving agency decision making, international advisory committee and international collaboration programs were seen as effective, while national regulatory and HTA informal information exchange were recommended to enable process efficiency.

Future ecosystem for interaction between regulators, HTA agencies and companies

When asked about the ideal ecosystem for multi-stakeholder interactions in the future, 4 key principles emerged from the responses:

1. Separate remit and functions of the regulator and HTA agency: to acknowledge and provide clarification on scope and remit between regulators and HTA agencies, while increasing mutual understanding between the two stakeholders.
2. Convergences of evidence: develop common methodology and evidence standards where possible, so that drug development is aimed to meet both regulatory and HTA requirements.
3. Align process and use reliance: where appropriate, further align regulatory and HTA process with formal and/or informal information exchange to ensure process efficiency, advance reliance mechanisms for regulators, and enhance collaboration among HTA agencies such as work sharing or leveraging other agencies' work.
4. Transparency: increase trust between multiple stakeholders and propose a transparency agreement for information sharing. At the jurisdictional level, there should be collaborative approaches on horizon scanning to support innovation and facilitate patient access.

Workshop breakout groups

Details of workshop presentations, case studies and panel discussions have been published (CIRS, 2021). This paper focused on the breakout discussions during the workshop. The discussants reviewed the survey results and reflected on their own experiences of stakeholder interactions. EUnetHTA parallel advice was reported to promote cross-function collaboration within companies and among agencies. Nevertheless, challenges were identified by discussants, for example, companies need to achieve consensus on the evidence generation plan among internal regulatory and HTA functions; companies may assume that not following the scientific advice will impact the HTA recommendation; there is a lack of consensus on post-licensing data sharing between regulatory and HTA agencies; and multiple data sources can be an issue. Participants emphasized the evidence needs for comparative effectiveness post-approval and suggested that HTA agencies and payers align on affordability. Four success indicators to measure interactions were recommended: speed (time to patient access), 'correctness' of decisions (subject to each stakeholder's perspective), patient relevance of the evidence generated and

equity of access (Figure 3). However, discussants noted that measures should not be unidimensional; the speed to patient access cannot be compromised by the quality of decision making. The correctness of decisions was suggested to balance with the speed of decision, which was subject to different stakeholders' perspectives; further research is needed to understand and define this indicator. Agencies indicated that the intangible aspects of interactions were important, such as building relationships and trust with their peer agencies and improving knowledge of a new technology, which were difficult to measure qualitatively. It was suggested to assess the change of decision-making behaviors of stakeholders as a consequence of interactions.

Finally, the breakout group participants reviewed different types of stakeholder interaction and their future evolution (Figure 4). They also considered the impact of the COVID-19 pandemic, which has changed ways of working and accelerated the decision-making process; there was a concern that "vaccine nationalism" may reverse this and potentially lead to more divergence among jurisdictions. The discussants illuminated the future ecosystem for interactions. During drug development, stakeholders would have shared language to agree on the unmet need, clinical effectiveness, uncertainty and methodology; a stable platform for early dialogue that would enable alignment at the start of process, and networks to help foster valuable collaborations. During the post-licensing stage, there would be clear requirements and standards for post-approval data collection and better use of historical control data. Discussants also suggested that further interaction could take the form of an informal network that may focus on public health-related or policy-related topics.

DISCUSSION

Over the past decade, interactions between regulators and HTA agencies, as well as multi-regulator and multi-HTA interactions, have taken place to better support companies on clinical development, align the decision-making process among agencies to encourage efficiency and better-informed decision making, and promote trust and reliance between all stakeholders (Tafuri, Lucas et al. 2018, Keyter, Salek et al. 2020, Ofori-Asenso, Hallgreen et al. 2020). This multi-stakeholder survey and workshop assessed the current landscape of multi-stakeholder interactions, their added value, and the future development of these activities.

The survey illustrated different level of interactions; more formal work sharing between regulators compared to informal exchange of information among HTA agencies. This may relate to the longer history of regulatory agencies compared to the formal initialization of HTA, which has allowed mechanisms to be tested and trust to be built. Formal processes such as reliance models and standardized technical requirements through ICH fostered collaboration between regulators (Keyter, Salek et al. 2020, O'Brien, Lumsden et al. 2020). EUnetHTA has provided the platform to test multi-HTA collaboration, which led to the formal production of joint clinical assessment (JCA) to be fully implemented by 2029

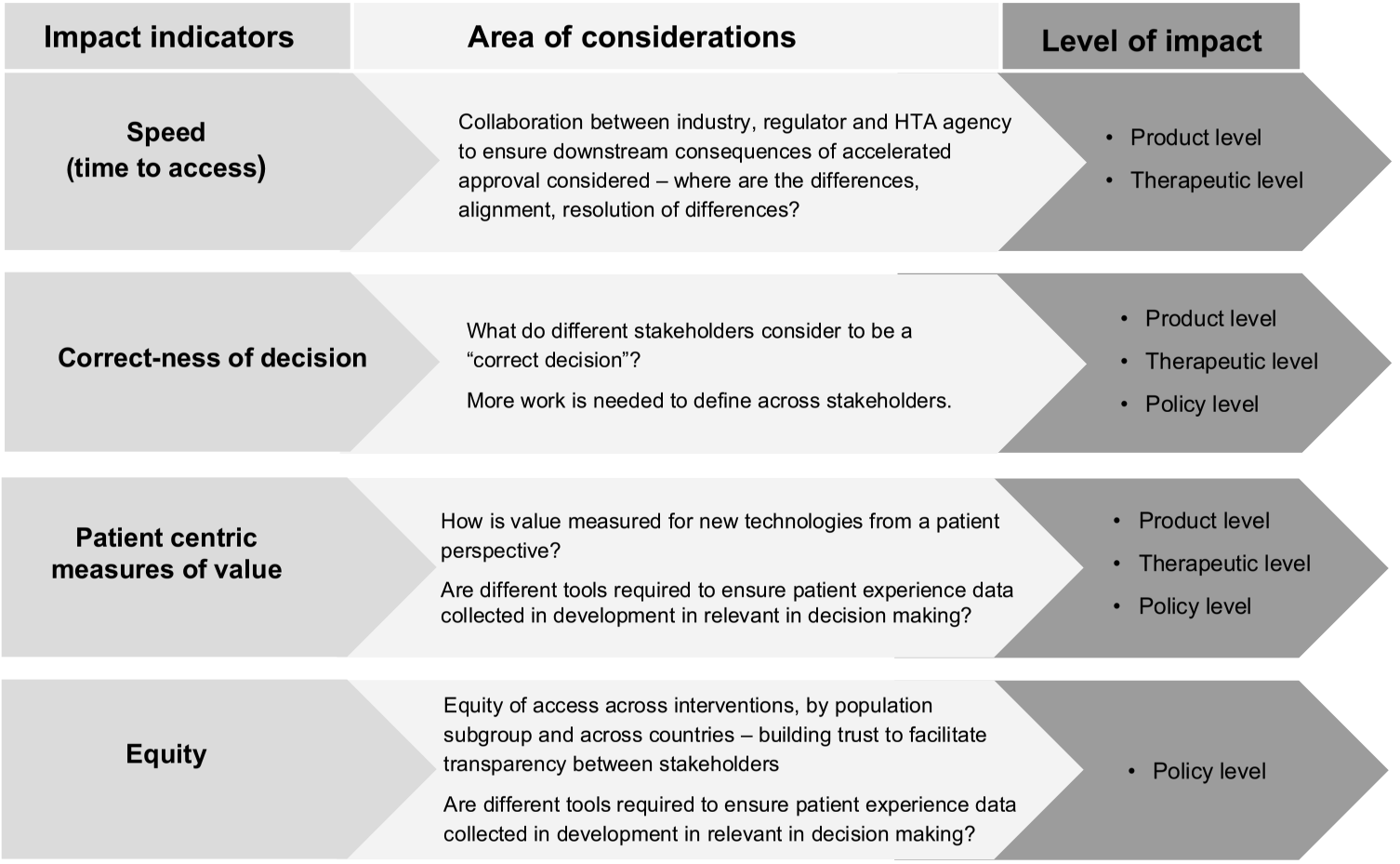

Figure 3. Recommendation on the indicator to measure the impact of stakeholder interactions

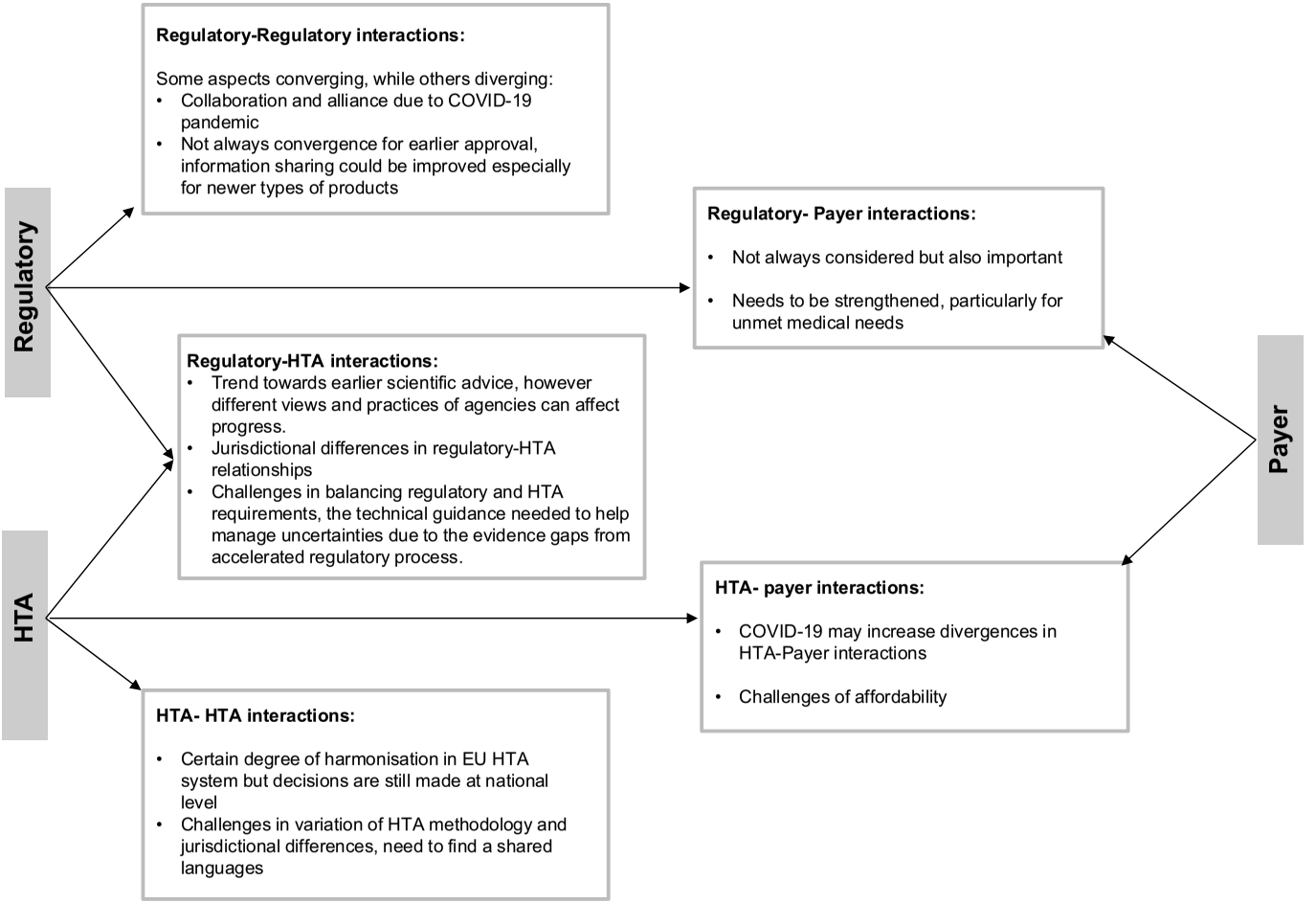

Figure 4. The current direction of evolution between different stakeholders

(European Commission, 2021). It is however critical for stakeholders in member states to collaborate in coming years to ensure that JCA will be used effectively in local decision making, rather than being a duplicative process. Our study also identified the appetite for HTA agencies to learn from the collaborative models of regulators, such as the Orbis project, to expand collaboration outside Europe. To achieve this goal, capacity building and alignment in HTA methodology/framework will be important; these two areas were rated as the top areas of focus by HTA respondents in the study.

Faster patient access is one of the measures rated by companies that indicates a valuable interaction. Procedure alignment is available in Australia and Canada, which allows HTA submission before regulatory approval; although there are no formal interactions between the agencies, the overlap in decision making results in shorter roll-out time (Wang, Sola et al. 2021). In the Netherlands, a pilot was launched in 2019 for a parallel process with formal coordination between MEB and ZIN. A recent example for Astellas' roxadustat showed that the parallel process allowed ZIN to rule on the reimbursement immediately after registration (ZIN, 2022). The successful pilot demonstrated a time saving of 3 months and has moved into a more structural collaboration. The Netherlands' model provided learnings for future national regulatory and HTA collaboration. Our findings acknowledged that regulatory and HTA should remain separate in function and remit, but more work could be done to converge evidence requirements where possible. For example, palbociclib was approved by EMA in 2016 for the treatment of breast cancer. However, the uncertainty due to lack of evidence on overall survival and treatment length led to divergent HTA recommendations in Europe. To investigate the evidence gap for palbociclib, a EUnetHTA PLEG pilot was conducted in 2021; this interaction identified common research recommendations among participating agencies, and saw the opportunity for collaboration between HTA agencies using cross-nationwide real-world evidence (RWE) to facilitate the initial HTA decision and subsequent reassessment (EUnetHTA, 2021).

Early scientific advice developed in recent years supported development and PLEG for companies, facilitated conversations among agencies and enabled better understanding between stakeholders. Nevertheless, these activities are resource consuming, and the workshop discussants raised the question of the capacity for companies and agencies to participate in such activities. This in turn requires prioritization. EUnetHTA joint scientific consultation listed its essential criteria: unmet medical needs; first in class; potential impact on patients/public health; significant cross-border dimension; major union-wide added value or research priorities; and breakthrough technology for oncology products and/or advanced therapy medicinal products (EUnetHTA, 2021). The criteria ensured that the resources from agencies were prioritized, in particular for interactions involving multiple agencies. These principles are mirrored with companies' priorities, as noted in our survey results. Studies on aligning each stakeholder's definition on unmet medical need contributed to mutual understanding of stakeholders' priorities (Vreman, Heikkinen et al. 2019, Moseley, Vamvakas et al. 2020).

Planning for early advice is also key; this needs to be early enough to shape the development plan, but not too early to ensure that sufficient evidence has been generated to support a meaningful dialogue. Therefore, future improvement should focus on clarifying the optimal timing to seek advice from regulators and HTA agencies; our research suggested that the interaction should not be a one-off activity but allow for a more flexible and iterative process for advice, especially considering the life cycle approach to collect data for medicines' review and reimbursement. In addition, early advice could be more transparent in a later stage of life-cycle decision making. Operational actions were suggested to improve efficiency, including consolidating learnings from scientific advice and speeding up administration steps. We also saw opportunity for informal networks to complement formal advice and contribute to not only product-related topics, but also policy and public health-related discussions.

Stakeholder interactions were seen as critical and beneficial for future drug development and availability; the workshop breakout groups pictured the ideal future ecosystem. However, the agility of regulatory and HTA systems have been tested through the COVID-19 pandemic. Researchers have analysed potential scenarios for the future of medicines and social policy in 2030; increased knowledge sharing, trust and openness in science, as well as partnership have been identified as key drivers for sustainable flow and transformative healing scenarios (Leufkens, Kusynova et al. 2022). The optimal direction of travel requires further dialogue, interaction and trust among stakeholders. Suggestions were proposed to improve current experiences, such as patient centricity, sharing common objectives among stakeholders and establishing a stable platform for continuous dialogue. To move from identifying divergence to enabling more convergence, the breakout groups suggested more work sharing and reliance models between regulators, alignment on affordability between HTA agencies and payers and increased transparency of PLEG requirements between regulators and HTA agencies.

Our research identified four potential areas to measure value: time to access, correctness of decision, patient centric measure of value and equity. Findings from this study will contribute to further discussion on building good practice into stakeholder interactions. An immediate next step can be a study to develop performance metrics to measure the value of interactions from the perspectives of regulators, HTA agencies and companies. Apart from potential quantitative indicators, the participants also raised qualitative value in interacting with other stakeholders, such as learning of new technology, validating internal thinking, building trust and improving understanding of other agencies. An interesting suggestion for further discussion was the possibility to assess behavior changes in decision making following these interactions.

STUDY LIMITATION

This study addressed the key components of stakeholder interactions from the regulator, HTA agency and company perspective. Its limitation is the lack of patient and payer's

feedback in the survey. Nevertheless, patient representatives and payer organizations were present at the workshop, which added their voice into the overall discussion and development of suggestions. Another limitation is the number of survey respondents, which, due to the study time frame, was limited to 7 regulators, 7 HTA agencies and 9 companies. However, this is complimented by the larger number of participants at the workshop, which provided further insights on the topics addressed in the survey.

CONCLUSIONS

The multi-stakeholder interactions among regulators and HTA agencies, as well as between regulators and HTA agencies, are important for ensuring a more efficient process from development to patient access. The outcome of the survey and workshop identified current landscapes and gaps, and suggested indicators that could be built to measure the value of interactions. This research also assessed perceptions of the future evolvement of these activities. Four key principles were identified for further development of interactions: keep the remit and functions of stakeholders separate; align process; converge evidence requirements when it is scientifically justifiable; and increase transparency to build trust.

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APPENDIX 1: QUESTIONNAIRES

QUESTIONNAIRE FOR HTA AGENCIES

Part A: Agency overview

1. Is your agency currently involved in any interaction/collaboration with other stakeholders? Please select all that applies from the options on below
   - ❑ Yes, interaction/collaboration with a Regulatory agency (or agencies) (if yes, please go to question 2.1)
   - ❑ Yes, interaction/collaboration with another HTA agency (or agencies) (if yes, please go to question 2.2)
   - ❑ Yes, interaction/collaboration with a payer agency (or agencies) (if yes, please go to question 2.3)
   - ❑ Yes, involvement in public-private partnership/ topic driven taskforce (if yes, please go to question 2.4)
   - ❑ No - no involvement in any interactions/collaboration with other stakeholders (Please go to question 3)
   - ❑ Others, please specify:

2. If "Yes", please provide the areas of the interactions/collaborations

   2.1. Current interaction/collaboration with a Regulatory agency (or agencies) (select all that apply)
   - ❑ Horizon scanning
   - ❑ Parallel early scientific advice on drug development
   - ❑ Informal exchange of knowledge and information during regulatory and HTA review
   - ❑ Discussion on flexible regulatory and early access pathway
   - ❑ Alignment/harmonisation of evidence requirements
   - ❑ Post-licensing evidence generation
   - ❑ Other, please specify:

   2.2. Current interaction/collaboration with another HTA agency (or agencies) (select all that apply)
   - ❑ Horizon scanning
   - ❑ Multi-HTA early scientific advice on drug development
   - ❑ Informal exchange of knowledge and information during HTA review
   - ❑ Joint HTA assessments
   - ❑ Alignment/harmonisation of evidence requirements
   - ❑ Post-licensing evidence generation
   - ❑ HTA methodology/value framework
   - ❑ HTA capacity building
   - ❑ Other, please specify:

2.3. **Current interaction/collaboration with a payer agency (or agencies)** (please select all that apply)

- ❑ Horizon scanning
- ❑ Parallel/joint early scientific advice on drug development
- ❑ Informal exchange of knowledge and information
- ❑ Alignment/harmonisation of evidence requirements
- ❑ Discussion on conditional reimbursement/managed entry scheme
- ❑ Pricing and budget impact
- ❑ HTA recommendation implementation
- ❑ Other, please specify:

2.4. **Current public-private collaboration/ topic driven taskforce** (free text)

Please specify the key areas of collaboration

3. **Please provide information on any interactions/collaborations that were not covered above.**

Part B: Assessment of the key interactions

4. In your opinion, what are the added value of stakeholder interactions/ collaborations for your agency? Please select all options that apply from the table below

Aspect of added value of stakeholder interactions/ collaboration for your agency	Regulatory and HTA interaction	HTA and HTA interaction	HTA and payer interaction	Public-private partnership/ Topic driven taskforce
Early signal to my agency on what is the areas of unmet needs and healthcare priorities	❑	❑	❑	❑
Provides insight into policy implications of emerging technologies and health threats	❑	❑	❑	❑
Enables a more effective and efficient drug development	❑	❑	❑	❑
Provides early insights into new innovative medicines prior to their assessment	❑	❑	❑	❑
Supports internal agency decisions at time of assessment	❑	❑	❑	❑
Reduce duplication of work	❑	❑	❑	❑
Improves the timing of the submission and review process	❑	❑	❑	❑
Supports future HTA decisions	❑	❑	❑	❑
Supports post-approval activities	❑	❑	❑	❑
Improves understanding of the divergences across evidentiary requirements	❑	❑	❑	❑
Validates internal thinking within my agency	❑	❑	❑	❑
Provides a learning opportunity about complexity of multiple system interactions	❑	❑	❑	❑
Provides an opportunity for capacity building and strengthening	❑	❑	❑	❑
If the aspect of added value of these interactions to your agency is not captured in the statements above, please provide the details here:				

5. For each type of interaction/collaboration across different stakeholders, please provide an example that your agency perceives as an effective model of engagement and the rationale of your selection.

Type	Name of the interaction/collaboration	The reason why this is an effective model
Regulatory and HTA interaction		
HTA and HTA interaction		
HTA and payer interaction		
Public-private partnership		

Part C: Future ecosystem for multi-stakeholder interactions

6. In your agency, is further interaction/collaboration with stakeholders a priority in the strategic plan?
   - ❑ Yes, external collaboration is a priority for my agency and there are plans for future activities
   - ❑ Yes, in principle but it will be depending on the resource (financial, manpower, time etc)
   - ❑ No further plans beyond our current activities
   - ❑ There is a plan to reduce the number of interactions/collaborations
     Please provide a comment_____

7. Focus on 2030, what would you like to see as an ideal ecosystem for interactions and collaborations across stakeholders? eg. Separate, aligned, converged, harmonized, collaborative, reliant? And what are the building blocks that will enable such an evolution?

Expectation of the future ecosystem across regulatory, HTA, payer to support the development, review and access of new medicine	Please provide an example of potential building blocks that will enable such an evolution

QUESTIONNAIRE FOR REGULATORY AGENCIES

Part A: Agency overview

1. Is your agency currently involved in any interaction/collaboration with other stakeholders? Please select all that applies from the options on below
   - ❑ Yes, interaction/collaboration with another Regulatory agency (or agencies) (if yes, please go to 2.1)
   - ❑ Yes, interaction/collaboration with an HTA agency (or agencies) (if yes, please go to 2.2)
   - ❑ Yes, interaction/collaboration with a payer agency (or agencies) (if yes, please go to 2.3)
   - ❑ Yes, involvement in public-private partnership/ topic driven taskforce (if yes, please go to 2.4)
   - ❑ No - no involvement in any interactions/collaboration with other stakeholders (Please go to question 3)
   - ❑ Others, please specify:

2. If "Yes", please provide the areas of the interactions/collaborations

   2.1. Current interaction/collaboration with another regulatory agency (or agencies) (please select all that apply)
   - ❑ Horizon scanning
   - ❑ Joint early scientific advice on drug development
   - ❑ Informal exchange of knowledge and information
   - ❑ Formal work sharing during regulatory review
   - ❑ Regulatory reliance model
   - ❑ Regulatory strengthening through workshop and training
   - ❑ Alignment/harmonisation of evidence requirements
   - ❑ Post-licensing evidence generation
   - ❑ Other, please specify:

   2.2. Current interaction/collaboration with an HTA agency (or agencies) (please select all that apply)
   - ❑ Horizon scanning
   - ❑ Parallel early scientific advice on drug development
   - ❑ Informal exchange of knowledge and information during regulatory and HTA review
   - ❑ Discussion on flexible regulatory and early access pathway
   - ❑ Alignment/harmonisation of evidence requirements
   - ❑ Post-licensing evidence generation
   - ❑ Other, please specify:

2.3. Current interaction/collaboration with a payer agency (or agencies) (please select all that apply)

- ❑ Horizon scanning
- ❑ Parallel/joint early scientific advice on drug development
- ❑ Informal exchange of knowledge and information
- ❑ Other, please specify:

2.4. Current public-private collaboration/ topic driven taskforce (free text)

Please specify the key areas of collaboration

3. Please provide information on any interactions/collaborations that were not covered above.

Part B: Assessment of the key interactions

4. In your opinion, what are the added value of stakeholder interactions/ collaborations for your agency? Please select all options that apply from the table below

Aspect of added value of stakeholder interactions/ collaboration for your agency	Regulatory and Regulatory interaction	Regulatory and HTA interaction	Regulatory and payer interaction	Public-private partnership/ Topic driven taskforce
Early signal to my agency on what is the areas of unmet needs and healthcare priorities	❑	❑	❑	❑
Provides insight into policy implications of emerging technologies and health threats	❑	❑	❑	❑
Enables a more effective and efficient drug development	❑	❑	❑	❑
Provides early insights into new innovative medicines prior to their assessment	❑	❑	❑	❑

(Continued from previous page)

Aspect of added value of stakeholder interactions/ collaboration for your agency	Regulatory and Regulatory interaction	Regulatory and HTA interaction	Regulatory and payer interaction	Public-private partnership/ Topic driven taskforce
Supports internal agency decisions at time of assessment	❑	❑	❑	❑
Reduce duplication of work	❑	❑	❑	❑
Improves the timing of the submission and review process	❑	❑	❑	❑
Supports future regulatory decisions	❑	❑	❑	❑
Supports post-approval activities	❑	❑	❑	❑
Improves understanding of the divergences across evidentiary requirements	❑	❑	❑	❑
Validates internal thinking within my agency	❑	❑	❑	❑
Provides a learning opportunity about complexity of multiple system interactions	❑	❑	❑	❑
Provides an opportunity for capacity building and strengthening	❑	❑	❑	❑
If the aspect of added value of these interactions to your agency is not captured in the statements above, please provide the details here:				

5. For each type of interaction/collaboration across different stakeholders, please provide an example that your agency perceives as an effective model of engagement and the rationale of your selection.

Type	Name of the interaction/collaboration	The reason why this is an effective model
Regulatory and Regulatory interaction		
Regulatory and HTA interaction		
Regulatory and payer interaction		
Public-private partnership		

Part C: Future ecosystem for multi-stakeholder interactions

6. In your agency, is further interaction/collaboration with stakeholders a priority in the strategic plan?
   - ❑ Yes, external collaboration is a priority for my agency and there are plans for future activities
   - ❑ Yes, in principle but it will be depending on the resource (financial, manpower, time etc)
   - ❑ No further plans beyond our current activities
   - ❑ There is a plan to reduce the number of interactions/collaborations

   Please provide a comment_____

7. Focus on 2030, what would you like to see as an ideal ecosystem for interactions and collaborations across stakeholders? eg. Separate, aligned, converged, harmonized, collaborative, reliant? And what are the building blocks that will enable such an evolution?

Expectation of the future ecosystem across regulatory, HTA, payer to support the development, review and access of new medicine	Please provide an example of potential building blocks that will enable such an evolution

QUESTIONNAIRE FOR PHARMACEUTICAL COMPANIES

Section 1: Effective models of engagement

1. Does your company utilize any interaction/collaboration with other stakeholders to support evidence generation? Please select all that applies from the options on below
   - ❑ Early scientific advice during drug development from a regulatory agency
   - ❑ Joint early scientific advice on drug development from multiple regulatory agencies
   - ❑ Early scientific advice during drug development from an HTA agency
   - ❑ Early scientific advice during drug development from multiple HTA agencies
   - ❑ Parallel Early scientific advice during drug development given from regulatory and HTA agencies
   - ❑ Interaction with regulatory agencies on the post licensing evidence generation plan (PLEG)
   - ❑ Interaction with HTA agencies on the post licensing evidence generation plan (PLEG)_
   - ❑ Others, please specify _____

2. Is your company involved in any interaction/collaboration with other stakeholders regarding alignment/harmonization on evidence standard? Please select all that applies
   - ❑ Harmonization evidence requirements for regulatory agencies (eg. ICH)
   - ❑ Standardized evidence requirements by HTA agencies (eg. EUnetHTA core model)
   - ❑ Public-private partnership/ topic driven taskforce on evidence requirements, such as Real-World Evidence
   - ❑ Input into evidence standard at policy level (eg, responses to agencies' public consultation guidelines)
   - ❑ Others, please specify _____

3. a) For each purpose of interaction/collaboration across stakeholders, please provide an example that your company perceives as an effective model of engagement and the rationale of your selection.

Purpose of the interaction	An example of an effective interaction/collaboration	The reason why this is an effective model
To support evidence generation during development		
To support evidence generation during post-approval		
To align/ harmonize evidence standard		

3. b) For each purpose of interaction/collaboration across stakeholders, please comments on the main challenges you perceive and what will be the potential solutions?

Purpose of the interaction	Main challenges	Potential solutions
To support evidence generation during development		
To support evidence generation during post-approval		
To align/ harmonize evidence standard		

Section 2: Convergence through collaboration

4. Does your company have a systematic process to decide which agencies to interact with during development, when to interact and for what products?
   - ❑ Yes, fully integrated systematic decision-making process on stakeholder interactions
   - ❑ Yes, partial integrated approach with decisions made on ad hoc basis
   - ❑ No
   - ❑ Others, please specify_____

5. In your opinion, what types of products will benefit the most from the stakeholder interactions/collaborations?

Purpose of the interaction	Type of products that will benefit from the interaction
To support evidence generation during development	❑ All New Active Substances (NASs) ❑ Products responding to rare disease ❑ Products responding to chronic disease ❑ Products responding to unmet medical need ❑ New technology, such as Cell/gene therapy, ATMP ❑ Repurposed medicine responding to healthcare urgency (eg. COVID-19) ❑ Others
To support evidence generation during post-approval	❑ All New Active Substances (NASs) ❑ Products responding to rare disease ❑ Products responding to chronic disease ❑ Products responding to unmet medical need ❑ New technology, such as Cell/gene therapy, ATMP ❑ Repurposed medicine responding to healthcare urgency (eg. COVID-19) ❑ Others
To align/ harmonize evidence standard	❑ All New Active Substances (NASs) ❑ Products responding to rare disease ❑ Products responding to chronic disease ❑ Products responding to unmet medical need ❑ New technology, such as Cell/gene therapy, ATMP ❑ Repurposed medicine responding to healthcare urgency (eg. COVID-19) ❑ Others

Section 3: Focus on 2030 and what would an ideal ecosystem be for interactions and collaboration

6. In your company, is interaction/collaboration with stakeholders a priority in the strategic plan?
   - ❑ Yes, external collaboration is a priority for my company and there are plans for future activities
   - ❑ Yes, in principle but it will be depending on the resource (financial, manpower, time etc)
   - ❑ No further plans beyond our current activities
   - ❑ There is a plan to reduce the number of interactions/collaborations

   Please provide any comment you may have: _____

7. Focus on 2030, what would you like to see as an ideal ecosystem for interactions and collaborations across stakeholders? eg. Separate, aligned, converged, harmonized, collaborative, reliant? And what are the building blocks that will enable such an evolution?

Expectation of the future ecosystem across regulatory, HTA, payer to support the development, review and access of new medicine	Please provide an example of potential building blocks that will enable such an evolution

Section 4: Ensuring that interactions and collaborations between different stakeholders are adding value

8. In your company, is there a set of indicators developed to measure the success of stakeholder interactions/collaboration
   - ❑ Yes, a set of formal indicators is in place. Please provide an example:
   - ❑ Partially, the success of interaction/collaboration is measured subjectively
   - ❑ No, no indicators in place
   - ❑ Others

   Please provide a comment_____

9. In your opinion, what are the key areas that the success indicators could be built on? Please select top three for each level.

Level	Key areas to build success indicators
Product level	❑ Shape the development plan ❑ Support the PLEG plan ❑ Improve the timeline of regulatory process ❑ Positive HTA recommendation ❑ Faster patient access ❑ Other, please specify:
Therapeutic level	❑ Internal expertise development ❑ Knowledge on the therapeutic area ❑ Understanding of the disease pathway ❑ Horizon scanning ❑ Value framework/evidence standard for the disease ❑ Other, please specify:
Policy level	❑ Input into guideline development ❑ Regulatory strengthening ❑ Best regulatory review practice ❑ HTA capacity building ❑ Good HTA review practice ❑ Other, please specify:
Others	

APPENDIX 2: WORKSHOP PARTICIPANTS

Agency participants

Agency for Care Effectiveness (ACE), Ministry of Health, Singapore
AOK Health Insurance, Germany, MEDEV, Brussels
Canadian Agency for Drugs and Technologies in Health (CADTH), Canada
Center for Drug Evaluation (CDE), Chinese Taipei
Department of Health, Pharmaceutical Benefits Advisory Committee (PBAC), Australia
European Commission/DG SANTE, Belgium
European Medicines Agency (EMA), The Netherlands
Food and Drug Administration (FDA), USA
Federal Joint Committee (G-BA), Germany
GKV-Spitzenverband, National Association of Statutory Health Insurance Funds, Germany
Health Canada, Canada
Medicinal Products Agency (MPA), Sweden
Medicines Evaluation Board (MEB), The Netherlands
Medicines and Healthcare products Regulatory Agency (MHRA), UK
Ministry of Health, Israel
Zorginstituut Nederland (ZIN), The Netherlands
National Institute for Clinical Excellence in Health and Social Services (INESSS), Canada
National Institute for Health and Care Excellence (NICE), UK
South African Health Products Regulatory Authority (SAHPRA), South Africa
Scottish Medicines Consortium (SMC), UK
Swiss Federal Office of Public Health, Switzerland
Swissmedic, Switzerland
Taiwan Food and Drug Administration (TFDA), Chinese Taipei
Therapeutic Goods Administration (TGA), Australia
The Dental and Pharmaceutical Benefits Agency (TLV), Sweden
Turkish Medicines and Medical Devices Agency (TMMDA), Turkey

Company participants

Abbvie
Amgen
Astellas
AstraZeneca
Bayer
Biogen
CSL Behring
Eisai
Eli Lilly
F. Hoffmann-La Roche

GlaxoSmithKline
H Lundbeck
Ipsen
Janssen Pharmaceuticals
LEO Pharma
Lundbeck A/S
MSD
Novartis
Pfizer
Sanofi
Takeda

Others

Bill and Melinda Gates Foundation, UK
Center for the Evaluation of Value & Risk in Health, Tufts Medical Center, USA
Centre of Regulatory Excellence, Singapore
Consilium Salmonson & Hemmings, Sweden
Critical Path Institute, USA
Danish Centre for Health Economics, Faculty of Health Sciences, University of Southern Denmark
Golden Jubilee National Hospital, UK
Office of Health Economics, UK
PharmaExec Consulting AB, Sweden
University of Adelaide, Australia
Utrecht University, The Netherlands

CHAPTER 8

GENERAL DISCUSSION

INTRODUCTION

As positioned in the introduction to this thesis, Health Technology Assessment (HTA) has been established as "A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" (O'Rourke, Oortwijn et al. 2020). The ultimate purpose of HTA is to inform public health decision-making and promote an efficient and value-based healthcare system. In this thesis, we focussed on HTA for new medicines and investigated the HTA practice within agencies and companies.

The structure, scope, review process, and methodologies may be divergent among HTA agencies, which may result in variation in their recommendations. A cross-agency comparison will enable a better understanding of different settings of the HTA system and may support performance improvement within agencies. This topic has been addressed in Chapter 2, providing a systematic framework to support the evolvement of HTA agencies. Subsequently, companies need to address the requirements of HTA agencies to achieve optimal market access for new medicines. The HTA strategy and submission actions by companies in individual jurisdictions should be fit-for-purpose to address the local context of healthcare needs; the experiences and learnings should then be fed back to the drug development plan so that the evidence generated at a global level will meet the HTA needs. Both these topics have been addressed in Chapters 3, 4, and 5. The investigation from both agencies' and companies' perspectives reflected the evolution and mindset changes from the stakeholders, such as aligning the different evidentiary requirements between regulators and HTA agencies, the early interactions between agencies and companies, and a more streamlined process between the regulators and HTA agencies. These topics have been explored in chapters 6 and 7.

THE EVOLUTION OF THE HTA AGENCY

Benchmarking HTA agencies – performance improvement

Rising costs of healthcare expenditure and increasing demand for new, innovative medicines have contributed to the fast growth of HTA agencies in the past 30 years (Banta 2003, Liu, Wu et al. 2020). Several studies have been conducted that review the institutionalization of HTA in Europe (Kristensen F 2008, Banta, Kristensen et al. 2009), Canada (Menon and Topfer 2000, Menon and Stafinski 2009), and Australia (Hailey 2009). Interest in the organization of HTA agencies has led to a series of publications by Drummond et al that propose' key principals' and a scoring system to audit agencies (Drummond, Schwartz et al. 2008, Drummond, Neumann et al. 2012).

Timely access to new medicines is crucial for patients and has been a marker for comparing the HTA agencies' performances. However, such an approach to timelines has proven controversial due to the application of homogeneous audit criteria across agencies with different remits (Drummond, Neumann et al. 2012) and concerns about the potential for unfair comparison due to varying contexts of HTA agencies. Therefore, there is a need to systematically review the organization of HTA agencies so that

the time to reach a recommendation and the outcome of the recommendation can be interpreted appropriately. A previous study reviewed the structural and procedural elements of HTA agencies with selected agencies and identified diversity in HTA settings (Schwarzer and Siebert 2009). Still, there is a lack of common measures to compare the organization of HTA.

To assess the practice of HTA agencies, we established a systematic methodology to benchmark HTA, developed in collaboration with agencies. The methodology and its 'application are reported in Chapter 2. The framework looks at the organization of HTA agencies in five domains: scope and remit, resource and budget, appraisal/scientific committee, transparency and review procedure and process. Particularly for the review procedure and process domain, a clearly defined and agreed-upon common milestone and terminology were developed to account for the differences between agencies. Based on the common milestone we have shown in Chapter 2, when applying this methodology, it is feasible to compare HTA performance in terms of timeline for the overall process, as well as where time was spent at each stage between HTA submission and recommendation. Large variation in overall HTA recommendation-making time has been observed among studied agencies, from 99 days to 862 days in median. We found several organizational aspects attributing to the timelines: resources allocated for the HTA activities within the agency; the extent of stakeholder involvement in the process (including patients, clinicians and companies), public consultation of draft recommendations or the appeal procedure available in case of negative HTA outcome; frequency of the committee meetings. We did not explore any potential statistical relationship between the timelines and 51 organizational aspects in the framework; because time will also be affected by companies' practices, such as the submission strategy, communication during the assessment for clarification questions, and the quality of evidence submitted.

Given the findings, we emphasized in our study that an in-depth understanding of the organization of HTA is needed to interpret timelines. In turn, the timeline comparison based on common milestones will facilitate agency internal performance improvement and process streamlining. A benchmarking study on regulatory agencies by Hirako M et al. showed the benefit of understanding the time taken at individual steps; the long queueing time during dossier validation was identified in one agency and resolved by an increase of administration resources (Hirako, McAuslane et al. 2007). Similarly, if benchmarking showed extensive time spent on clarification with companies or requirements on additional data, it may be resolved by adding a screening process for submission dossier or providing pre-submission advice to improve the quality of applications and minimizing the additional communication during HTA assessment. Benchmarking timelines will also allow agencies to assess their adherence to target review time for quality assurance and increase the transparency of HTA decision-making for external stakeholders in the healthcare systems.

In addition to timelines, quality of the HTA process and decision-making is also an important measure of performance. A multi-stakeholder workshop conducted

by CIRS recommended areas that can be built to assess the quality of HTA decision-making: the quality of the clinical assessment and economic assessment; the quality of the recommendation such as the extent the ultimate recommendation decision was driven by science; and the opportunity for discussion and negotiation with the HTA agency (Wang 2015).

Capacity building of HTA – self-improvement

Capacity building in the context of HTA has been defined as: "The process by which individuals and organizations develop or strengthen abilities related to understanding, providing input to, conducting, or utilizing HTA for health policy and decision-making, as well as, developing awareness and support in the environment within which HTA is being used." Capacity building of the HTA agency enables a more efficient decision-making process, and HTA capacity building should anchor on good HTA practices (Pichler, Oortwijn et al. 2019). Considering the increasing use of HTA and interest from stakeholders in healthcare systems, good practices of conducting HTA have been examined by researchers (Busse, Orvain et al. 2002, Rocchi, Chabot et al. 2015).

A recent literature review study by the ISPOR HTA Council Working Group assessed the current guidance on good HTA practice; the finding showed a lack of good practices in defining the organizational aspects of HTA and measuring the impact of HTA (Kristensen, Husereau et al. 2019). This means there is a potential for further research. The systematic methodology in Chapter 2 can provide a baseline for agencies to compare and improve their organizational settings. For example, the domain of appraisal and scientific committees looks at the professional disciplines, educational background, and the year of experience of committee members. If an HTA agency has not had a competent or experienced health economist or statistician, the ability to address reviews with methodological or evidence challenges will be limited (Drummond, Neumann et al. 2012).

This was also reflected in our findings in Chapter 7. We analysed the top areas where HTA agencies interact with peer agencies; the key focus is on HTA capacity building and informal exchange of knowledge and information. Global networks have been established to enable capacity building and shared learnings, such as HTA international (HTAi) and The International Network of Agencies for Health Technology Assessment (INATHTA) at the global level, and HTAsiaLink and Health Technology Assessment Network of the Americas (RedETSA) at regional level (Longson 2014, Schuller and Soderholm Werko 2017, Teerawattananon, Luz et al. 2018). This underscored the willingness and importance of cross-agency learning, which can be facilitated by future benchmarking research.

The criteria used in HTA recommendations go beyond just clinical effectiveness and/or cost effectiveness, factors considering equity, ethical and social aspects are important when making decision on healthcare resources. Currently there is lack of international comparison and standards on these aspects and paves the path for further research

in this area (Tantivess 2014, Ali-Khan, Black et al. 2015, Norheim 2016, Bernier, Legault et al. 2020).

The new way of working: mindset change to lifecycle and collaborative HTA

The introduction of the "lifecycle approach" has changed the paradigm of HTA (Husereau, Henshall et al. 2016). Interests in exploring how HTA has been and/or been applied in the new medicine's lifecycle led to growing research in recent years (Henshall, Schuller et al. 2013, Ciani and Jommi 2014, Husereau, Henshall et al. 2016). Early HTA can be applied to assess the potential cost-effectiveness of new medicine and inform clinical development (Grutters, Govers et al. 2019, Vreman, Geenen et al. 2019). Although early HTA is not part of formal activities at HTA agencies, there are opportunities for companies to conduct early HTA and test the cost-effectiveness modelling at early advice meetings with the agency (NICE, 2022). Horizon scanning has been introduced as part of HTA practice to assess the potential impact of emerging new technologies on the healthcare system (Douw and Vondeling 2006, O'Malley and Jordan 2009, Ciani and Jommi 2014). The EUnetHTA report recommended that horizon scanning be proactive and reactive for topic identifications (EUnetHTA, 2020). The benchmarking framework illustrated in Chapter 2 included the elements on topic selections, such as criteria for priority setting, topic selection process and explicit criteria for topic selections. Periodical assessment of HTA organizations using the framework will enable comparison of the role of HTA agencies in horizon scanning and also reflect changes in the future.

A key area of HTA activities during development is providing early scientific advice to companies. As shown in Chapter 4, the current early HTA advice is limited to European and Canadian agencies, indicating a gap for HTA agencies in other jurisdictions to be more involved in drug development. With the adoption of EU HTA regulation (HTAR), EUnetHTA 21 joint scientific consultation (JSC) will continue to provide early advice to companies led by G-BA. Meanwhile, as no longer part of EU, NICE in England continues its service in providing standard early advice and European concurrent advice (NICE, 2022). This is reflected in our findings in Chapter 7, the survey with HTA agencies also implied a disparity in providing early advice among HTA agencies globally; however, they also indicated in the study that the stakeholder interaction is a high priority for their agencies. Agencies recognized that early advice would be valuable to provide early insights into new innovative medicines before their assessment; and early advice jointly with regulators would be of great value, especially for conditional approvals (Chapter 6).

In addition to advice on development evidence generation, agencies also welcome the discussion on post-licensing evidence generation (PLEG) at early advice meetings; it is recommended that companies identify the potential evidence needs at the time of licensing or HTA assessment and discuss them at early advice meting how to fill the anticipated gap. (Moseley, Vamvakas et al. 2020). Once a medicine is approved and reimbursed for access, the HTA agency may also re-evaluate the product periodically

if new evidence emerges to ensure that decisions are appropriately made (HAS, 2021; EUneHTA 2018). Disinvestment has also become a part of HTA activities at the post-approval stage to reassess medicines and provide recommendations on withdrawal if they no longer deliver value and do not represent efficient health resource allocation (Elshaug, Hiller et al. 2008, Bastian, Scheibler et al. 2011, Calabro, La Torre et al. 2018). These areas have been less studied due to a lack of frameworks and guidelines and paved the way for future research on the role of HTA at post-approval (Calabro, La Torre et al. 2018).

As discussed above, the activities of HTA have extended through the lifecycle of a drug; questions remained on the most appropriate role for HTA agencies, their remit, capacity and resource. A new way of working has been discussed and considered regarding work sharing and collaboration to ensure efficiency and shared learnings among HTA agencies. In Chapter 7, we observed more formal work sharing between regulators than the informal information exchange among HTA agencies. Formal process such as the reliance model and standardized technical requirements through ICH fostered the collaboration between regulators (Keyter, Salek et al. 2020, O'Brien, Lumsden et al. 2020). EUnetHTA has provided the platform to test out multi-HTA collaboration, which led to the formal production of joint clinical assessment (JCA) to be fully implemented by 2029 (European Commission, 2021). It is critical for stakeholders in member states to collaborate in the coming years to ensure the JCA will be used effectively in local decision-making rather than as a duplicative process. In addition to HTA collaboration in the EU, cross-regional initiatives have been established. For example, NICE and CADTH have launched a parallel scientific advice process to provide the opportunity for early engagement with companies targeting the UK and Canadian markets (NICE, 2019). Our study in Chapter 7 identified the appetite for HTA agencies to learn from regulators' collaborative models, such as the Orbis project (FDA, 2022), to expand the collaboration outside Europe. "Like-minded" regulatory agencies have been collaborating and work-sharing through the Access Consortium, which enabled agencies in Australia, Canada, Singapore, Switzerland and the UK to share reviews across regions and streamline company interactions (TGA, 2021). The latest research by CIRS showed that medicines reviewed through the Access route had a faster approval time in Australia and Canada (CIRS, 2022). A future research question will be to investigate these medicines through their HTA process in these jurisdictions and also begs the question of whether a potential collaboration of these HTA agencies can be formed.

In this thesis, we established a systematic framework to benchmark the organization and milestone performance of HTA agencies. It provided a baseline and tool to assess the evolvement of HTA; qualitative surveys with HTA agencies showed the actions taken so far and willingness to expand the role of HTA along the lifecycle of new medicines.

THE HTA PRACTICE IN THE INDUSTRY

Experiences and strategy during development – Upstream decision making

Target product profile (TPP) is an essential tool in the upstream decision-making by companies and serves as a roadmap for a product's development. Traditionally utilised in the regulatory area (Breder, Du et al. 2017), the concept of the TPP is not commonly used by HTA agencies. No current research assesses how the TPP is evolving with the increasing influence of HTA. Nevertheless, our study showed that companies had been actively incorporating HTA perspectives into the TPP, but the timing and process varied among companies (Chapter 5). HTA perspectives were mainly built into three areas in the TPP: health problem and treatment pathway, clinical efficacy/effectiveness, and safety; Chapter 3 listed further details of HTA requirements included in development: safety measures, HTA acceptable primary and secondary endpoints, patient selection criteria, and trial duration.

A similar concept to TPP, Target Development Profile (TDP) has been introduced in the UK (ILAP); this is a living document that contains key development features for coordinated and efficient evidence generation and evaluation (MHRA, 2021). A company has also piloted a framework for internal evidence generation based on the EUnetHTA Core Model (Ducournau, Irl et al. 2019). An iterative process leads to creating a dynamic TPP document, which will initially be developed focusing on a core list of evidentiary requirements and then is updated as new outcomes are generated from the clinical trial and the treatment landscape changes. This means there is much more potential for an integrated evidence generation tool to evolve from TPP to be used internally by companies during development and as an iterative stakeholder communication tool with regulators, HTA, payers and patient groups.

In this thesis, we investigated the HTA perspectives in TPP from clinical aspects. Study has also been undertaken to explore how early HTA can inform the development of TPP, by establishing the economic model during drug development. Several case studies showed that early HTA can provide a preliminary estimation of cost-effectiveness of the medicine under development, comparing to the current standard of care (Vreman, Geenen et al. 2019, Broekhoff, Sweegers et al. 2021). Therefore, early HTA can be used to determine the desired or maximum price for a new medicine to be cost-effective. Accordingly, the insights can help companies to balance between the TPP target and the uncertainties showed in the early HTA, in order to inform the improvement development plan through TPP (Wang, Rattanavipapong et al. 2021). A key strategy to seek HTA insight is early stakeholder engagement. We identified various company approaches, such as internal qualitative or quantitative payer research, consultation with internal therapeutic head, external advice meeting with payer advisory board and key opinion leader (KOL). In Chapter 4, we assessed the early HTA scientific advice from companies' perspectives and observed that companies used a mix of options to gain insight from agencies, with a preference for a single national HTA agency advice (71%). We found that the most

frequently sought-after single agency advice was from G-BA and NICE. This result sheds light on the business priority to gain access in the largest economic markets in Europe. The availability of the scientific advice programme provided by agencies, as well as the different methodology that the agencies utilize could have driven this approach: G-BA uses added clinical benefit as a key decision criterion, whereas NICE uses cost-effectiveness (Allen, Liberti et al. 2017). Although taking early advice from HTA agencies has become a standard operation, decisions not to take advice is also key to ensuring that resource is prioritized (Chapter 4).

We further measured the utilization of early HTA advice by companies. Parallel regulatory-HTA 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 good compliance with companies' advice on the primary endpoint (Tafuri, Lucas et al. 2018). We showed 42% of advice outcomes of a single HTA meeting and 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. Companies should disseminate their learnings and exchange experiences collaboratively. There were different types of question that companies wanted to address at each type of advice meeting (Chapter 4), suggesting companies have been carefully considering the topics to ensure the discussion were fit for purpose.

Beyond the assessment of early advice during development, we should further investigate how the advice provided has been or will be articulated in the HTA submissions. For example, if the interaction with HTA agencies will be included in the submission, the advice received and if they have been followed, and the justification if advice were not followed. Continuous research should keep tracking the trend of taking advice from companies and assess the impact of JSC and Brexit on the advice strategy by companies. Future study could also assess the impact of scientific advice on the HTA decision-making and recommendations, and finally the impact on the patient access.

Experiences and practice at key HTA markets -downstream decision making

Research has been undertaken to compare the HTA bodies based on public domain information, while in this thesis we reported the experiences from companies' perspectives (Nicod and Kanavos 2012, Lipska, Hovels et al. 2013, Allen, Lipska et al. 2014, Salas-Vega, Bertling et al. 2016, Allen, Liberti et al. 2017). In Chapter 5, companies reported that in Australia, Canada and England, the most frequently raised issues on the evidence of a new medicine were "not cost-effective" and "lack of longer-term outcomes." In Germany and France, where the HTA recommendation is mainly based on added therapeutic value, the outstanding issues centered around comparators, such as insufficient improvement over comparator, comparator choice being unacceptable, the validity of the endpoint and lack of longer-term outcomes or follow-up. In turn, HTA agencies may require additional

evidence to support their recommendation-making to be local relevant: we noted that 44% of additional required evidence by HTA agencies was related to the use of a locally relevant comparator, 35% were for a sub-group analysis, 26% were for a locally relevant economic analysis, 24% were to contextualize the evidence to the local population, 21% were for the use of a different analysis methodology, 13% were related to the use of a network meta-analysis, and 10% were requests for trial data in the local population. Regarding comparator choices, HTA agencies that conducted benefit assessment showed the highest proportion of comparator rejections: 12% in France and 27% in Germany of total submissions (Chapter 3). This may be because the added benefit of new medicines was assessed on subsets of the population by Institut für Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) (Kaiser et al., 2015); therefore, additional comparators were utilised to identify benefits in the subgroups.

To best support the HTA submissions at the local level, companies generated local contextualized information before submission to meet the specific requirement of an HTA body. A high proportion of submissions to England (90%) incorporated local contextual information, followed by Germany (82%), Italy (80%), and Spain (79%). Companies sought advice from agencies before HTA submission; the study showed that Germany has the highest proportion of pre-submission advice among its total submissions (73%), followed by Australia (69%), France (35%) and Canada (23%). These results demonstrated that companies had been proactively addressing the needs of HTA requirements at individual jurisdictions, moving forward, resources from companies could be saved in the future HTAR with the hope of a more aligned process and agreed on PICO (patient, indication, comparator, outcome) research questions.

Timely HTA recommendation of a new medicine is a marker for patient availability and companies' commercial access. It is crucial to evaluate the timeliness of the HTA process in the right context, which is related not only to the HTA agency's process and performance (Chapter 2) but also to companies' submission strategy and the time taken to provide additional information during HTA review (Chapter 3) (Schoot, Otth et al. 2022). Our results showed that HTA submissions were conducted across all the studied European HTA agencies within two months of EMA approval, implying companies can submit the HTA dossiers to these jurisdictions alongside the regulatory process. However, research also identified the submission gap is lager in Central Eastern European (CEE) countries, for example submission to HTA agencies in Poland which can take more than one year from EMA approval (Wang, Sola et al. 2021), In the proposed EU JCA process, the submission of the HTA dossier is aimed at 45 days before the CHMP opinion, and the JCA report is to be delivered 30 days after the EMA approval (EUnetHTA, 2022). The timeline projection is promising for patients and companies. However, speedy national adoption of JCA and decision-making is essential in driving timely patient access in the EU. Therefore, continuous monitoring of roll-out timelines of medicines in key HTA markets using the benchmarking methodology will help capture the changes in the process of HTA agencies and the practice of companies in the future.

The evolvement of HTA in companies – mindset change

To coordinate evidence generation, companies have implemented cross-functional collaborations within their organizations to bring clinical, regulatory, health economics and outcomes research (HEOR) and access teams together during the drug development process (van Nooten, Holmstrom et al. 2012). Good levels of engagement of clinical, regulatory, HEOR, and pricing and reimbursement teams were observed in TPP development in Chapter 5. However, the cross-functional approach was not a guarantee for aligned internal decision-making; prioritization gave way to regulatory requirements compared to HTA needs. Internal structure and strategy need to be adjusted to tackle issues such as resource constraints, lack of appropriate infrastructure, lack of awareness of HTA requirements, and development plans driven by the US market (Chapter 6). A more aligned process with systematic internal decision-making will facilitate the efficient development of the TPP. At the same time, a systematically developed TPP can also help to align objectives across different company functions and accelerate development timelines (Lambert 2010).

Individual companies and industry associations have published their policy statements on key HTA principles, which covered aspects such as the structure of HTA program, methodology, process and utilization of HTA in decision making (Merck, 2019; Roche, 2020; EFPIA, 2022). A company has also collaborated with EUnetHTA to test the HTA Core model internally and viewed it as a valuable framework to standardize the domain of HTA questions and understand the common terminology (Gyldmark, Lampe et al. 2018). These reflect the company mindset changes from reactive to proactive, with a critical emphasis on broad stakeholder engagement in the future HTA process.

MULTI-STAKEHOLDER INTERACTIONS

Convergences of evidence where possible

The interface between regulators and HTA agencies is developing rapidly, mainly driven by the increasing demand for faster patient access to new medicines. Regulatory agencies also indicated that information sharing to reduce duplication of work was a key driver, and HTA agencies were keen to support relevant evidence generation during drug development (Chapter 6). However, challenges remain in developing evidence that meets the requirements of both regulatory and HTA agencies at the point of launch (Eichler, Bloechl-Daum et al. 2010). The difference in the remit, methodology and evidence requirements between regulator and HTA agencies, as well as variability across HTA agencies, introduces uncertainty into drug development decisions and can result in a potential mismatch of regulatory and HTA outcomes. It has been suggested by a company to focus on a core list of elements such as avoidable uncertainty during development and make changes to adapt to HTA needs (Facey K, 2015). Results showed in Chapter 6 that two main areas in which regulatory and HTA divergences occurred related to products for which there was a high level of clinical uncertainty, for example, oncology products,

orphan drugs, and products receiving conditional and accelerated approval. Evidentiary divergences most frequently observed were the inclusion of an active comparator arm in the trial and the choice and use of surrogate endpoints.

The impact of the surrogate endpoint on the regulatory and HTA decisions has been researched extensively (Garrido and Mangiapane 2009, Es-Skali and Nijhuis 2013, Lipska, Hoekman et al. 2015, Droeschel, Hartmann et al. 2016, Kleijnen, Lipska et al. 2016, Vreman, Bouvy et al. 2019). Nevertheless, less is studied on the rationale of choosing a surrogate endpoint from both agencies' and the companies' perspectives. In our study, the companies implied that the precedent choice informed their decisions on the surrogate endpoint by HTA agencies; however, agencies indicated that the surrogate endpoint needs to be clinically and locally relevant and should be assessed as individual cases. Companies therefore call for regulatory and HTA agencies to work together to develop a joint list of acceptable and validated biomarkers and surrogate endpoints (Chapter 6).

Active comparators included in the global development were generally well accepted by HTA agencies, with additional local relevant comparators being required during HTA review, mostly through indirect comparison (Chapter 3). Inevitably, the choice of the comparator will vary among healthcare systems. However, the comparator in global development should ensure the potential indirect comparison required by HTA agencies. Using an external comparator in HTA submission is evolving, especially in the rare disease area where there is no currently available treatment (Patel, Grimson et al. 2021). Understanding where the divergences occur will facilitate the future convergence of evidence where possible. Regulators, HTA agencies and companies agreed that the choice of comparators in global trials can be further aligned (Chapter 6); our study suggested a few building blocks: aligning on minimum thresholds for clinical trials, aligning where appropriate and acknowledge national differences, and developing common methodology and evidence standard where possible (Chapter 7). The EUnetHTA 21 is actively developing guidance and seeking public consultation on a number of topics, such as the choice of comparator and indirect comparison, subgroup analysis, types of evidence in the assessment report. Alignment is expected in the future EU JCA; the policy questions on intervention and population are suggested based on the EMA approval (EUnetHTA, 2022). For conditional approvals, the evidentiary requirements need to be aligned not only at the initial approval stage but also during post-authorisation to best fulfill the follow-up evidentiary requirements of regulatory and HTA agencies (Chapter 6).

Joint scientific advice is a good platform to gain input from regulatory and HTA agencies regarding the evidence generated during development and post-authorisation (Chapter 6). Research reviewing EMA and HTA agencies' parallel scientific advice meeting minutes also demonstrated the need to discuss the choice of a surrogate endpoint; some HTA agencies requested a demonstration of a correlation of the surrogate endpoint with clinical outcomes and quality of life (Tafuri, Pagnini et al. 2016). The definition of unmet medical needs was also viewed as one of the important topics to be discussed during joint advice meetings, particularly regarding the selection of products for conditional or

accelerated regulatory routes of review (Chapter 6). Unmet medical needs are criteria for products applying for the EUnetHTA 21 JSC. However, the EMA conditional or PRIME pathway can reflect the unmet medical needs; but no quantifiable methodology was established to define unmet medical needs across all stakeholders (Vreman, Heikkinen et al. 2019). Future research could follow the products going through the JSC and assess if the advice led to convergences in the evidence generation and supported the harmonization of requirements in future.

Align process and work sharing where appropriate

Companies utilised the parallel regulatory/HTA review processes currently available in Australia and Canada, which showed an overlap between the regulatory and HTA process of 107 days in Australia and 30 days in Canada and shortened the time from regulatory submission to HTA recommendation (Chapter 3). Nevertheless, there are no formal interactions between agencies during the review process. The aligned process has evolved from just a process in parallel to a more coordinated approach. In Netherland, the parallel process with formal coordination between MEB and ZIN demonstrated a time saving of 3 months to receive the HTA recommendation (ZIN, 2022). The UK Innovative Licensing and Access Pathway aimed to bring companies, regulators and HTA agencies to accelerate the time for patient access through development to launch (MHRA, 2022). As the regulator and HTA are improving and aligning their processes within one country, we need to be mindful that no one system model will fit all. There are differences in organizational aspects, resources and capacity, legislative aspects, and working cultures. Regulator and HTA agencies should build allowed time to test ways to align and build trust over time. We foresee future improvement in aligning the regulatory and HTA process with formal and/or informal information exchange to ensure efficiency, advance reliance mechanism for regulators, and collaboration among HTA, such as work sharing or leveraging other agencies' work (Chapter 7). A policy implication for companies on more aligned regulatory and HTA process is early preparation by the local market access team: local submission strategy and actions such as pre-submission advice and generation of locally relevant data need to take place ahead of time to ensure the readiness for HTA submissions during regulatory review.

As regulatory agencies are implementing flexible mechanism in their processes, such as expedited regulatory pathways, conditional approvals and priority approvals, the question for companies is to find the right balance between timely access and optimal reimbursement. Although conditional reimbursement schemes existed in specific HTA systems, these were not believed to be aligned with conditional approvals; no association was found between the type of EMA approvals and HTA decisions within selected European Union countries (Desjardins and Conti 2015, Lipska, Hoekman et al. 2015). These results raised questions regarding the benefit of conditional approvals as an early access route to patients. Therefore, regulatory and HTA agencies must work more aligned for conditional approvals. For countries with no conditional pathway, a collaborative

approach may be worth considering when setting up a formal procedure for applying for flexible regulatory routes.

Iterative interactions through the lifecycle

Stakeholder interaction in the context of lifecycle HTA could occur between agencies, such as horizon scanning, joint early scientific advice, informal work-sharing, capacity building, joint assessment, and agencies and companies in early scientific advice pre-submission advice (Chapter 7). Nevertheless, these activities are resource-consuming (Ofori-Asenso, Hallgreen et al. 2020), and the results of our study raised the question of the capacity of companies and agencies. Therefore, stakeholders must understand the benefit of interactions for future engagement. Measures can be built to assess the value of interactions: time to access, correctness of decision, patient-centric measure of value and equity (Chapter 7). A future research recommendation is to develop performance metrics to measure value from the regulator, HTA and companies' perspectives on interactions. Apart from potential quantitative indicators, our study also identified qualitative value in interacting with other stakeholders, such as learning of new technology, validating internal thinking, building trust, and improving understanding of other agencies.

Timing is critical for the interactions. For example, HTA advice needs to be early enough to shape the development plan, but not too early to ensure sufficient evidence has been generated to support a meaningful dialogue (Vlachaki, Ovcinnikova et al. 2017). Therefore, future improvement should focus on clarifying the optimal timing to seek advice from regulators and HTA (Chapter 7). One of the current challenges companies face in the early advice is that the advice provided today may not reflect the future healthcare setting when launching the product (Chapter 5). Therefore, internal activities are critical to enabling good competitor intelligence and scenario planning, considering the evolving treatment and reimbursement landscape. We suggested that the interaction should not be a one-off activity but allow a more flexible and iterative process for advice, especially considering the life cycle approach to collect data for medicines' review and reimbursement. In addition, early advice's provision and compliance could be more transparent later in the decision-making. Long-term optimization of early HTA advice is needed. For example, HTA agencies should list frequently asked questions from advice meetings to share their perspectives on common topics, such as comparator choice. This may eventually lead to disease-specific guidelines that could describe for instance the most relevant clinical and patient reported outcomes for a certain indication.

Strengths and limitations

A key strength of our research approach is that it provides insights from both HTA agencies and the pharmaceutical industry. Qualitative data on stakeholders' perception and experiences, as well as quantitative metrics on medicines were collected, this evidence supported way to assess not only the strategy but also the practices of HTA by both stakeholders.

Our research has a number of limitations. Firstly, we excluded jurisdictions with maturing HTA systems due to their different capacity levels and focused on jurisdictions with mature HTA agencies, including Australia, Canada and selected European countries. Therefore, agencies in the research potentially leading to more positive perspectives regarding the performance, self-improvement willingness and awareness of and readiness for alignment. Similarly, the companies assessed in the research are international companies that are focusing on development of innovative medicine, therefore have more advanced thinking in HTA and more strategic practice. Finally, the focus of this thesis is on the single technology assessment for new medicines. It should be noted that HTA remit can cover wider aspects such as vaccine, medical devices, diagnosis, therefore wider scope could be applied to assess the HTA approach and practices in the future research.

Future research suggestions

By systematically benchmarking HTA organizations and process timelines, research could further assess existing and newly established agencies to identify gaps in the HTA organization, enhance review efficiency, and streamline process, thereby improving patients' access to medicines.

Building on the metrics to assess early HTA scientific advice, it should be investigated in future how the advice process will evolve such as the EU JSC, and to what extend the advice can facilitate the evidence generation. In addition, the impact of early advice on the quality of HTA submission, the HTA decision-making process, the HTA recommendations and finally the patient access.

More collaborative approach between regulatory and HTA, as well as HTA agencies can be explored in future. To support this policy discussion, research should be taken to assess the impact of reliance model of regulatory decisions on HTA, the timing and decision criteria of HTA agencies for products undergo flexible regulatory pathways.

Additional research is also needed to develop indicators to measure stakeholder interactions. The quantitative and qualitative measure will enable stakeholder to identify the benefit of interactions and promote the willingness for further collaboration across regulator, HTA and companies.

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ADDENDUM

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SUMMARY

SAMENVATTING

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LIST OF CO-AUTHORS

LIST OF PUBLICATIONS

ABOUT THE AUTHOR

SUMMARY

Introduction

Health Technology Assessment (HTA) has emerged as an important tool to support healthcare decision-makers to make rational reimbursement decisions, with the ultimate purpose of promoting an efficient healthcare system. HTA is defined as "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle".

The role of HTA agencies as advisors to reimbursement decision-makers is crucial for the application of public funding by the health care system. There is a common understanding that HTA should adhere to certain key principles, including: independence, transparency, inclusiveness, being based upon established science, timeliness, consistency, and operating within a legal framework. There is a societal and political expectation public expenditure decisions are justifiable and accountable. Thus, HTA agencies are continuously improving their processes, procedures, and methods for efficient and quality decision-making.

Differences between HTA agencies have been a subject of considerable research. Differences are rooted in the variation in the national healthcare systems, reflecting divergent healthcare resources, and different economic, political and social conditions. Hence, challenges arise for pharmaceutical companies who seek to achieve successful market access of their products within different markets, as HTA assesses the relative and cost-effectiveness of new medicines in comparison to existing technologies based on local context. Therefore, pharmaceutical companies need to address the expected HTA requirements during drug development in order to improve the HTA outcomes and to maximise patient access and commercial success.

Interactions between HTA agencies and companies through the form of early scientific advice have been increasingly used to support evidence generation during development, in order to improve market access. Interactions between regulators and HTA agencies to streamline the decision-making process, as well as collaboration amongst HTA agencies have also helped to accelerate the access for new medicines.

Thus, the objective of this thesis is to examine the processes and performance of HTA agencies; to evaluate the HTA practices of pharmaceutical companies; to better understand decision-making on reimbursement of pharmaceuticals during development and at launch; and to identify good practice across both stakeholders.

This thesis is organized following three parts: Part A focuses on the HTA practices of agencies, Part B assesses the HTA practice of companies, Part C explores the multi-stakeholder interactions regarding to HTA.

The evolution of the HTA agency

Divergences were observed among HTA agencies in their mandate, assessment, and appraisal process and how recommendations are made based on local context. A cross-

agency comparison enabled a better understanding of different settings of the HTA system and may support performance improvement within agencies. In Chapter 2, we established a systematic benchmarking framework to measure the evolution of HTA agencies. The framework evaluated the organization of HTA agencies in five domains: scope and remit, resources and budget, appraisal / scientific committee, transparency, and review procedures and process. Particularly for the review procedures and process domain, a set of clearly defined and agreed-upon common milestones and terminology were developed to account for the differences between agencies. Based on the common milestones we have shown in Chapter 2, when applying this methodology, it is feasible to compare HTA performance in terms of timeline for the overall process, as well as where time was spent at each stage between HTA submission and recommendation.

We found several organizational aspects contributing to the timelines: resources allocated for the HTA activities within the agency; the extent of stakeholder involvement in the process (including patients, clinicians and companies); public consultation of draft recommendations or the appeal procedure available in case of a negative HTA outcome; and frequency of the committee meetings. Given the findings, we emphasized that an in-depth understanding of the organization of HTA is needed to interpret timelines. In turn, the timeline comparison based on common milestones will facilitate agency internal performance improvement and process streamlining.

Over the past decade the role of HTA has also evolved from a standard activity after a medicine's market authorisation to a life cycle approach. A key area of HTA activities during development is providing early scientific advice to companies. Agencies recognized that early advice would be valuable to provide pharmaceutical companies with early insights on how new and innovative medicines might be viewed prior to their assessment. Agencies also recognised that early advice jointly with regulators would be of great value, especially for medicines that are expected to use the conditional marketing approval pathway (Chapter 6). In Chapter 7, we observed that the current early HTA advice is limited to European and Canadian agencies, indicating a gap for HTA agencies in other jurisdictions to be more involved in drug development. However, it is important to note that these agencies that current don't provide early advice indicated that stakeholder interaction is a high priority for them.

A new way of working has been discussed and considered regarding work sharing and collaboration to ensure efficiency and shared learnings among HTA agencies. The European Network for Health Technology Assessment (EUnetHTA) has provided the platform to test out multi-HTA collaboration, which led to the formal production of joint clinical assessment (JCA) to be fully implemented by 2029. In Chapter 7, it was reported that stakeholder interactions are high priority for HTA agencies. However, we observed more formal work sharing between regulators than the informal information exchange among HTA agencies. Consequently, there was an appetite for HTA agencies to learn from regulators' collaborative models, such as The Access Consortium, to expand the collaboration outside Europe.

The HTA practice in the industry

In this thesis we also reported the HTA practice from companies' perspectives. During the jurisdiction submission, companies generated local contextualized information before submission to meet the specific requirement of an HTA body (**Chapter 3**). Companies also sought pre-submission advice from agencies; the study in chapter 3 showed that Germany has the highest proportion of pre-submission advice among its total submissions (73%), followed by Australia (69%), France (35%) and Canada (23%). These results demonstrated that companies had been proactively addressing the needs of local HTA agencies. However, challenges remain. In **Chapter 5,** companies reported that in Australia, Canada and England, the most frequently raised issues on the evidence of a new medicine were that they were "not cost-effective", and where there was a "lack of longer-term outcomes." In Germany and France, where the HTA recommendation is mainly based on added therapeutic value, the outstanding issues centred around comparators, such as insufficient improvement over comparator treatments, comparator choice being unacceptable, the lack of validity of the endpoint, and lack of longer-term outcomes or follow-up. Therefore, companies need to explore the most efficient internal practices during drug development to ensure that the best data can be obtained to address jurisdictional HTA expectations.

A key strategy to seek HTA insight is early stakeholder engagement. In **Chapter 4,** we identified various company approaches to test their development plan, such as internal qualitative or quantitative payer research, consultation with the internal therapeutic head, external advice meetings with payer advisory boards and key opinion leaders (KOLs). We observed that companies used a mix of options to gain insight from agencies, with a preference for obtaining advice from a single national HTA agency (71%). The agencies most frequently sought-after where single agency advice was pursued were the German G-BA and NICE in the UK. This result sheds light on the business priority to gain access in the largest economic markets in Europe. There were different types of questions that companies wanted to address at each type of advice meeting (**Chapter 4),** suggesting companies have been carefully considering the topics to ensure the discussions were effective.

During the drug development, our study showed that companies had been actively incorporating HTA perspectives into the Target Product Profile (TPP), but the timing and process varied among companies, depending on the companies' experiences and strategy (**Chapter 5**). HTA perspectives were mainly built into three areas in the TPP: health problem and treatment pathway, clinical efficacy/effectiveness, and safety; There is much more potential for an integrated evidence generation tool to evolve from TPP to be used internally by companies during development and as an iterative stakeholder communication tool with regulators, HTA, payers and patient groups.

We also observed evolution in the company strategies in development. From organizational structure point of view, good levels of engagement of clinical, regulatory, HEOR, and pricing and reimbursement teams were reported during development in

Chapter 5. However, the cross-functional approach was not a guarantee for aligned internal decision-making; prioritization gave way to regulatory requirements compared to HTA needs. Internal structure and strategy need to be adjusted to tackle issues such as resource constraints, lack of appropriate infrastructure, lack of awareness of HTA requirements, and development plans driven by the US market (Chapter 6). From a policy point of view, companies are working on advocating good practice of HTA. Individual companies and industry associations have published their policy statements on key HTA principles, which covered aspects such as the structure of HTA program, methodology, process and utilization of HTA in decision making. These reflect the company mindset changes from reactive to proactive, with a critical emphasis on broad stakeholder engagement in the future HTA process.

Multi-stakeholder interactions

The difference in the remit, methodology and evidence requirements between regulators and HTA agencies, as well as variability across HTA agencies, introduces uncertainty into drug development decisions and can result in a potential mismatch of regulatory and HTA outcomes. We studied the interaction between regulatory and HTA bodies from two perspectives: potential alignment of evidentiary requirements, and more streamlined decision-making processes.

Results showed in Chapter 6 that two main areas in which regulatory and HTA divergences occurred related to products for which there was a high level of clinical uncertainty, for example, oncology products, orphan drugs, and products seeking for conditional and accelerated approval. Evidentiary divergences most frequently observed were the inclusion of an active comparator arm in the trial and the choice and use of surrogate endpoints. In our study, the companies implied that the precedent choice informed their decisions on the surrogate endpoint by HTA agencies; however, agencies indicated that the surrogate endpoint needs to be clinically and locally relevant and should be assessed as individual cases. Companies therefore call for regulatory and HTA agencies to work together to develop a joint list of acceptable and validated biomarkers and surrogate endpoints (Chapter 6). Joint scientific advice is a good platform to gain input from regulatory and HTA agencies regarding the evidence generated during development and post-authorisation. The definition of unmet medical needs was also viewed as one of the important topics to be discussed during joint advice meetings, particularly as only products that qualify as 'addressing unmet medical need' are eligible for conditional or accelerated approval and used in selection of regulatory routes of review (Chapter 6).

Active comparators included in the global development were generally well accepted by HTA agencies, with additional local relevant comparators being required during HTA review, mostly through indirect comparison (Chapter 3). Inevitably, the choice of the comparator will vary among healthcare systems. However, the comparator in global development should ensure that the potential indirect comparison required by HTA agencies can be performed. Regulators, HTA agencies and companies agreed that

the choice of comparators in global trials can be further aligned (**Chapter 6**); our study suggested a few building blocks: aligning on minimum thresholds for clinical trials, aligning where appropriate and acknowledge national differences, and developing common methodology and evidence standards where possible (**Chapter 7**).

To enable a more streamlined process, we observed that companies utilised the parallel regulatory/HTA review processes currently available in Australia and Canada, which showed an overlap between the regulatory and HTA process of 107 days in Australia and 30 days in Canada and shortened the time from regulatory submission to HTA recommendation (**Chapter 3**). The aligned process has evolved from parallel working to a more coordinated approach. Nevertheless, there are no formal interactions between agencies during the review process. Going forward, Regulatory and HTA agencies should allow time to test ways to improve alignment and build trust. We foresee future improvement in aligning the regulatory and HTA processes with formal and/or informal information exchange to ensure efficiency, advance reliance mechanism for regulators, and collaboration among HTA agencies, such as work sharing or leveraging other agencies' work (**Chapter 7**).

Conclusion

The research in this thesis has demonstrated a continuous evolution of HTA agencies throughout product lifecycles to support drug development, improve their methodology and processes, and engage in interaction with regulators and peer HTA agencies. By establishing a systematic framework to benchmark the organization and milestone performance of HTA agencies, we provided a baseline and tool to assess the evolvement of HTA. We also observed a mindset change within companies to embed HTA considerations during drug development, in order to improve the jurisdictional submission and proactively promote good HTA practice.

Future opportunities for research can be built on this thesis in the context of lifecycle HTA. For example, indicators can be established to measure the interactions between agencies through development to review and assessment of a new medicine. One may think of alignment of evidentiary requirements, joint early scientific advice, informal work-sharing, joint assessment. Measures can be built to track the interactions between agencies and companies, in regard to process and impact of early scientific advice, and post licensing evidence generation. Finally, the agency benchmarking framework can be utilised as a foundation for capacity building for emerging HTA agencies, track and improve performance metrics and ensure a good practice of HTA.

SAMENVATTING

Inleiding

Health Technology Assessment (HTA) is tegenwoordig een belangrijk instrument om beleidsmakers in de gezondheidszorg te ondersteunen bij het nemen van rationele beslissingen over vergoedingen - met een efficiënt gezondheidszorgstelsel als uiteindelijk doel. HTA wordt gedefinieerd als "een multidisciplinair proces waarbij expliciete methoden worden gebruikt om de waarde van een gezondheidstechnologie op verschillende momenten in de levenscyclus te bepalen."

De rol van HTA-organisaties als adviseurs voor besluitvormers op het gebied van vergoedingen is van cruciaal belang voor de overheidsfinanciering van geneesmiddelen vanuit het zorgstelsel. Iedereen is het erover eens dat HTA moet voldoen aan bepaalde kernprincipes, waaronder onafhankelijkheid, transparantie, inclusiviteit, gebaseerd zijn op gevestigde wetenschap, tijdigheid, consistentie en dat HTA dient te opereren binnen een wettelijk kader. Zowel de maatschappij als de politiek verwachten dat beslissingen over overheidsuitgaven gerechtvaardigd en verantwoord zijn. Daarom zijn HTA-organisaties voortdurend bezig om hun processen, procedures en methoden ten behoeve van efficiënte en kwalitatieve besluitvorming te verbeteren.

Er is uitgebreid onderzoek gedaan naar de verschillen tussen HTA-organisaties. De verschillen komen voort uit de verschillen in nationale gezondheidszorgstelsels en zijn een afspiegeling van de uiteenlopende beschikbare middelen voor gezondheidszorg en de economische, politieke en sociale omstandigheden waarin zij opereren. Daarmee ontstaan er uitdagingen voor farmaceutische bedrijven die hun producten in verschillende landen op de markt willen brengen, aangezien HTA de relatieve effectiviteit en kostenefficiëntie van nieuwe geneesmiddelen beoordeelt in vergelijking met bestaande technologieën in de lokale context. Farmaceutische bedrijven dienen al tijdens de ontwikkeling van geneesmiddelen rekening houden met de verwachte HTA-vereisten om zo een grotere kans te hebben tot een positieve beoordeling, en daarbij de toegang voor patiënten en commercieel succes te garanderen.

Er wordt tijdens de ontwikkeling van geneesmiddelen steeds vaker gebruikgemaakt van interacties tussen HTA-organisaties en bedrijven in de vorm van wetenschappelijk advies ter ondersteuning van het genereren van bewijsmateriaal om de toegang tot de markt te verbeteren. Ook interacties tussen geneesmiddelenautoriteiten en HTA- organisaties ten behoeve van stroomlijning van het besluitvormingsproces en samenwerking tussen HTA- organisaties onderling hebben bijgedragen aan een snellere en beter onderbouwde toegang tot nieuwe medicijnen.

Het doel van dit promotieonderzoek was om de processen en prestaties van HTA-organisaties te onderzoeken; om de HTA-praktijken van farmaceutische bedrijven te evalueren; om de besluitvorming over de vergoeding van geneesmiddelen tijdens de ontwikkeling en bij de lancering beter te begrijpen; en om *good practices* bij en tussen beide belanghebbende partijen te identificeren.

Dit proefschrift is opgebouwd uit drie delen: Deel A richt zich op de praktijken van HTA-organisaties; deel B beoordeelt de HTA-praktijken van bedrijven; en deel C onderzoekt de interacties tussen meerdere belanghebbenden met betrekking tot HTA.

De ontwikkeling van HTA- organisaties

HTA- organisaties bleken aantoonbaar te verschillen in hun mandaat, toetsing en beoordelingsproces en de manier waarop ze aanbevelingen deden op basis van de lokale context. Een vergelijking tussen organisaties onderling zorgde voor een beter begrip van de situationele verschillen binnen het HTA-systeem. In **hoofdstuk 2** hebben we een systematisch benchmarkkader ontworpen om de ontwikkeling van HTA- organisaties te meten. Het raamwerk evalueerde de inrichting van HTA- organisaties op vijf domeinen: reikwijdte en opdracht, middelen en budget, beoordelings-/wetenschappelijke commissie, transparantie en toetsingsprocedures en -proces. Met name voor de toetsingsprocedures en het procesdomein zijn duidelijk omschreven en samen overeengekomen algemene mijlpalen en terminologie ontwikkeld om recht te doen aan de verschillen tussen de HTA-organisaties. Op basis van de algemene mijlpalen die we in **hoofdstuk 2** hebben laten zien, is het bij het toepassen van deze methodologie haalbaar om HTA-prestaties te vergelijken qua tijd die nodig was voor het algehele proces en voor elke fase tussen de indiening voor HTA en de aanbeveling.

We ontdekten dat verschillende organisatorische aspecten bijdroegen aan de benodigde beoordelingstijd: toegewezen middelen voor de HTA-activiteiten binnen het bureau; de mate van betrokkenheid van belanghebbenden bij het proces (zoals patiënten, clinici en bedrijven); openbare raadpleging van ontwerpaanbevelingen of de mogelijke beroepsprocedure in geval van een negatief HTA-advies; en de frequentie van de commissievergaderingen. Gezien de bevindingen benadrukten we de noodzaak van een diepgaand inzicht in de HTA organisaties om de tijdlijnen te kunnen interpreteren. Die tijdlijnvergelijking op basis van de algemene mijlpalen zou dan kunnen bijdragen aan de interne prestatieverbetering van de HTA-organisaties en het stroomlijnen van hun processen.

In de afgelopen tien jaar is ook de rol van HTA geëvolueerd van een standaardactiviteit na de markttoelating van een geneesmiddel tot een levenscyclusbenadering. Een belangrijk onderdeel van de HTA-activiteiten tijdens de ontwikkeling van een geneesmiddel is het verstrekken van vroegtijdig wetenschappelijk advies aan bedrijven. De HTA-organisaties erkenden dat vroegtijdig advies waardevol zou zijn om farmaceutische bedrijven al vóór de toetsing te laten weten hoe nieuwe en innovatieve geneesmiddelen mogelijk zouden kunnen worden bekeken. De organisaties erkenden ook dat dergelijk advies in samenwerking met geneesmiddelenautoriteiten van grote waarde zou zijn, vooral voor geneesmiddelen die naar verwachting het traject van voorwaardelijke goedkeuring ingaan (**hoofdstuk 6**). In **hoofdstuk 7** zagen we dat het vroegtijdige HTA-advies thans beperkt bleef tot Europese en Canadese organisaties, het lijkt ons raadzaam dat HTA- organisaties

in andere jurisdicties ook meer betrokken zouden kunnen zijn bij de ontwikkeling van geneesmiddelen. Het is echter wel het vermelden waard dat de HTA-organisaties die momenteel geen vroegtijdig advies geven, aangaven dat interactie met belanghebbenden hoog op hun prioriteitenlijst staat.

Er is een nieuwe manier van werken besproken en overwogen op het gebied van werkverdeling en samenwerking tussen HTA- organisaties ten behoeve van efficiëntie en gezamenlijk leren. Het *European Network for Health Technology Assessmen*t (EUnetHTA) zorgde voor een platform om samenwerking tussen meerdere HTA- organisaties te testen, wat heeft geleid tot een gezamenlijke klinische toetsingsprocedure die tegen 2030 volledig moet zijn geïmplementeerd. In **hoofdstuk 7** werd gemeld dat interactie met belanghebbenden een hoge prioriteit heeft voor HTA- organisaties. We zagen echter dat er veel meer sprake was van een meer formele werkverdeling tussen geneesmiddelenautoriteiten dan de informele informatie-uitwisseling die werd gezien tussen HTA- organisaties. De HTA- organisaties wilden dan ook graag leren van de samenwerkingsmodellen van de geneesmiddelenautoriteiten, zoals in het 'Access Consortium', om hun samenwerking buiten Europa uit te breiden.

De HTA-praktijk in de industrie

In dit proefschrift hebben wij ook verslag uitgebracht over de HTA-praktijk vanuit het perspectief van farmaceutische bedrijven. Bij het indienen van een dossier bij een enkele HTA-organisatie genereerden bedrijven reeds vóór de indiening lokale gecontextualiseerde informatie om te kunnen voldoen aan de specifieke vereisten van de betreffende HTA-organisatie (**hoofdstuk 3**). Bedrijven wonnen ook vooraf advies in bij organisaties; uit de studie in **hoofdstuk 3** bleek dat men in Duitsland percentueel het vaakst vooraf advies inwon (73%), gevolgd door Australië (69%), Frankrijk (35%) en Canada (23%). Deze resultaten toonden aan dat bedrijven proactief hadden ingespeeld op de behoeften van lokale HTA- organisaties. Er blijven echter uitdagingen. In **hoofdstuk 5** meldden bedrijven dat in Australië, Canada en Engeland de meest gehoorde bezwaren tegen het bewijs van een nieuw geneesmiddel waren dat het "niet kosteneffectief" was, en dat er een "gebrek aan resultaten op langere termijn" was. In Duitsland en Frankrijk, waar de HTA-aanbeveling voornamelijk gebaseerd wordt op toegevoegde therapeutische waarde, hadden de lopende kwesties betrekking op voorgestelde referentiemiddelen (*comparators)*, zoals onvoldoende verbetering ten opzichte van bestaande behandelingen, een onaanvaardbare keuze van referentiemiddelen, het gebrek aan validiteit van het eindpunt en het ontbreken van langere termijn resultaten. Daarom moeten bedrijven tijdens de ontwikkeling van geneesmiddelen nagaan hoe ze het efficiëntst de beste data kunnen verzamelen om aan de verwachtingen van de bevoegde HTA-organisaties te kunnen voldoen.

Een belangrijke strategie om inzicht in HTA te verkrijgen, is vroegtijdige betrokkenheid van belanghebbenden. In **hoofdstuk 4** hebben we voor bedrijven verschillende benaderingen vastgesteld om ontwikkelingsplannen te testen, zoals intern kwalitatief

of kwantitatief onderzoek naar vergoedingsinstantiesbetalers, overleg met eigen adviseurs over markttoegang en externe adviesbijeenkomsten met adviesraden met vertegenwoordigers van vergoedingsinstanties en belangrijke opinieleiders. We stelden vast dat de bedrijven een combinatie van opties gebruikten om kennis te vergaren met een voorkeur voor advies van één nationale HTA-organisatie (71%). Waar dit het geval was, waren de Duitse G-BA en NICE in het Verenigd Koninkrijk de organisaties die het vaakst om advies werden gevraagd. Dit resultaat werpt licht op de prioriteit om toegang te krijgen tot de grootste economische markten in Europa. Er waren verschillende soorten vragen die bedrijven tijdens elk type adviesgesprek wilden behandelen (**hoofdstuk 4**), hetgeen erop wijst dat ze de onderwerpen zorgvuldig hadden gekozen om ervoor te zorgen dat de gesprekken effectief waren.

Uit ons onderzoek bleek dat bedrijven tijdens de ontwikkeling van een geneesmiddel actief rekening hielden met HTA in het zogenaamde Target Product Profile (TPP) - maar dat de timing en het proces varieerden van bedrijf tot bedrijf, afhankelijk van de ervaringen en bedrijfsstrategie (**hoofdstuk 5**). In het TPP was het vooruitlopen op HTA vooral terug te vinden bij de indicatie en behandeltraject, klinische effectiviteit, en veiligheid. Dat laat nog volop ruimte voor een geïntegreerd instrument voor het genereren van bewijsmateriaal dat uit het TPP kan voortkomen en dat intern door bedrijven kan worden gebruikt tijdens de ontwikkeling - en als een iteratief instrument voor communicatie van belanghebbenden met geneesmiddelagentschappen, HTA-organisaties, vergoedingsinstanties en patiëntenverenigingen.

Wij hebben ook trends gezien in de bedrijfsstrategieën die nog worden ontwikkeld. Vanuit het oogpunt van de organisatiestructuur werd in **hoofdstuk 5** gemeld dat de betrokkenheid van de klinische, besluitvormende, HEOR-, prijsstellings- en terugbetalingsteams tijdens de ontwikkeling goed was. De functieoverschrijdende aanpak was echter geen garantie voor een afgestemde interne besluitvorming; door prioritering kwam de nadruk op de eisen van de geneesmiddelenautoriteiten te liggen in plaats van op HTA-vereisten. De interne structuur en strategie moeten worden aangepast om problemen als een gebrek aan middelen, het ontbreken van een passende infrastructuur, onvoldoende bekendheid met de HTA-vereisten en door de Amerikaanse markt gestuurde ontwikkelingsplannen aan te pakken (**hoofdstuk 6**). Vanuit beleidsoogpunt pleiten bedrijven voor goede HTA-praktijken. Sommige bedrijven en brancheverenigingen hebben hun beleidsverklaringen over de belangrijkste HTA-beginselen gepubliceerd. Deze hebben betrekking op bijv. de structuur van het HTA-programma, de methodologie, het proces en het gebruik van HTA bij de besluitvorming. Ze weerspiegelen de veranderingen in bedrijfsmentaliteit van reactief naar proactief, met een kritische nadruk op een brede betrokkenheid van belanghebbenden in het toekomstige HTA-proces.

Interacties tussen meerdere belanghebbenden

Het verschil in bevoegdheid, methodiek en bewijsvereisten tussen geneesmiddelenagentschappen en HTA- organisaties zorgt voor onzekerheid in

de besluitvorming tijdens de ontwikkeling van een geneesmiddel, waardoor de uitkomst van autorisatie en HTA beoordeling niet altijd met elkaar overeenstemmen. Wij hebben de interactie tussen geneesmiddelenagentschappen en HTA-organisaties vanuit twee invalshoeken bestudeerd: de potentiële afstemming van bewijsvereisten en meer gestroomlijnde besluitvormingsprocessen.

Uit de resultaten in **hoofdstuk 6** bleek dat de twee belangrijkste gebieden waarin verschillen optraden, betrekking hadden op producten met een hoge mate van klinische onzekerheid, bijvoorbeeld oncologische producten, weesgeneesmiddelen en producten die voorwaardelijk dan wel versneld worden goedgekeurd. De verschillen qua bewijs die het vaakst werden waargenomen, waren de inclusie van vergelijkende behandeling (en geen placebo) in de trial en de keuze en het gebruik van surrogate eindpunten. In ons onderzoek impliceerden de bedrijven dat de keuze van precedent mede de beslissingen van HTA-bureaus over het surrogaateindpunt bepaalde; de geneesmiddelenagentschappen gaven echter aan dat het surrogaateindpunt klinisch en lokaal relevant moest zijn en per geval moest worden beoordeeld. Bedrijven roepen daarom op om geneesmiddelenautoriteiten en HTA- organisaties samen te laten werken aan een gezamenlijke lijst van aanvaardbare en gevalideerde biomarkers en surrogaateindpunten (**hoofdstuk 6**). Gezamenlijk wetenschappelijk advies is een goed uitgangspunt om van geneesmiddelenautoriteiten en HTA- organisaties input te krijgen over het bewijs dat dient te worden gegenereerd tijdens de ontwikkeling en na autorisatie. De gehanteerde definitie van de zogenaamde 'unmet medical need' werd ook gezien als een van de belangrijke onderwerpen die tijdens gezamenlijke adviesbijeenkomsten moesten worden besproken, met name omdat alleen producten die aan die omschrijving voldoen, in aanmerking komen voor voorwaardelijke of versnelde goedkeuring en het autorisatietraject bepalen (**hoofdstuk 6**).

Vergelijkende behandelingen die in wereldwijde ontwikkelingsprocessen werden gebruikt, werden over het algemeen goed ontvangen door HTA- organisaties, naast de aanvullende, lokaal relevante vergelijkende behandelingen waarvan tijdens de toetsing sprake moest zijn, meestal door indirecte vergelijking (**hoofdstuk 3**). Het is mogelijk dat de keuze van vergelijkende behandeling per zorgstelsel kan verschillen. Maar in wereldwijde ontwikkelingsprocessen moet de vergelijkende behandeling ervoor zorgen dat de mogelijk indirecte vergelijking die HTA- organisaties elders kunnen verlangen, kan worden uitgevoerd. Geneesmiddelenautoriteiten, HTA- organisaties en bedrijven waren het erover eens dat de keuze van vergelijkende behandelingen in wereldwijde trials verder kan worden afgestemd (**hoofdstuk 6**); vanuit ons onderzoek deden we enkele suggesties: aanpassing aan drempelwaarden voor klinische trials, afstemming waar nodig, erkenning van nationale verschillen en, waar mogelijk, het ontwikkelen van gemeenschappelijke methoden en bewijsstandaarden (**hoofdstuk 7**).

Om een meer gestroomlijnd proces mogelijk te maken, zo zagen wij, maakten bedrijven gebruik van de parallel lopende autorisatie/HTA-toetsingsprocessen die momenteel beschikbaar zijn in Australië en Canada. Deze overlapten elkaar 107 dagen in Australië

en 30 dagen in Canada en verkortten de tijd tussen indiening voor autorisatie en de HTA-aanbeveling (**hoofdstuk 3**). Het afgestemde proces is geëvolueerd van parallel werken naar een meer gecoördineerde aanpak. Desalniettemin zijn er geen formele interacties tussen de organisaties tijdens het toetsingsproces. In de toekomst moeten de geneesmiddelenautoriteiten en HTA- organisaties de tijd nemen om de afstemming te verbeteren en vertrouwen op te bouwen. Wij voorzien verbeteringen in het afstemmen van de autorisatie- en HTA-processen op formele en/of informele informatie-uitwisseling om efficiëntie te waarborgen, een beter werkend mechanisme van afhankelijkheid voor geneesmiddelenautoriteiten, en samenwerking tussen HTA- organisaties, zoals het delen van werkzaamheden of het benutten van het werk van andere organisaties (**hoofdstuk 7**).

Conclusie

Het onderzoek in dit proefschrift heeft aangetoond dat HTA- organisaties gedurende de hele levenscyclus van geneesmiddelen voortdurend evolueren om de ontwikkeling van te ondersteunen, hun methodieken en processen te verbeteren en interacties aan te gaan met geneesmiddelenagentschappen en collega- organisaties. Door een systematisch raamwerk op te zetten om de organisatie en mijlpaalprestaties van HTA- organisaties te benchmarken, hebben we een basis en een hulpmiddel geboden om de ontwikkeling van HTA te beoordelen. We zagen ook een mentaliteitsverandering binnen bedrijven die HTA-overwegingen inbouwen in de ontwikkeling van geneesmiddelen, om zo de wettelijke vereiste aanvraag te verbeteren en proactief goede HTA-praktijken te ontwikkelen.

Dit proefschrift kan als basis dienen voor toekomstig onderzoek naar HTA op basis van levenscyclus. Er kunnen bijvoorbeeld indicatoren worden vastgesteld om de interacties tussen organisaties te meten tijdens de ontwikkeling tot aan de toetsing van een nieuw geneesmiddel. Te denken valt aan de afstemming van bewijsvereisten, gezamenlijk vroegtijdig wetenschappelijk advies, informele werkverdeling en gezamenlijke toetsing. Er kunnen meetinstrumenten worden ontwikkeld voor het monitoren van de interacties tussen bureaus en bedrijven voor wat betreft het proces en de impact van vroegtijdig wetenschappelijk advies en het genereren van bewijs na vergunningverlening. Ten slotte kan het raamwerk voor het benchmarken van HTA- organisaties worden gebruikt als basis voor de opbouw van de capaciteit van opkomende HTA- organisaties, voor het opsporen en verbeteren van prestatiecijfers en voor het waarborgen van goede HTA-praktijken.

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LIST OF CO-AUTHORS

Affiliation during the conduct of research

Marie L De Bruin

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Helga Gardarsdottir

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Wim G Goettsch

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; National Health Care Institute, Diemen, the Netherlands; Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Anke Hövels

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Hubert GM Leufkens

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Lawrence Liberti

Centre for Innovation in Regulatory Science, London, UK

Iga Lipska

Centre for Innovation in Regulatory Science, London, UK and Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Neil McAuslane

Centre for Innovation in Regulatory Science, London, UK

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ABOUT THE AUTHOR

Ting (Tina) Wang is Senior Manager - HTA Programme and Strategic Partnership at the Centre for Innovation in Regulatory Science (CIRS). Tina leads CIRS' work on HTA strategy and research as part of the CIRS mission to advance regulatory and HTA policies and processes. Tina's scope of responsibilities covers all aspects of HTA activities from concept through to delivery. These include project managing the CIRS HTA Programme and coordinating a HTA steering committee, executing and implementation of metrics studies evaluating the HTA processes within companies and agencies on annual basis, conducting independent literature research and designing specialised surveys, and construction of and maintenance of the Regulatory and Reimbursement Atlas Platform. Tina is also responsible for developing the CIRS HTA Programme research strategy, ensuring alignment between the overarching CIRS regulatory and HTA vision, and leading the strategic partnership with multi-stakeholders globally. Prior to joining CIRS in 2010, Tina worked as a research scientist at Medpharm and GlaxoSmithKline.

Tina received her undergraduate degree in Applied Chemistry from the Beijing University of Technology and a Master of Science in Pharmaceutical Analysis and Quality Control from Kings College, University of London.

Tina is a member of longstanding international scientific societies such as Health Technology Assessment international (HTAi), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and is a frequent speaker at various international conferences. Tina's main field of interest is international HTA policy and intelligence.