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Access in all areas? A round up of developments in market access and health technology assessment: part 1

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In this new series reviewing recent developments in market access, we highlight publications investigating health technology assessment (HTA) guidance, review processes and outcomes across the world and discuss how forthcoming changes in the HTA and regulatory environment in the European Union may allow for more consistency in decision making.

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It is known that there are differences in health technology assessment (HTA) outcomes across the world, leading to differential patient access to medicines. A recent study by Jenei and colleagues sought to look at this in more detail for oncology treatments by investigating HTA criteria and decisions made across Australia, Canada, England, France, Germany, Italy, Japan and New Zealand [1]. The selection of countries was guided by factors such as health spending per gross domestic product (GDP), the existence of publicly funded healthcare systems and national HTA bodies that inform public coverage decisions. Jenei *et al.* found that HTA agencies in many countries use largely overlapping assessment criteria with clinical benefit being the main component; however, there were variations between countries, including the consideration of evidence quality, equity and defining specific cost–effectiveness thresholds. Despite similarities in assessment criteria there was discordance in reimbursement outcomes for the same cancer medicines. This suggested that assessment criteria are either weighted differently by different HTA bodies and/or other factors that are not explicitly stated play a role. The authors suggest that the differences in reimbursement outcomes for the same drugs across countries with overlapping criteria indicate a need for improved transparency around how HTA agencies make their decisions. While this study echoes the findings of previous studies [2], it nevertheless highlights to countries that may be developing or evolving their HTA processes the importance of being clear to stakeholders as to how decisions are made. Transparency is important for many stakeholders, including manufacturers, as learnings can be made from past submissions, and future submissions can include the most appropriate evidence base for HTA agencies to enable patient access to medicines.

In 2018, the ISPOR Special Task Force concluded that while conventional cost–effectiveness analyses based on quality adjusted life years (QALYs) serve as a valuable foundation for value assessments, decisions based solely on these analyses, without considering other factors may be potentially undervaluing health interventions [4]. The ISPOR value flower was developed as a convenient visual representation to highlight an array of elements of value that may be overlooked or neglected in traditional cost–effectiveness analysis. To see how these additional elements of value are being assessed by HTA agencies, Breslau *et al.* reviewed 53 HTA guidelines representing 52 countries and collected data on whether each guideline mentioned societal or novel elements of value [3]. Societal elements were defined as benefits occurring outside the healthcare system such as time lost by patients in receiving care and also time given by informal caregivers, transportation costs and increases in future productivity and consumption.

The term 'novel elements' stems from the ISPOR Strategic Task Force [4], and includes labor productivity, adherence improving factors, reduction of uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity and scientific spillovers. In total there were ten societal value elements and 11 novel value elements investigated, and Breslau and colleagues found that HTA guidelines mention on average 5.9 of the 21 value elements identified, including 2.3 of the ten societal elements and 3.3 of the 11 novel value elements. Only four value elements (productivity, family spillover, equity and transportation) appeared in over half of HTA guidelines. The authors' conclusion brings attention to the fact that most HTA guidelines do not provide explicit recommendations for incorporating societal or novel value elements. Additionally, among the guidelines that do address these elements, there is a lack of consistency in terms of including them in the base case, sensitivity analysis, or qualitative discussion. It is crucial to note that merely recommending the consideration of novel elements in guidelines may not guarantee their actual inclusion in assessments or decision-making processes. The paper emphasizes the importance of incorporating novel value elements into HTA guidelines, despite the technical complexities and uncertainties involved as doing so allows for a comprehensive assessment of new technologies. The paper also recommends manufacturers take proactive steps in developing robust evidence on societal and novel value elements, enabling HTA agencies to evaluate these factors and by providing transparency in their assessment process allowing stakeholders to learn from their assessments.

In addition to varying HTA outcomes across different countries, the time to availability of new medicines is also highly disparate across countries. A study by Post *et al.* assessed the time between marketing authorization for oncology medications given by the European Commission and reimbursement given by national HTA agencies of Germany, France, UK, The Netherlands, Belgium, Norway and Switzerland [5]. A total of 25 medicines with EMA authorization given between 2016 and 2021 were assessed. Time between EMA authorization and reimbursement ranged from -81 days to 2320 days (median 407 days). Time to reimbursement varied significantly between countries. Factors associated with shorter time to reimbursement were higher GDP (thought to be related to higher GDP countries having HTA agencies with more capacity), absence of a pre-assessment procedure (as seen in Germany where product launch is possible immediately following EMA approval), and submission by a big pharmaceutical company (defined as being one of the 12 largest pharmaceutical manufacturers, and postulated to be because larger companies are more resourced and have more experience with HTA submissions in multiple countries). As before, the work of Post and colleagues confirms previous analyses [6], with the ultimate conclusion that time to reimbursement is variable between countries and long in many, leading to inequity in patient access to medicines.

A potential solution to this problem may come from the harmonization of clinical assessment in the European Union (EU), which may be especially helpful as smaller countries can leverage shared resources and knowledge to overcome their capacity limitations. Indeed, the EU HTA regulation aims to establish a collaborative framework for the coordinated assessment of health technologies, promoting transparency, efficiency, reducing duplication of work and the exchange of information among member states (MSs) aiming to improve patient access across the EU. This is expected to take effect in 2025, with an initial focus on oncology and advanced therapy medicinal products (ATMPs) and further expansion to orphan drugs (2028) and other products (2030). The aim of this collaborative framework is to establish joint clinical assessments (JCAs) conducted by assessors and co-assessors from MS, under the supervision of a Coordination Group. Other MS should give appropriate consideration to these JCA reports, although they may choose to conduct additional complementary analyses at their discretion. It is important to note that economic and other value assessments and overall conclusion of benefit will still be carried out at the MS level, hence pricing and reimbursement decisions remain local. Although the JCA strives to create more predictable processes through harmonization, there are concerns [7] that the current plans for implementation avoid seeking alignment on common European methodologies and data requirements. Stakeholders noted that it appears to be a mere amalgamation of national practices, and therefore, it may not alleviate the current administrative burden resulting from numerous and differing processes and data requests from MSs.

Another anticipated change in the EU pharmaceutical environment is the proposed changes to the EU general pharmaceutical legislation, one of which includes shortening the period of regulatory protection from 8 to 6 years [8], along with 2 years of market protection. However, there could be (conditional) extensions for various reasons, including an additional 2 years for launching new drugs in all EU MSs within 2 years of marketing authorization. Although theoretically, this could help shorten the time from marketing authorization approval to reimbursement and close the health equity gap, unless things change from the current state of play as described by Post and colleagues, it may be extremely challenging for manufacturers to negotiate reimbursement across the EU within the timeframe

proposed by the European Commission. Post *et al.* did not include the time to reimbursement for countries with a medium-to-low GDP as compared with the average in the EU, and available data for these MSs suggest that they would highly struggle to absorb all new technologies within 2 years post marketing authorization. An additional point to consider is that currently, these proposed changes to legislation put the onus on pharmaceutical companies; however, this requires close collaboration and coordination among the MSs as well and unless the MSs are also incentivized to make medicines available within 2 years of marketing authorization, this is going to be extremely challenging for pharmaceutical companies to achieve. Changes in regulatory and HTA frameworks in the EU are currently a highly evolving area and further updates will be shared when announced in future parts of this series.

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