VALUE IN HEALTH 20 (2017) 67–76

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jval

Variation in Health Technology Assessment and Reimbursement Processes in Europe

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ABSTRACT

Background: It has been suggested that differences in health technology assessment (HTA) processes among countries, particularly within Europe, have led to inequity in patient access to new medicines. **Objectives:** To provide an up-to-date snapshot analysis of the present status of HTA and reimbursement systems in select European countries, and to investigate the implications of these processes, especially with regard to delays in market and patient access. **Methods:** HTA and reimbursement processes were assessed through a review of published and gray literature, and through a series of interviews with HTA experts. To quantify the impact of differences among countries, we conducted case studies of 12 products introduced since 2009, including 10 cancer drugs. **Results:** In addition to the differences in HTA and reimbursement processes among countries, the influence of particular sources of information differs among HTA bodies. The variation in the time from the authorization by the European Medicines Agency to the publication of HTA decisions was considerable, both within and among countries, with a general lack of transparency as to why some assessments take longer than others. In most countries, market access for oncology products can occur outside the HTA process, with sales often preceding HTA decisions. **Conclusions:** It is challenging even for those with considerable personal experience in European HTA processes to establish what is really happening in market access for new drugs. We recommend that efforts should be directed toward improving transparency in HTA, which should, in turn, lead to more effective processes.

Keywords: cancer, decision making, Europe, pharmaceuticals.

Introduction

In many countries, the efficacy, safety, and value of medical innovations are assessed through a formal health technology assessment (HTA) system. The goals of an HTA are to examine the consequences of the adoption of a particular technology and ensure that these represent good value for money. It has, however, been suggested that differences in HTA processes among countries, particularly within Europe, have led to inequity in patient access to new medicines.

Ensuring access to effective new medicines is challenging, with the introduction of expensive, innovative, and targeted agents having a substantial impact on health care costs, particularly in areas such as orphan diseases and oncology. Issues surrounding access to innovative medicines are exemplified by the large number of cancer treatments that have recently received European marketing authorization, but which are not always reimbursed in all European countries [1]. Europe has approximately one-quarter of global cancer cases, despite representing only one-eighth of the world population [2]. There is wide variation among European countries in the incidence of particular cancers and in cancer treatment and survival [3,4]. Some of the variation in cancer statistics is a reflection of differences in social and epidemiological factors. It has, however, been speculated that some of the variation in cancer outcomes may be due to the differences in health care systems and access to new interventions [5,6].

In 2005, a study of cancer drug access in Europe, focusing on the role of HTA, noted that some of the considerable variation in availability and uptake of new drugs was explained by differences in reimbursement processes [7]. For example, in Germany, cancer drugs were immediately available once marketing authorization was granted, whereas in Denmark and Austria drugs were typically available within 2 to 3 months of marketing authorization. In contrast, in France, Italy, and Spain, where the HTA process is a prerequisite for market access, there was a delay of 1 year on average because of the time required for formal reimbursement decisions [7]. This study is now a decade old—the purpose of the work reported here was to investigate whether its conclusions remain valid.

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2016.08.725

HTA and reimbursement processes were assessed through a review of published and gray literature, and through a series of interviews with HTA experts in eight European countries, representing a number of different health care systems and processes. To quantify the impact of differences among countries resulting from variations in processes, we studied the experience of 12 products introduced since 2009, including 10 cancer drugs approved by the European Medicines Agency (EMA) in 2010 to 2012.

Methods

Literature Review—Electronic and Gray Literature

Searches were carried out in April and May 2014 (for the full search strategy and search terms, see Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.08.725). When information in included references was presented only in graphical form (e.g., in the study by Benoff et al. [8]), data were digitally extracted using the GetData Graph Digitizer software (GetData Software, Hurstvile, Australia).

Expert Interviews

Semistructured, anonymized interviews were conducted with experts from eight European countries: France, Germany, Italy, Poland, Spain, Sweden, the Netherlands, and the United Kingdom (UK interviewees had specific experience of the National Institute for Health and Care Excellence [NICE]). Experts were recruited from an internal contact list from BresMed Health Solutions Ltd. (Sheffield, UK). Interview recruitment was double-blinded: the experts were not aware of the identity of the sponsor, and the sponsor was not aware of which experts were interviewed. Contact was made through gatekeepers and snowball sampling. For each country one clinical expert and one economic expert with knowledge of the local HTA and reimbursement systems were recruited. Additional interviews were conducted in Spain and Italy to capture the regional nature of the HTA and reimbursement processes in these countries. Efforts were made to engage with individuals who could provide insight into the country-specific reimbursement as well as HTA processes because of their previous or present involvement in those processes. A screening survey was developed to assess the participants' relevance. It comprised questions relating to their country's HTA and reimbursement processes and their experience with the 10 oncology products, including the extent to which they had been involved in the decision making.

Interviews were conducted between October 2014 and May 2015. In total, 18 interviews were conducted—8 with clinical experts and 10 with experts in health economics. Two interviews were carried out for each country, with an additional interview with a second health economics expert conducted in Italy and Spain to capture the regional nature of the HTA and reimbursement processes in these countries.

Interviewees were briefed about the objectives of the research and all gave their informed written consent to participate and for the interviews to be recorded. Participants were given flow diagrams of their country's HTA and reimbursement processes on the basis of the results of the literature review, and they were asked to provide their opinion on whether the information was a true representation of actual practice.

Interviewees were asked about sources of information and decision-making criteria used for HTA in their countries. Participants were asked to apply values to a series of decision criteria using a structured survey, with 5 points assigned to the most important decision criterion or criteria and 0 to the least important.

Qualitative analysis was carried out through coding the transcripts using the NVivo 10 software program (QSR International, Daresbury, United Kingdom) to identify any trends, differences, and similarities specific to the HTA and reimbursement processes, decision making, challenges, and promoting market access across the study countries. While presenting the results, anonymity of the participants was protected by removing names and creating broad interview categories (e.g., clinical expert and economic expert).

Product Case Studies

In total, 10 oncology products authorized by the EMA between 2010 and 2012 were selected for investigation. The selected products, presented in Table 1, were considered by the authors to be innovative drugs and/or novel entities—8 of the 10 were given ratings of I to IV of the Amélioration du Service Médical Rendu (ASMR) [The improvement in actual benefit (IAB)] by the Haute Autorité de Santé (HAS [French National Authority for Health]). For comparison, two nononcology products were also selected for investigation: Gilenya® (fingolimod; for multiple sclerosis) and Onbrez Breezhaler® (indacaterol; for chronic obstructive pulmonary disease).

The relevant HTA and reimbursement Web sites for each country were used to identify decision information and dates for specific products. Potential delays in market access were assessed as the difference between the date of EMA regulatory approval for each product and the date of country-specific HTA or reimbursement approvals as documented on the relevant agency Web sites. In Germany, market access is granted at the time of EMA authorization. Therefore, for this analysis the time from EMA approval to the publication of a recommendation by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) decision support unit was assessed. To investigate whether patient access was delayed by HTA and reimbursement processes, we assumed that product sales are a reasonable proxy for patient access. Quarterly product sales data for each country were obtained from IMS Health. For the United Kingdom, the IMS data included information for the whole country; nevertheless, only the

Table 1 – Products selected for analysis.

Disease area	Product brand name (generic name)
Oncology products	
Non–small cell lung carcinoma	Xalkori® (crizotinib)
Stomach neoplasms	Teysuno® (combination: tegafur, gimeracil, and oteracil)
Medullary thyroid cancer	Caprelsa® (vandetanib)
Breast cancer	Halaven® (eribulin)
Renal cell carcinoma	Inlyta® (axitinib)
Prostatic neoplasms	Jevtana® (cabazitaxel)
Hodgkin lymphoma	Adcetris® (brentuximab vedotin)
Melanoma	Yervoy® (ipilimumab) Zelboraf® (vemurafenib)
Non-Hodgkin lymphoma	Pixuvri® (pixantrone dimaleate)
Nononcology products	
Relapsing-remitting multiple sclerosis	Gilenya® (fingolimod)
Chronic obstructive pulmonary disease	Onbrez Breezhaler® (indacaterol)

Table 2 – Key process differences among the selected countries.

Country	Agency	Published guidelines to support submission [19]	Published timeline for both HTA and reimbursement decisions (mo) [19]	Agency initiates submission [9]	Formal appeal process [9]	Discussions on price* [9]	Legally binding decisions for reimbursement [9]
England	NICE	Yes	Yes (6)	Yes	Yes	Yes	Yes
France	HAS	Yes	Yes (6)	No	Yes	No	Yes
Germany	IQWiG, G-BA	Yes	Yes (12)	No	No	No	No
Italy	AIFA	No	Yes (12)	No	Yes	Yes	Yes
Poland	AOTM	Yes	Yes (3–6)	No	Yes	Yes	No
Spain	AEMPS	No	Yes (12)	Yes	Yes	No	Yes
Sweden	TLV	Yes	Yes (4)	No	Yes	Yes	Yes
The Netherlands	ZINL	Yes	Yes (6)	No	No	No	No

AEMPS, Agencia Española del Medicamento Y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; AOTM, Agencja Oceny Technologii Medycznych; G-BA, Gemeinsame Bundesausschuss; HAS, Haute Autorité de Santé; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; TLV, Tandvårds-och läkemedelsförmånsverket; ZINL, Zorginstituut Nederland.
* Price negotiation as part of the reimbursement decision-making process, undertaken either by an agency or by an expert committee.

results of the NICE recommendations for England and Wales were considered. As sales data cover 3-month periods, the alignment of sales information and HTA dates is not exact, but should be sufficient to allow any trends in sales associated with decisions to be identified. The specific data sources used for the identification of HTA and reimbursement decisions and associated dates for each country are detailed in Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.08.725. When uncertainty arose as a result of the difficulty in retrieving or translating information, information was confirmed via contacts in each country.

Results

Literature Review Findings

All the European countries included in the literature review (England, France, Germany, Italy, the Netherlands, Poland, Spain, and Sweden) have HTA bodies with bespoke processes for assessing pharmaceutical products. All the included countries have centralized reimbursement systems [9]. Nevertheless, in addition to national HTA and reimbursement organizations, there are also influential regional bodies in Italy, Spain, and Sweden that conduct some or all elements of these activities; there is some variation among the countries in the responsibilities assigned to national versus regional bodies.

Each HTA agency generally follows five distinct phases: horizon scanning, topic determination, collection and assessment of evidence, appraisal, and funding and policy determination. Although all assessments follow a clinical assessment similar to that performed by the EMA, each country also assesses the evidence on the basis of country-specific factors (e.g., disease prevalence and severity, patient population, and the availability of alternative treatment options). In addition, all HTA bodies have an impact on pricing and reimbursement [10–15]. Nevertheless, there are also significant differences between countries in the processes for HTA and reimbursement, including availability of guidelines to support submission, timelines for decisions (before or after launch), whether submissions are initiated by HTA bodies or manufacturers, and whether price is negotiated as part of the decision-making process (Table 2).

The literature review also highlighted some of the challenges faced in understanding the processes in place across Europe. In many cases, the rules and guidelines for HTAs, reimbursement, and pricing were not clearly defined, and practical guidance or evidence on the Web sites of HTA and reimbursement bodies often contradicted the academic literature. In addition, despite the potential impact of these changes, there is only limited

Table 3 – Variation in time delays (in days) to market access per country in published studies.

Country	Benoff et al. [8] data (d)		EFPIA [17] 2010–2011 data (d)	Degrassat-Theas et al. [16] 2005–2011 data (d)
	2010 data	2011 data		
England	162	89	118	106
France	349	284	316	334
Germany	106	66	–	67
Italy	419	417	347	368
The Netherlands	367	247	209	–
Poland	89	232	–	–
Spain	304	261	352	262
Sweden	143	128	272	–

EFPIA, European Federation of Pharmaceutical Industries and Associations.

published literature addressing how NICE might adopt a value-based assessment system, how HAS evolved its assessment process to include economic assessments, and how the ongoing European network for Health Technology Assessment project is affecting the HTA landscape.

Overall, we found the published literature insufficient to understand HTA and reimbursement processes in Europe. Studies are typically published by academics, who may not be directly involved in the HTA and reimbursement processes, and are rapidly out of date, given the pace of change in assessment approaches. In addition, publications are often contradictory, and it can be difficult to separate out the rules and guidelines for national HTA, national pricing and reimbursement, and regional decision-making systems. Nevertheless, differences in HTA and reimbursement processes described in the literature do provide a starting point for understanding why market access for some products may differ across Europe.

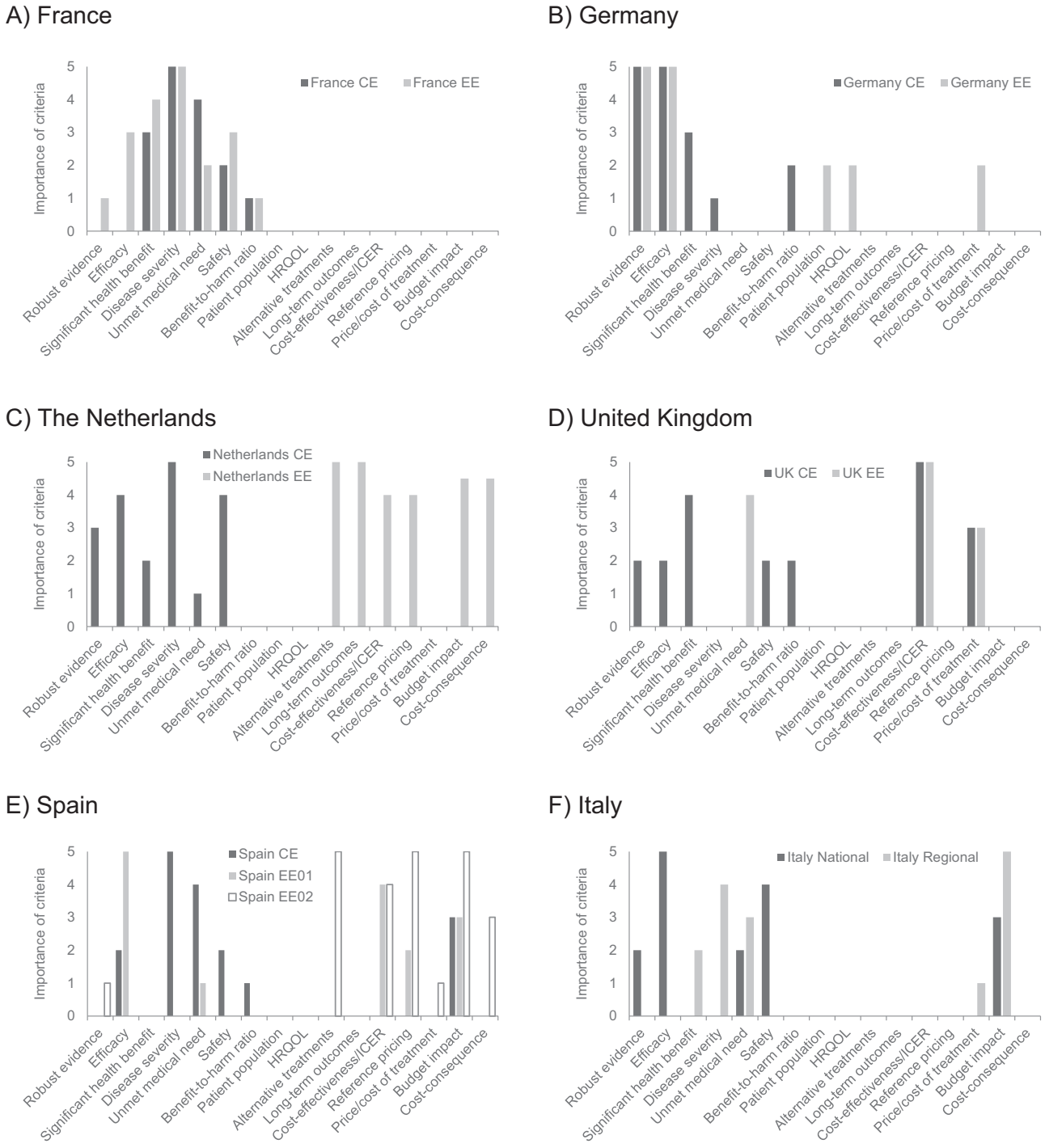

Fig. 1 – Most influential decision criteria in selected European countries. CE, clinical expert; EE, economic expert; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio.

Three studies were identified that assessed time delays from EMA approval to market access (Table 3) [8,16,17]. In general, market access was the fastest in Germany and the slowest in Italy. There was, however, substantial variation between study findings, and between data for different years. Although factors such as the need to conduct regional as well as national assessments in some settings may explain some of the variation, differences in methodologies and in the products included in each analysis make more detailed comparisons difficult.

Expert Interviews

To address some of the limitations of the published literature, and to try to understand some of the causes of variation in market access across Europe, we conducted a series of interviews with experts in each country. Using the literature review as background, we prepared flow diagrams describing the HTA and reimbursement processes in each of the included countries, and conducted a series of interviews with relevant experts.

In general, most experts felt that the flow diagrams were broadly accurate representations of actual practice in their respective countries, but 14 of the 18 interviewees noted at least minor discrepancies between the literature and the actual processes. In Italy, Spain, and Sweden, experts noted that regional reimbursement processes are not represented in the literature, whereas in Sweden and Poland alternative routes to market access exist that were not identified in the literature. In France, a single publication described the temporary authorization for use system [16]. Nevertheless, illustrating the speed at which published studies become out of date, there was no mention in the literature of the forthcoming Commission for Economic Evaluation and Public Health, established less than 6 months after the literature search. In Germany, IQWiG does not typically conduct assessments on orphan disease products, which are instead assessed by the Gemeinsame Bundesausschuss (G-BA). This distinction, however, was not clear in the published sources reviewed.

Interviewees were asked about the most important sources of information for decision-making committees in their countries. The manufacturer's dossier was seen as the most influential source of information used in meetings for France (both experts), Germany (economic expert), and Sweden (both experts), but was the least influential source for two out of the three Spanish experts (the third Spanish expert said the manufacturer's dossier was the most important source). Nonindustry evaluations, including briefing documents and independent assessment reports such as those submitted by the evidence review groups to NICE, are seen as the most important types of sources for the United Kingdom, Germany (clinical expert), and Poland. In contrast, published literature of the key clinical studies written by the primary investigator of the study is seen as the key source of evidence for Italy, Spain, and the Netherlands. Experts at committee meetings are, at times, highly influential in the United Kingdom, Italy, and Germany.

Interviewees were also asked to assess the importance of a set of decision-making criteria. The reported influence of different criteria in each country varied (as shown in Fig. 1; see also Fig. 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.08.725). For example, in France both clinical and economic experts considered the most influential criterion to be disease severity; in contrast, in the United Kingdom both experts felt that cost-effectiveness (measured using the incremental cost-effectiveness ratio) was the most important factor. Economic factors were not considered to be influential criteria in France and Germany. In some countries, there was disagreement between experts. In the Netherlands, the clinical and economic experts considered nonoverlapping sets of criteria to be influential, whereas the three Spanish experts all suggested different criteria to be the most important. In Italy, differences in experts' opinions reflected different levels of decision making, with an

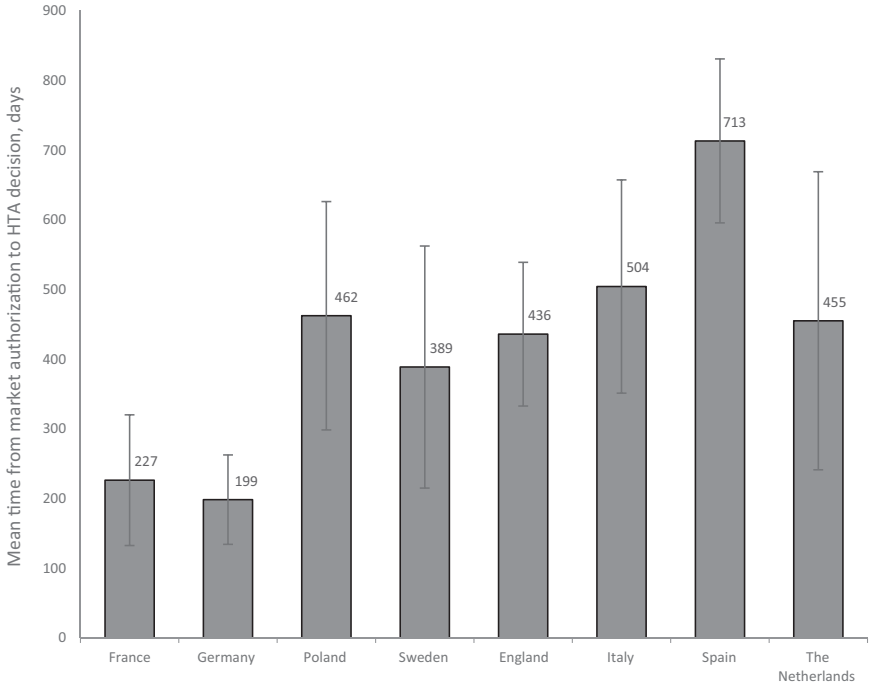

Fig. 2 – Mean length of time from EMA authorization to HTA decision for oncology products. Dates are taken from the product decision/publication date on the relevant country agency Web pages. For Germany, the time is from EMA authorization to IQWiG recommendation. Error bars: SD. EMA, European Medicines Agency; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen.

Table 4 – Summary of time from EMA authorization to HTA decision and outcome.

Product brand name (generic name)	England (NICE)	France (HAS)	Germany (IQWiG)	Italy (AIFA)	Poland (AOTM)	Spain (AEMPS)	Sweden (TLV)	The Netherlands (ZINL)
Xalkori (crizotinib)	327 d Rejected	162 d Approved (ASMR III)	113 d Added benefit not proven	153 d Approved with conditions	321 d Rejected	– –	493 d Approved with conditions	– –
Teysuno (combination: tegafur, gimeracil, and oteracil)	– –	569 d Rejected	– –	982 d Approved	805 d Rejected	– –	375 d Approved	560 d Rejected
Caprelsa (vandetanib)	– –	124 d Approved with restrictions (ASMR IV)	121 d Added benefit not proven	497 d Approved with conditions	– Under assessment	644 d Approved	– No national HTA recommendation	258 d Approved
Halaven (eribulin)	395 d Rejected	125 d Approved with restrictions (ASMR IV)	319 d Added benefit not proven	279 d Approved with conditions	854 d Rejected	925 d Approved with restrictions	– No national HTA recommendation	770 d Approved with restrictions
Inlyta (axitinib)	– Under assessment	128 d Approved (ASMR IV)	109 d Recommended with restrictions	765 d Approved with conditions	280 d Approved	– –	151 d Approved	– –
Jevtana (cabazitaxel)	425 d Rejected	216 d Approved (ASMR IV)	301 d Proven	275 d Approved with conditions	466 d Rejected	– –	– No national HTA recommendation	193 d Approved
Adcetris (brentuximab vedotin)	– Under assessment	132 d Approved (ASMR III)	119 d Added benefit	606 d Approved	284 d Rejected	763 d Approved	238 d Approved with restrictions	– –
Yervoy (ipilimumab)	521 d Approved with PAS	154 d Approved (ASMR IV)	289 d Added benefit	590 d Approved	406 d Approved	590 d Approved	314 d Approved	212 d Approved with conditions
Zelboraf (vemurafenib)	302 d Approved with PAS	229 d Approved (ASMR III)	663 d Added benefit	473 d Approved	283 d Approved	644 d Approved	762 d Rejected	738 d Approved with restrictions
Pixuvri (pixantrone dimaleate)	646 d Approved with restrictions	426 d Approved with restrictions (ASMR V)	293 d No added benefit	424 d Approved with conditions	– Under assessment	– –	– –	– –

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Gilenya (fingolimod)	365 d Approved with PAS	125 d Approved (ASMR IV)	305 d Minor added benefit	236 d Approved	571 d Approved	–	162 d Approved	329 d Positive recommendation
Onbrez Breezhaler (indacaterol)	– –	380 d Approved (ASMR V)	– –	247 d Approved	1499 d Approved	– –	376 d Approved	158 d Positive recommendation

Note. Dates are taken from the product decision/publication date on the relevant country agency Web pages. For Germany, the time is from EMA authorization to IQWiG recommendation. For France, Italy, and Sweden, the HTA decision date is also the date of reimbursement [20].
AEMPS, Agencia Española del Medicamento y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; AOTM, Agencja Oceny Technologii Medycznych; ASMR, Amélioration du Service Médical Rendu; EMA, European Medicines Agency; HAS, Haute Autorité de Santé; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; TLV, Tandvårds-och läkemedelsförmånsverket; ZINL, Zorginstituut Nederland.

interviewee with experience at national level rating efficacy as the most influential criterion, but budget impact being ranked the highest by an expert with regional experience.

Uncertainty was frequently mentioned as an issue by interviewees. In Germany, France, and the Netherlands, uncertainty is typically managed through requests for additional information; in France and the Netherlands, these may include sensitivity analyses as well as clinical data, and may be associated with delays in market access. In Sweden and the United Kingdom, sensitivity analysis is used to explore uncertainty when a product is judged to be at or near the cost-effectiveness threshold on the basis of cost/quality-adjusted life-year. In Italy and Spain, however, uncertainty often leads to the product's indication being restricted, and may lead to the use of risk-sharing schemes. Risk-sharing schemes are also used in Poland, and products with a high level of uncertainty not offset by such a scheme are likely to receive a negative recommendation.

Product Case Studies

To assess whether the variation in HTA and reimbursement processes across Europe leads to differences in market access, we used product sales data to compare market access delays for a set of 12 selected products (Table 1). The mean time from EMA authorization to HTA decision for oncology products, taken from the decision publication date on the HTA agency Web pages, is shown in Figure 2. Spain takes the longest on average to reach an HTA decision (713 days), followed by Italy and Poland (504 and 462 days, respectively). The fastest publication of a national assessment was found in Germany, with a mean time from EMA authorization to an IQWiG decision of 198 days. As additional time is needed in Germany for the G-BA to assess the additional benefit of a product, in this analysis France is likely to be on average the fastest country to complete the assessment process, with a mean time from EMA authorization to HTA decision of 227 days (ranging from 124 days for Caprelsa to 569 days for Teysuno). Nevertheless, market access is the fastest in Germany, with reimbursement granted at the time of EMA authorization.

The time taken from EMA authorization to HTA decision and the HTA recommendation for each product are presented in Table 4. There were differences among countries in whether a given product was reviewed, but all countries assessed at least half of the selected products. There are also substantial differences between countries in the time taken to review a particular product, and within countries in the time taken to review different products. In Italy, for example, the evaluation of Teysuno took more than 6 times as long as that of Xalkori. The time taken to review Teysuno was longer than average in all five countries that undertook an evaluation; there was, however, no information in the sources investigated to explain the delays for this product.

In general, we identified a lack of consistent transparency in why the assessment of some products was delayed or not performed. When information is available, it appears that several different factors can contribute to delays in HTA decisions. It is possible that some products perceived to have only minor benefits over current care represent more "difficult" decisions, which therefore take longer. In France, for example, of the 12 products assessed, the 3 with the longest times from EMA authorization to the publication of an HAS decision were either rejected (Teysuno) or given a rating of V (no improvement; Pixuvri and Onbrez Breezhaler) by the Amélioration du Service Médical Rendu. Uncertainty over clinical efficacy and safety, comparators, and cost-effectiveness may also lead to delays while discussions are ongoing, particularly if additional data and analyses are required. For example, the longest time we

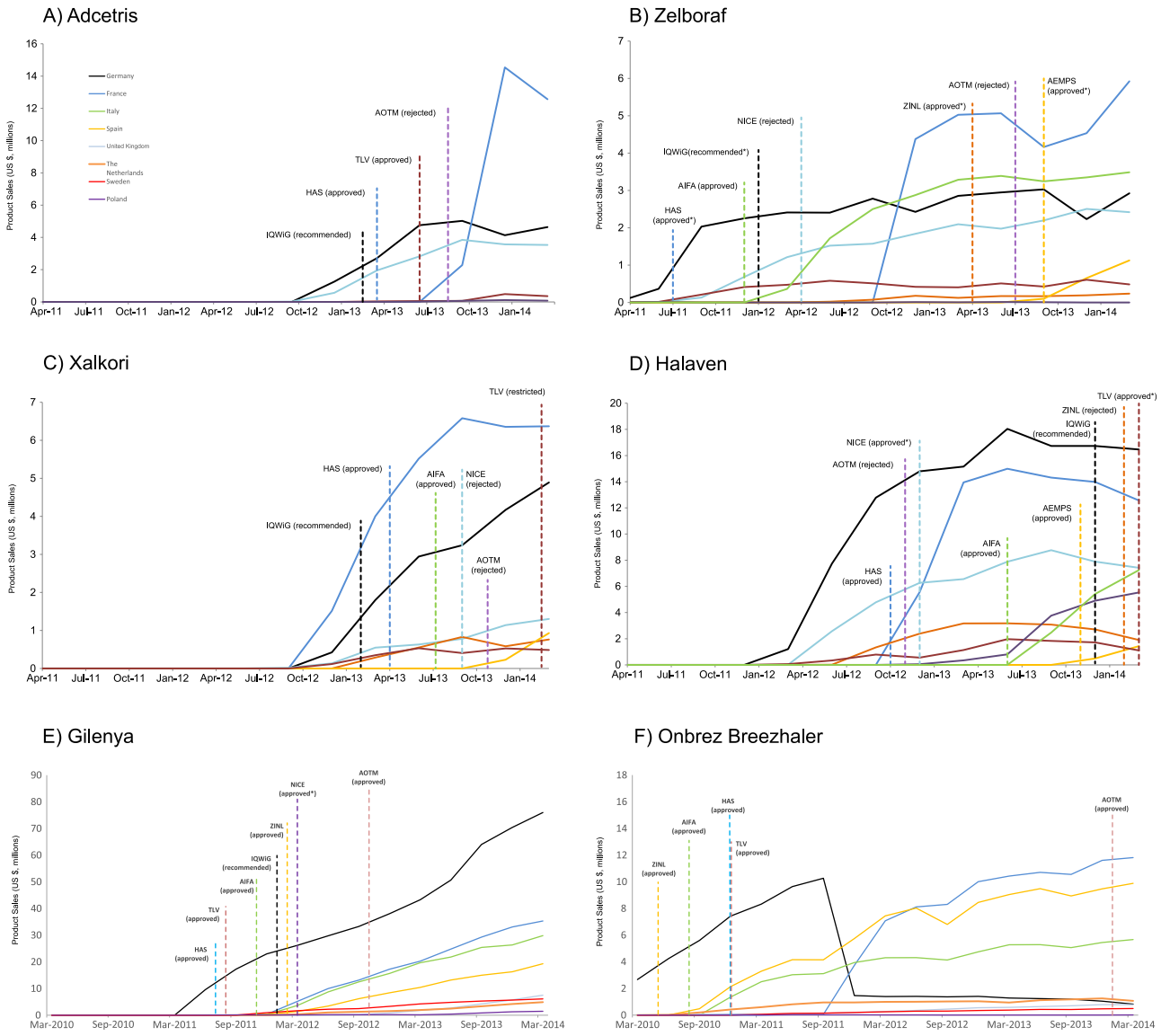

Fig. 3 – Relationship between HTA decisions and sales for selected products. Conditions applied to approval. AEMPS, Agencia Española del Medicamento Y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; AOTM, Agencja Oceny Technologii Medycznych; HAS, Haute Autorité de Santé; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; TLV, Tandvårds-och läkemedelsförmånsverket; ZINL, Zorginstituut Nederland.

identified from EMA authorization to NICE decision was for Pixuvri, for which there was uncertainty over subgroup analyses and the cost-effectiveness ratio; Pixuvri was eventually accepted within a restricted population. In some countries, drugs were approved with specific conditions of use, or for restricted populations (Table 4). There was, however, no clear relationship between the time taken for decisions and whether conditions were applied.

Several additional factors may explain some of the variation in HTA times. In Germany, the IQWiG review period is set at 93 days by law, leading to the generally short times from EMA authorization to HTA recommendation. It is possible that the additional time elapsed between marketing authorization and the publication of IQWiG decisions may reflect delays in products being launched in Germany. In Spain, a technical pre-authorization approval is given for products with EMA authorization and deemed of great interest to clinicians, usually taking only a few months before being posted on the Medicine Information Centre. Some products then undergo a full HTA, which appears to take considerably longer. This may be the reason for the long mean times found in this analysis.

Comparison of product sales data with HTA decision dates (Fig. 3; see also Figure 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.08.725) demonstrates that in most countries market access for oncology products can occur outside the HTA process. Product sales generally followed HTA approval in France (with the exception of Xalkori), but in other systems there was little alignment between product sales and HTA decision making. In Germany this is expected because products are available immediately upon EMA authorization. Nevertheless, despite the relatively long time until a NICE decision is made in England, sales data show that it is common for oncology products to be available shortly after marketing authorization. This is in agreement with the findings of the

literature review, which suggest that, along with Germany, England has the shortest time from EMA authorization to market access [8,16]. This lack of alignment between HTA decisions and sales is further illustrated by the continuation in sales growth for Xalkori and Halaven after the rejection of these products by NICE.

In contrast, the alignment between HTA decisions and sales appeared to be stronger for the two nononcology products assessed (Fig. 3). With the exception of Germany, sales began only after approval by the respective HTA body. In the case of Onbrez Breezhaler, a drop in sales in 2011 followed approval of the product with price restrictions by G-BA.

Discussion

All of the sources of information considered for this project confirm that market access varies across Europe, probably as a result of a number of differences among countries. Both the literature review and the expert interviews confirmed the existence of differences in HTA and reimbursement processes. In addition to process differences, interview responses indicated that different HTA bodies give different weights to different sources of information in their decision making, potentially explaining some of the variation in the resultant recommendations. Valuation of decision criteria by HTA experts also revealed differences in emphasis among countries. Some countries focus on disease severity and drug efficacy, whereas others concentrate on cost-effectiveness; in addition, within some countries, experts with different perspectives on the HTA process had different views on which criteria are most significant within their systems. Some of the general issues in HTA in Europe are well illustrated by the results of recent evaluations of novel cancer therapies.

The analysis of selected products described here broadly confirms the results found in the literature review, with Germany and France having generally the fastest HTA processes. Nevertheless, the variation in the time from EMA authorization to publication of HTA decisions was considerable, both within and among countries. Some of these differences may reflect uncertainty in the evaluation of particular products, but in general we found a lack of transparency as to why some assessments take longer than others. In contrast to the two nononcology products included in our analysis, we found that in most countries market access for oncology products can occur outside the HTA process, with sales often preceding HTA decisions. This was expected in Germany, where new drugs are available for prescription as soon as they are approved by the EMA, but in other countries these observations suggest that different "rules" may apply to oncology products. The difference between oncology and nononcology products may reflect the role of early access programs for cancer treatments (e.g., in France, Xalkori was made available through a temporary authorization for use system) as well as parallel funding systems such as the Cancer Drugs Fund in England [18].

This study has several limitations. The analysis of product case studies in particular is sensitive to the exact definitions used. For example, HTA decisions do not necessarily equate to market access in all countries. Although reimbursement decisions are sometimes incorporated into the HTA, in some countries a separate process exists. For example, in France there may be additional delays in market access because of assessment by the economic committee. Similarly, in Germany, the IQWiG scientific evaluation process is followed by an assessment of additional benefit, conducted by G-BA. The delays identified here, from EMA authorization to publication of a decision by IQWiG, do not therefore correspond directly to the end of the assessment process (or to market access, which in Germany is granted at the time of EMA authorization). The IQWiG review period is set at 93 days by law, and it seems possible that the additional time elapsed before the publication of IQWiG decisions may reflect delays in products being launched in Germany. This may be a more general limitation, and some apparently long delays may be a result of a product not being launched in a particular market until sometime after marketing authorization is granted. We have taken sales data to be a proxy for patient access to new products. Although sales are a straightforward measure to use, these data can be complicated by factors such as rebates and parallel trade, and comparisons between products and countries should be treated with caution. Our analysis appears to show a difference between oncology and nononcology products in the impact that HTA decisions have on market access; nevertheless, only two nononcology products were included in this study, and investigation of further examples would be needed to confirm this trend. Experiences in oncology are likely to reflect the wider issues surrounding the introduction of new, innovative, and expensive therapies; generalizations, however, should be made with caution.

Conclusions

The main conclusion that we can draw from this research is that it is challenging even for those with considerable personal experience in European HTA processes to establish what is really happening in market access for new drugs, and why there are differences among countries. Although some of the variation can be understood, it appears that issues and forces (including budget impact and political factors) other than the HTA processes of various countries can contribute to decisions and to time to patient access. Although it is important to measure delays in patient access resulting from differences in HTA processes, we recommend that efforts should be directed toward improving transparency in HTA, which should, in turn, lead to more effective processes.

Acknowledgments

We thank Nicola Mason and Ann-Marie Chapman (BresMed Health Solutions Ltd., Sheffield, UK) for conducting the literature review, expert interviews, and product case studies. We also thank Paul Overton (independent medical writer) for providing editorial assistance in the preparation of this article.

Source of financial support: Research and editorial support was funded by Novartis Pharma (Basel, Switzerland) under the AGORA initiative (a European Think Tank that aims to optimize access to innovative treatments for patients). The final content of the publication is fully owned by the authors.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.08.725 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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