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Orphan drug considerations in health technology assessment in eight european countries

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ABSTRACT

Health Technology Assessment (HTA) is used to assess the value of new technologies and by producing coverage recommendations it indirectly controls the uptake of new technologies in many European countries. While HTA generally relies on a robust assessment of the clinical cost-effectiveness of a new technology, the clinical and economic evidence required for this purpose is often not available for Orphan Drugs (ODs), partly because of challenges related to the recruitment of patients to participate in clinical trials. A number of European HTA agencies have started to implement specific policies to address the challenges related to evidence requirements for the case of ODs. In this study, we map out the policies currently in place in eight European countries regarding HTA and its application to the case of ODs and explore the implications these policies have for coverage decisions.

KEYWORDS

health technology assessment, rare diseases, orphan drugs, health systems, comparative health policy, risk sharing

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INTRODUCTION

Across many European Union (EU) health systems, well-defined processes are in place to determine expected value for money when new health care technologies, among them pharmaceuticals, come to market. These processes, collectively referred to as Health Technology Assessment (HTA), differ between countries in their methodological basis, and in the way value is determined, implying that the outcome of assessments can differ significantly [1] with consequences for access to medicines across member states (MS) [2].

Orphan drugs (ODs) treat conditions recognised as "rare" by generally accepted thresholds, with a prevalence of less than 5 cases per 10,000 population in the EU [3]. Because markets for ODs by definition are small, a variety of incentives exist to stimulate research and development into these disease areas both at national and EU level. In order to incentivise the process of drug approval, all new ODs seeking marketing authorisation (MA) are assessed at EU level by the European Medicines Agency (EMA). This ensures homogeneity in the assessment process. However, such homogeneity does not exist at the point where newly authorised ODs seek reimbursement by health systems in individual MS. This is because processes assessing reimbursement and value for money of new drugs, including orphans, differ quite significantly across EU MS. As part of this variability in value assessment processes, including the way HTA is implemented, it is not uncommon for two health systems to arrive at different conclusions about the value of a new product [4]. Indeed, recent evidence suggests that there is significant variation in the outcomes of HTA processes for ODs across some MS, suggesting access to these drugs could be different across different health systems [5].

This is supported by a survey showing that 90% of a sample of 60 ODs was found to be available in France, the Netherlands and Denmark, whereas only one third were available in Spain, Greece and Romania [6]. Financial considerations often influence access to medicines in many countries. A recent survey reported that nearly a quarter of the 22 European countries surveyed (Estonia, Latvia, Lithuania, Poland and Romania) restricted access to ODs due to budgetary constraints. Based on the same survey, only 5 countries always granted access to ODs, while several authorised access but with possible restrictions, such as prior authorisation [7].

In many cases, it is the outcome of the HTA process that determines on which grounds ODs should be made available or not. The conduct of HTA appraisals for ODs is associated with its own challenges, one of which is the recruitment of adequate numbers of patients into clinical trials due to the small overall patient population for a given indication [8]. Consequently, the extent of clinical evidence available at marketing authorisation (MA) and the level of statistical confidence authorities can place in this evidence may fall short of what HTA agencies normally consider to be adequate [9].

This is particularly relevant for rare diseases (RDs), because the higher prices may not be commensurate to the expected level of evidence regarding benefit. As a consequence, ODs are often not considered a cost-effective use of resources under standard criteria; this has led to a number of exceptions in the way ODs are appraised, such as taking into account the severity of disease or the availability of therapeutic alternatives [10].

The relatively small budget impact of ODs in some cases has often facilitated their market entry, for example with Germany or France reimbursing ODs if the total budget for a particular indication is under a certain ceiling [11]. However, the overall budget impact of ODs has been increasing in recent years, raising questions for policy makers about the value for money they offer relative to other health interventions. In particular the European system of orphan drug designation has been criticised as a mechanism whereby pharmaceutical manufacturers "game" the system, achieving higher prices for their products across multiple indications [4]. There are also examples of ODs being approved for wider use, and of older molecules (e.g. thalidomide) being re-branded under an orphan indication with a mani-fold price increase [12].

The aim of special European legislation to encourage research and development in ODs was to make new treatments available to patients, but it has been argued that high prices often associated with ODs are having the opposite effect. Additionally, the practices of international price referencing and parallel trade ensure that these high prices are similar across all EU countries. With the dominant position of an orphan MA, which in most cases will face no competition, it has even been suggested that it may be necessary to invoke EU competition law (Article 102 of the Treaty on the Functioning of the European Union) to scrutinise the fairness of these prices [13].

Such observations underline the need for a comprehensive understanding of value assessment mechanisms of ODs, so that prices may be understood and debated in their proper context. The European Commission has promoted the creation of a mechanism for the exchange of knowledge between the EU MS and European Authorities on Clinical Added Value for Orphan Drugs (CAVOD), whereby a mechanism has been proposed to facilitate MS in the scientific assessment of the clinical effectiveness of ODs and develop a bridge between pre-market authorisation phases (clinical development) at EU level **and post-marketing au**thorisation phases at MS level [14]. More recently, the Mechanism of Coordinated Access to Orphan Medicinal Products (MOCA) led by the European Commission aimed to enhance patient access to ODs based on programmes between manufacturers and groups of competent authorities [15].

Many aspects need to be considered in the context of national OD reimbursement: The lack of existing treatment options due to rarity of the condition and equity of access to treatment among different population segments, as well as providing fair returns on investment for research-based entities, while facing the reality of budget constraints. The objective of this study is to outline the existing national policies for ODs with particular emphasis on special considerations made in the HTA process in order

to understand the explicit criteria in place for OD reimbursement. The study goes beyond HTA to encompass aspects of policy such as risk-sharing agreements at MS level and explores the implications for access.

METHODS

The study relies on primary and secondary evidence drawn from eight EU Member States. The study countries are England, France, Germany, Italy, Poland, Scotland, Spain and Sweden and were selected because of the variety in their health system financing (tax and social insurance-based), organisation (central and regional organisation and delivery of services) and HTA processes they use. For example, the National Institute for Health and Care Excellence (NICE) in England implements a health system perspective, while Sweden follows a societal approach to value assessment; France, on the other hand, implements a clinical approach to value assessment rather than relying on cost-effectiveness (until the end of 2013), for prescription medicines licensed for the first time, whereas in Spain HTA may be used at regional level to inform decision-making in some technologies, although this is not routine practice across all health technologies and, in particular, pharmaceutical products.

Formal processes within each country for the appraisal of ODs were identified and reviewed by searching the relevant government agency websites for "rare diseases" in the local language, supplemented by searches of the peer review literature. The search strategy for the identification of OD assessment processes is presented in detail in *Table 1*. To ensure consistency of the search algorithm, Google (http://www.google.com) was used to perform the search using the "site" modifier, and the first 20 results were screened for relevance for each country.

Table 1. Search strategy for the identification of orphan drugs assessment processes

COUNTRY	SEARCH TERM
England	Site: nice.org.uk rare diseases
Scotland	Site: scottishmedicines.org.uk rare diseases
Sweden	Site: tlv.se sällsynta diagnoser
France	Site: has-sante.fr maladies rares
Germany	Site: iqwig.de seltene Erkrankungen
Spain	Site: aemps.gob.es enfermedades raras Site: isciii.es enfermedades raras
Italy	Site: agenziafarmaco.gov.it malattie rare Site: sihta.it malattie rare Site: agenas.it malattie rare
Poland	Site: aotm.gov.pl rzadkie choroby

The findings were confirmed and supplemented by 15 national key informants (KIs) by conducting semi-structured interviews, which took place from May 2013 to August 2013. KIs were presented with results from the grey literature search and were invited to add any additional information or clarifications. The questions shown on *Table 2* have guided these discussions. The

Table 2. Semi-structured interview guide to inform primary data collection from key informants on national rare disease policies (May - August 2013)

QUESTION	
1	Please describe any processes and policies that could affect the appraisal of medicines for rare diseases in your country. This does not have to be explicit "rare disease" policies/processes, but any aspects that could be relevant (for example, whether there are special criteria for unmet clinical need, fast-track procedures for innovative medicines, among others).
2	If there are specific processes/policies for rare diseases: What are the official documents/sources describing these? How do HTA processes for orphan drugs deviate from standard HTA processes, if at all? Are there different criteria used in the final decision (e.g. unmet need, disease severity, lower statistical thresholds for evidence used, among others)? In what way(s) are relevant stakeholders (e.g. patients, clinicians, etc) involved in orphan drug appraisal? Is this involvement different for orphan drug assessment than it is for non-orphan drugs? Is there a different (explicit or implicit) willingness to pay threshold for rare disease drugs?
3	If there are **no** specific processes/policies for rare diseases: Are there any technical barriers hindering this? (for example, lack of evidence, lack of funds, lack of technical expertise) Are there political barriers?

Table 3. Summary of HTA criteria directly and indirectly relevant to orphan drugs, 2013 (Continues)			
	Specific OD criteria for HTA	Other policies and HTA criteria that are not specific to ODs but can also apply to ODs	
	Policy	Policy [criteria]	Responsible authority
England	NICE HST[1] section for appraising ultra-orphan drugs; no explicit remit for ODs unless it is for cancer indications	IFR[2] for medicines not routinely reimbursed, but must consider "exceptionality rule"	PCTs[3] (prior to ongoing NHS reforms)
France	Benefit considered proven at MA if budget impact is less than €30m per annum for a particular indication	ATU[4] if condition is life-threatening or/and there is no therapeutic alternative; Temporary Treatment Protocols	ANSM[5]
		Fast track HTA in place if: (a) new therapeutic modality, (b) high unmet need, (c) demonstrated efficacy/tolerability	Transparency Commission
Germany	Lower accepted significance levels for p-values (e.g. 10% significance levels) for small sample sizes such as RD populations; acceptance of evidence from surrogate endpoints rather than only 'hard' endpoints; Additional benefit is considered proven at MA[6] if budget impact is less than €50m per annum	n/a	n/a
Italy	n/a	Reimbursement procedure considers, among other things, clinical need, existing therapies and budget impact.	AIFA[7]
		National Health Care Plan for Rare Diseases for the period 2013-16 is under development, including a section on access to ODs.	Ministry of Health
		In the event an OD is not reimbursed centrally, it can be purchased or imported directly by Local Health Authorities.	Local Health Authorities
		Fast-track mechanism for ODs to enter pricing/reimbursement negotiation before MA	AIFA
		Access to innovative treatments for disorders where no alternative therapy is available is provided by law (No. 648/96). The law applies 1) to (innovative) medicines already approved in other countries but not yet in Italy, 2) to products, which have demonstrated clear benefit while "under clinical investigation" and 3) for off-label use.	AIFA CTS[8]
		"Fondo AIFA 5%" (established under Law No. 326/2003). Half of the fund should be devoted to providing access to medicines for rare diseases before MA.	AIFA
		Single patient access to specific drugs (law n. 94/1998 and ministerial decree n. 8 May 2003)	
Poland	n/a	Therapeutic Programmes provide access to expensive drugs (including ODs).	Ministry of Health
		Direct funding through Ministry of Health in exceptional cases, eg. haemophilia in children.	

Summary of HTA criteria directly and indirectly relevant to orphan drugs, 2013 (Continued)			
Scotland	Lower levels of evidence are accepted for clinical trials (e.g. on efficacy and safety), but with possible requirement for additional data in other areas (e.g. surrogate markers and quality of life data)	IPTR[9] may be used to gain access while medicine is under appraisal by the SMC[10]	NHS Scotland Boards
	Higher levels of uncertainty are accepted in the economic case for ODs	Requests for level 1 non-formulary drugs without going through an IPTR (usually in very low quantities and cost)	Monitored by NHS Scotland Board Prescribing Advisory Teams
		Higher cost per QALY accepted in HTA (> £30,000) [including but not limited to: substantial life expectancy or quality of life improvement; no therapeutic alternatives]	SMC
Spain	n/a	Pricing and reimbursement takes into account, among other things: severity of indication; needs of patient groups; therapeutic options; and degree of innovation	Ministry of Health, Social Services and Equality
Sweden	n/a	Flexibility in willingness-to-pay threshold, due to disease severity (higher cost/QALY accepted)	TLV[11]
		Higher degrees of uncertainty accepted in the case of ODs	
		County Councils can decide to reimburse drugs independently of TLV recommendation [no criteria]	County Councils, New Drug Therapies board (if applicable)

Source: *The authors based on information extracted by government agency websites and insights from 15 national key informants.*

Notes: *[1]NICE Highly Specialised Technologies; [2]Independent Funding Request; [3]Primary Care Trusts; [4]Authorisation for Temporary Use; [5]Agence Nationale de Sécurité du Médicament et des Produits de Santé (French National Agency for Medicines and Health Products Safety); [6]Marketing Authorisation; [7]Agenzia Italiana del Farmaco (Italian Medicines Agency); [8]Commissione Tecnico Scientifica (AIFA's Technical Scientific Committee); [9]Individual Patient Treatment Request; [10]Scottish Medicines Consortium; [11]Tandvårds- och Läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency).*

difference in the number of individuals contacted and interviewed reflects differences in the input provided by each informant and the structure of the health system in each of the study countries: England (1), France (3), Germany (2), Italy (3), Poland (1), Scotland (2), Spain (2) and Sweden (1). All 15 key informants gave their informed consent for their comments to be reported anonymously.

The study is not without limitations. First, it is a selective sample of 8 countries and does not include all EU-28 MS. Smaller or resource-poor MS are known to face access problems with regards to ODs [6,7] and the extent to which they have specific policies relating to orphan drugs is unknown. Second, the subject matter is relatively understudied and the literature search did not return any results relevant to orphan drug assessment for Poland, Spain and Sweden, but there was some input from the grey literature and insights from key informants. Finally, as this is a dynamically evolving policy field, this study may not have captured the very latest updates in some cases, although it is unlikely this will have influenced the study results or overall direction.

RESULTS

Search results

For England, the search returned the formal proposal for the appraisal of ODs submitted by NICE to the Department of Health in 2006. For France, the search did not identify documents describing particular processes for the appraisal of ODs. Documents were identified describing the National Plan for Rare Diseases, as outlined in the relevant results section. For Germany, the General Methods document published by the Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) outlines the overall methodological approach taken by the agency. For Italy, no reference to RDs was found on the website of the Italian Society of Health Technology Assessment (Società Italiana di Health

Technology Assessment, SIHTA). On the website of Italy's National Agency of Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali, AGENAS), there was reference to the inclusion of 109 new rare disease treatments in the basic benefits package, but no reference to processes or criteria for HTA in RDs. For Scotland, the search returned policy statements described in detail in the relevant country section. For Poland, Spain and Sweden, no relevant documents were identified.

NATIONAL POLICIES FOR ODs

In this section the policies and HTA criteria directly and indirectly used for rare diseases and orphan drugs are discussed that were revealed by the search, supplemented with the scientific literature and key informant input. In the sections that follow, countries appear in alphabetical order. The results of the review are summarised in *Table 3*.

ENGLAND

In England there are centres of reference for some RDs, but recent evidence from the peer review literature suggests there are neither explicit policy measures nor research incentives for RDs or ODs [16,17]. The value assessment procedure handled by NICE considers mainly cost-effectiveness, though additional criteria such as equity may also be considered [18]. In general, NICE does not appraise ODs routinely, but does so for those ODs that have an oncology indication. In response to ministerial requests on how ODs might be appraised, NICE advised that many ODs, in particular for "ultra-orphan" conditions with a prevalence of less than 1 in 50,000, would have unacceptable incremental cost-effectiveness ratios (ICERs) if no special criteria or weightings were applied, giving examples of drugs that cost approximately £200,000-£300,000 per Quality Adjusted Life Year (QALY) gained, where the normal threshold is approximately one tenth of these figures [19]. However, there were drugs with high ICERs that the appraisal committee has considered to be cost effective, such as in the case of Glivec for blast phase chronic myeloid leukaemia, where the ICER was calculated at £48,000 per QALY; but even for that case there were exceptional reasons enabling coverage.

Until April 2013 ultra-orphan drugs had been appraised by a specialist agency known as the Advisory Group for National Specialised Services (AGNSS). The role of AGNSS was to advise health ministers on the services that should be nationally commissioned and the centres that should provide them, as well as on which products and technologies should or should not be nationally commissioned [20, 21]. Reforms that have been ongoing from the end of 2012 until currently, and regard mainly structural changes in the NHS (whereby Clinical Commissioning Groups [CCGs] are replacing Primary Care Trusts [PCTs] and the new NHS Commissioning Board [NHS CB] has been created), as well as a development of a strategy for RDs [20] will separate the appraisal of drugs and services; drug appraisals will be handled by NICE, whereas service commissioning for people with RDs will be handled by the NHS CB [22].

The NICE Highly Specialised Technologies (HST) section will be responsible for appraising ultra-orphan drugs through a process that is largely similar to the existing Single Technology Appraisal process [23, 24]. The interim processes and methods for this section state that the topic selection will be based on the same criteria as those used by AGNSS. The recommendations made by the HST section are intended to inform which technologies should be adopted for national commissioning [25]. Where a positive recommendation by NICE is not likely on poor cost-effectiveness grounds or uncertainty on costs, manufacturers can propose a Patient Access Scheme (PAS) to facilitate patient access to a drug, including an orphan. England has so far focused mostly on financial-based PAS, which do not require outcome-based agreements [26].

When medicines are not recommended by NICE and therefore not made routinely available, patients can complete an Independent Funding Request (IFR) to seek public reimbursement for their treatment. Before the recent NHS reforms, successful IFRs were funded by Primary Care Trusts (PCTs). Though IFRs are not specifically intended for RDs, treatments for RDs that are not routinely commissioned by PCTs, are within the scope of the scheme. However, when PCTs are presented with an IFR, they need to consider the "exceptionality" rule, that is, the grounds on which the PCT can justify funding for a patient when others from the same patient group are not being funded [27]. In April 2013 the NHS CB issued an interim policy statement based on which an IFR can only be made if (a) it does not concern a service development, (b) the patient's particular medical situation does not apply to an existing commissioning policy, (c) the patient is able to participate in a clinical trial which requires individual funding by the NHS CB, or (d) the patient has a rare clinical condition, is not able to participate in a clinical trial and, therefore, the clinician wishes to test an existing treatment experimentally. NHS CB only considers IFRs if the number of patients presenting these particular circumstances per year is less than 5 and if the expected costs per patient are less than £150,000 per annum. The decision is made on the basis of (a) the potential benefits and risks of the treatment; (b) the biological plausibility of anticipated benefit for the patient based on evidence of this treatment in other similar disease states; (c) value for money; (d) affordability and priority compared to other competing needs; and (e) unfunded developments [28].

In November 2013 the Department of Health issued a "UK Strategy for Rare Diseases" outlining five key areas of action: (a) the empowerment of people suffering from RDs; (b) the identification and prevention of RDs; (c) the diagnosis and early intervention; (d) the coordination of care; and (e) the role of research into rare diseases. One of the 51 commitments of the Strategy is to ensure that costs and benefits of treatments are evaluated appropriately [29]. On this issue, the England Statement of Intent of February 2014 confirmed that the NHS would collaborate closely with NICE in the formal appraisal of technologies, including the HST, taking into account the specific needs of patients with RDs [30].

FRANCE

France has had a National Plan for Rare Diseases since 2005; there are currently 131 centres of reference and 501 centres of competence for 18 groups of RDs [31]. The original plan (2005-2008) was centred around 10 strategic priorities, which included improving access to treatment and the quality of patient care, as well as continuing efforts in favour of ODs [32]. The development of ODs is supported through special clinical research funding programmes, budgetary incentives and scientific advice from the National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM) and the French HTA body (Haute Autorité de Santé, HAS). [16].

Under the existing system of value assessment, the Medical Service Rendered (Service Médical Rendu, SMR) reflects the medical benefit of a drug integrating disease severity and determining the extent to which a treatment can be reimbursed, while the Improvement in Medical Service Rendered (Amélioration du Service Médical Rendu, ASMR) is a measure of innovativeness and determines the reimbursement price of a new technology. A new system of HTA appraisal is currently being implemented, whereby a new therapeutic index rating (Index Thérapeutique Relatif, ITR) will classify new pharmaceuticals against existing comparators, based on clinical benefit, alternative treatments, patient subgroup interest, pharmaceutical preparation and other attributes. Moreover, all drugs will be evaluated on the basis of their cost-effectiveness [33].

There are no specific criteria or exemptions applied by HAS in the assessment of ODs; prices and reimbursement are set according to standard procedures applying to non-orphan technologies. The clinical evidence used in the OD SMR rating is based on the same clinical evidence submitted for regulatory approval by the European Medicines Agency (EMA), which may be limited to Phase II trials and literature reviews [9]. However, the medical benefit is considered proven if the total budget impact for the indication is less than €30 million [34].

Almost all innovative drugs enter the French market as part of a price-volume agreement (PVA) with the goal to restrict treatment to the target population by defining a tiered repayment for different levels of sales. A price cut takes place at the end of the agreed period. This is for example the case of the ultra-orphan Soliris for paroxysmal nocturnal haemoglobinuria, which was supplied to all patients without restrictions. According to the agreement, the company would pay back to the national health insurance any turnover that exceeded an agreed maximum budget ceiling. Other types of managed-entry agreements (MEAs) in France include agreements on daily cost of treatment, study requirement, and risk-sharing agreements – or a combination of these [26].

Three types of fast-track procedures contribute to making medicines available with minimal delay: First, the Authorisation for Temporary Use (Autorisation Temporaire d'Utilisation, ATU) provides access to medicines before regulatory approval. The criteria for ATUs are life-threatening or rare diseases for which there is no alternative treatment, and the scheme is used for drugs with a good probability of a favourable benefit to risk balance [35]. Second, the Temporary Treatment Protocols are intended to temporarily extend the licensed indication of an existing medicine before the new indication receives regulatory approval [9]. One key informant confirmed that this process is progressively replaced by the Recommendation for Temporary Use (Recommendation Temporaire d'Utilisation, RTU), which will allow utilisation and reimbursement of drugs out of their MA indication in hospital settings and community pharmacies. These drugs have to satisfy certain conditions, namely that they should (a) treat a rare disease or a chronic condition, (b) be necessary for the health of the patient and (c) be the only existing treatment for the particular condition. Third, fast-track procedures exist for medicines considered "a priori innovative", allowing HAS to start the assessment before regulatory approval is obtained and make a reimbursement decision within a few weeks after MA [9]. As one key informant highlighted, for a drug to be considered innovative it must have a new therapeutic modality (mechanism of action, therapeutic class, target population, formulation/route of administration), cover an unmet clinical need and have demonstrated efficacy and tolerability. ATUs are granted by ANSM and fast-track procedures by HAS [9].

GERMANY

In Germany, pharmaceutical manufacturers are free to set ex-factory prices on all drugs with no government negotiations, international reference pricing or profit controls, though price setting generally takes into consideration the system of internal reference pricing for the reimbursement of medicines [36]. Medicines are automatically reimbursed after regulatory approval and the extent is determined by the additional therapeutic benefit: if there is no added benefit the medicine is included into the (internal) reference pricing system [9].

Though there are no specific pricing considerations for ODs, these are often characterised by having no therapeutic alternatives, making comparison with existing therapies impossible and theoretically resulting in free pricing [9]. The new Pharmaceutical Market Reorganisation Act (AMNOG), which rendered the early evaluation of the additional benefit of a pharmaceutical product by the Federal Joint Committee (G-BA) mandatory after (MA), treats ODs differently in that their additional benefit is considered proven with MA alone, provided their budget impact is less than €50 million per annum. Nevertheless, manufacturers need to submit a dossier so that G-BA assesses the level of additional benefit and uses this in price negotiations if needed [37]. A recent report found that the first four out of seven ODs to be launched through AMNOG were considered to offer only minor additional benefit, while for two other ODs the benefit was considered non-quantifiable [38]. Either way, the G-BA issues an order forming the basis for negotiations on the reimbursement rate between the National Association of Statutory Health Insurance

Funds and the marketing authorisation holder (MAH) [39].

The Institute of Quality and Efficiency in Health Care (IQWiG) may be commissioned by the G-BA to carry out an early benefit evaluation [37]. The General Methods report published by IQWiG contains a section on "Benefit assessment of medical interventions" and a subsection (3.2.5) on "Benefits and harms in small populations" [40]. The latter states that, for small sample sizes, it is reasonable to accept a higher than 5% p-value (e.g. 10%) to prove statistical significance and to accept evidence from surrogate endpoints.

Different types of MEAs have been implemented in Germany in the recent years. They all exist at a decentralised level and constitute agreements between the pharmaceutical companies and the sickness funds in order to speed up access to medicines that have an uncertain value. Recently, MEAs have been put under the provision of AMNOG, although manufacturers do not have the incentive to propose such an agreement, because when a drug is reimbursed by the G-BA, all sickness funds are obliged to reimburse it, whereas when a drug is not reimbursed, sickness funds are not allowed to reimburse it [26].

ITALY

No specific provisions are envisaged for the value assessment of ODs in Italy. Negotiations for the prices of ODs take place between the Pricing and Reimbursement Committee of the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and the pharmaceutical companies. These negotiations take into account the incremental cost-effectiveness ratio (though no formal willingness-to-pay threshold is prescribed), the comparison with existing therapies, efficacy of the OD, price comparisons with other countries, projected uptake, budget impact analysis and other financial factors such as overall impact on investment [16, 41]. The reimbursement procedure of AIFA considers clinical need, whether other therapies exist, the budget impact and cost-effectiveness of the OD. According to one key informant, an unfavourable mix of low level of evidence on efficacy and safety, a high price proposed by the manufacturer and low resource availability of the National Health System, leads to non-reimbursement. Under these circumstances, the OD can be reimbursed by the Local Health Authorities (Aziende Sanitarie Locali) and not by the National Health System.

The legal framework in Italy has evolved over the past 18 years to enable better access to ODs. Four particular legislative interventions are worth noting with notable implications for OD use. First, a fast track mechanism is available in Italy under the Balduzzi Law (Law No. 189/2012), allowing ODs to enter the pricing and reimbursement negotiation before MA is obtained. Second, with regards to availability of ODs to patients, law No. 648/1996 enables Italian patients to gain access to innovative treatments for disorders for which no alternative therapy is available. The law applies to (a) (innovative) medicines already approved in other countries but not yet in Italy, (b) products which have demonstrated clear benefit while "under clinical investigation" and (c) medicines destined for off-label use. A medicine is considered for inclusion under the 648/1996 law following an application to AIFA's Technical Scientific Committee (Commissione Tecnico Scientifica, CTS) [42]. Third, the "Fondo AIFA 5%", established under Law No. 326/2003, is designed to promote ODs and medicines awaiting market entry. According to the law, half of the fund should be devoted to providing access to medicines for RDs before MA. The other half should be devoted to promote independent research and related activities. Finally, law n. 94/1998 and the ministerial decree of 8 May 2003 are intended for specific situations where single patients need to obtain a drug and cover compassionate use. Based on these and using evidence from the literature, the physician must report that the patient cannot be treated with available drugs and that treatment with a drug under evaluation is indicated.

To date, the first National Health Care Plan for Rare Diseases is under development in Italy and will cover the 2013-16 period. In the first draft issued for public consultation on October 2012 [43], a specific section is devoted to ODs and is mainly focused on accessibility for patients. The draft plan also takes into consideration the CAVOD study on value assessment of ODs [14].

A variety of MEAs are used in Italy, including for ODs, in order to manage budget impact and uncertainty around clinical and cost-effectiveness, such as PVAs, cost-sharing, budget caps, therapeutic plans and monitoring registries, among others [26].

POLAND

The Agency for Health Technology Assessment in Poland (Agencja Oceny Technologii Medycznych, AOTM) acts as an advisory body to the Ministry of Health (MoH). AOTM produces recommendations for the inclusion or not of medicines in the benefits package. The review procedure includes a review of the submitted evidence as well as a search for new evidence, a review of the economic analysis, a recalculation of the submitted economic model and budget impact analysis. The recommendations of AOTM are not legally binding and the final decision rests with the MoH [44]. Both cost-effectiveness and cost-utility are allowed in the economic assessment, as is cost-minimisation if the effectiveness of the interventions analysed are the same [45].

The current focus on Polish pharmaceutical policy is on efforts to keep pharmaceutical spending under strict control, which is the main goal of the Reimbursement Act, effective from 1st January 2012. Health technology assessment plays a role towards meeting this objective through the existence of an explicit willingness to pay (WTP) threshold set at three times the GDP per capita per QALY (for Cost-Utility Analysis) or Life-Year Gained (LYG) (for Cost-Effectiveness Analysis), which in 2013 was approximately PLN 105,000 (€24,500). Pricing arrangements are not differentiated for ODs. If the WTP threshold is exceeded, risk-sharing schemes can be proposed. If there is a significant budget impact on the National Health Fund (NHF), a "rationalisation analysis" should be performed to propose sources of the additional funds required. Subsequently, AOTM appraises the price and

the reimbursement is negotiated between the MAH and the Economic Commission of the MoH.

The price of medicines is determined by the MoH and the reimbursement rate depends on the drug price relative to the minimum wage as well as whether the condition is acute or chronic. Decisions are supported by the AOTM President and the advisory board (Transparency Council) and are valid for up to five years. An advisory board established by the MoH known as the Economic Commission negotiates drug prices. Pharmaceuticals outside the positive list may be priced freely [44, 46].

Reimbursement of pharmaceuticals in Poland takes place under two main schemes, both of which are funded by the National Health Fund. The first scheme concerns the pharmacy drugs of the reimbursement list, which can be obtained by patients for up to 50% of the reimbursement limit set by the Ministry of Health. The second covers drug programmes (formerly known as therapeutic programmes) that concern hospital therapies that are free of charge for specific groups of patients, such as those suffering from selected types of cancer, inflammatory diseases or rare diseases. Drugs financed under these programmes are free for patients, but inclusion/exclusion criteria are described in detail and a committee of experts makes decisions on the inclusion of individual patients into the programme. The programme additionally implements a monitoring schedule, which informs whether the patient can stay in the programme according to pre-set criteria. It is the MAH who proposes inclusion in a therapeutic programme that subsequently needs to be approved by the MoH [47]. Currently there are approximately 50 such programmes, some of which include more than one drug, although in some ways they have proved controversial. As a key informant stated, the therapeutic programmes are not intended to make ODs and other expensive drugs widely available, but, rather, to restrict access to patients who are likely to benefit. A key informant also confirmed that in exceptional circumstances ODs may be funded directly through the MoH rather than through the NHF. This is the case for haemophilia treatment for children, but there are no standard implementation rules across all drugs or programmes.

Prior to January 2012, risk-sharing schemes in Poland were mainly informal and confidential. Currently, any scheme that decreases the price or increases patient access to treatment is permissible and the ability to negotiate these is enshrined into legislation, provided that the price be conditional on the sales of a drug, the reimbursement be conditional on the effectiveness and the statutory ex-factory price be conditional on ensuring partial supply of a drug with a rebate and on a partial pay-back of reimbursement [26]. Like most other settings applying risk-sharing agreements, strict confidentiality applies, with most of implemented agreements simply stating that the MAH is providing the product at a lower price. Discounting schemes form the majority of risk-sharing agreements in Poland, the remainder being various forms of payback schemes.

SCOTLAND

The Scottish Medicines Consortium (SMC) assesses all medicines that have obtained marketing authorisation [48]. NHS Boards are responsible for the uptake of new medicines and may use SMC appraisals as guidance, but are not obliged to follow its recommendations. Until 2012 medicines designated as "unique" by the SMC, meaning no other therapeutic options were available, were introduced into NHS Scotland under national programmes [49, 50]. This special arrangement was removed in 2012 as it was only invoked on one occasion since 2002, which was since annulled [51].

SMC applies the same procedure for ODs as for other drugs, but also recognises that less data on efficacy and safety may be available from clinical trials. In return, more detail may be required for other areas, for instance in the selection of particular surrogate markers or quality of life [52]. Though the SMC appraisal is intended to assess value for money based on a rigorous examination of clinical and cost-effectiveness, more flexibility in the decision making may be allowed in some specific circumstances. First, more uncertainty around the economic appraisal of a medicine may be accepted, and other modifying factors may be considered (life-threatening disease, increase in life expectancy and/or quality of life). Second, a higher than usual cost-per-QALY may be accepted under certain circumstances. The SMC does not have a fixed threshold under which treatments are considered cost-effective, but may accept a higher than £30,000 cost-per-QALY threshold for new medicines if some criteria are met, including, but not limited to, evidence of substantial improvement in life expectancy (median gain of 3 months) or quality of life, ability to treat subgroups with higher benefit and absence of other therapeutic options [53].

Discounts, free doses and outcome-guarantee PAS have been so far implemented in Scotland. In many cases, but not all, the same PAS will be in place across the UK [26]. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland, reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation [54].

For drugs that are not recommended by SMC or not yet appraised, patients can make an Individual Patient Treatment Request (IPTR) through their NHS Board to gain access to the drug. The Chief Medical Officer for Scotland has outlined that IPTRs should not be used as a way to circumvent established assessment procedures. IPTRs could be considered when a clinician believes that a delay in treatment is putting the patient's condition under threat [55]. As a key informant highlighted, there is also some use of non-formulary medicines across NHS Boards without having to resort to IPTR. These are for level 1 non-formulary medicines that precede the SMC or NHS-Healthcare Improvement Scotland advice, or medicines not recommended by SMC, usually prescribed in very low quantities at low cost. They are monitored by local Prescribing Advisors who discuss their level of use with the practice during routine exchanges. All non-formulary and IPTR prescribing costs are met by the NHS Board medicines budget [55].

A medicines review published in May 2013 considered every aspect of the introduction of new medicines from national advice to local decision making to establish whether any improvements could be made [56, 57]. One of the recommendations was that SMC should develop a policy specifically relating to ultra-orphan medicines to guide the process of considering all available evidence relevant to its advice on these medicines. An interim recommendation from the review has already been introduced, notably a £21 million fund for ultra-orphan medicines. Finally, following the UK Strategy for Rare Diseases [29], an Implementation Plan is currently being developed in Scotland in order to improve services for people suffering from RDs and their families [58].

SPAIN

Regional HTA bodies in Spain are coordinated under the National Network of HTA Agencies and Units (AUnETS), having previously collaborated in an informal and voluntary network with annual meetings [59]. This new national HTA network includes the HTA bodies at state and regional level. Although official legislation sets forth the criteria based on which new drugs will be assessed, including cost-effectiveness criteria, budget restrictions, reference pricing and value-based pricing [60], the use of cost-effectiveness is non-existent in the current setting and there is no clarity on the method of implementation and whether it should be based on QALYs or use an explicit threshold. The regulator negotiates prices with the manufacturer based on these criteria and external reference pricing with European countries, a system which will be supplemented by HTA evidence provided by regional agencies in the future.

Regional HTA agencies have traditionally produced assessment reports on drugs to support and, frequently, to limit appraisals made centrally by the Spanish Medicines Agency (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) in their respective regions. Some regions have "regional drug bulletin centres" which further evaluate medicines after AEMPS as an instrument for rational use of medicines. This is done against the current standard of care to assess the incremental value of the therapy. If there is no added value, the drug is not recommended for use.

Key informants from Spain mentioned that in the current system of pharmaceutical pricing and reimbursement the criteria applied include severity of illness, usefulness of the medicine, patient need, overall cost, existence of therapeutic alternatives and degree of innovation, although the latter criterion is vague and not quantified.

The reimbursement of prescribed medicines for NHS patients is the responsibility of regional governments. The reimbursement rate of most prescription outpatient medicines is 50-60% if prescribed by an NHS doctor, but may be as high as 90% for chronic or severe diseases. For vulnerable population groups the reimbursement rate is 100% [61]. One key informant confirmed that normally ODs are administered in inpatient settings and are, therefore, reimbursed 100%.

In Spain MEAs are implemented at regional level, usually as a PVA scheme; additional risk-sharing agreements can be implemented at individual hospital level and can be PVA and, exceptionally, pay-for-performance schemes. The expected number of units sold affects negotiated prices. Pharmacy directors in hospitals are those who decide how to manage the available budget; some choose to engage in confidential agreements, while others make information publicly available [26].

SWEDEN

The Dental and Pharmaceutical Benefits Agency (Tandvårds- och Läkemedelsförmånsverket, TLV) grants reimbursement based on three criteria: cost-effectiveness, the human value principle (all human beings are of equal value), and the need and solidarity principle (resources should be first utilised where the need is greatest). Cost-effectiveness is established based on the submitted price and reimbursement is either granted unconditionally, or granted with requirements for evidence generation including for specific subgroups, or rejected [62 - 64].

Sweden uses the same criteria for rare and non-rare diseases. During the first years of TLV's operation (2002 - 2005), several ODs were approved for unconditional reimbursement despite weak cost-effectiveness data, showing a propensity to accept lower levels of evidence for ODs where limited budget impact was expected [65]. An analysis of all TLV decisions between 2002 and 2007 suggests a positive correlation between severity of disease and willingness to pay, with costs-per-QALY in the region of €100,000 accepted for more severe conditions as compared with an average of €35,000/QALY [66]. It is, however, important to note that rarity per se does not have an influence on the willingness to pay. The human value principle implies equality of all people, while the principles of need and solidarity imply that conditions for which there is a greater need take precedence over others. In practice this means a higher cost-effectiveness threshold may be considered for ODs [16].

As per current arrangements, TLV acts as a regulatory body for drugs consumed on an out-patient basis. For in-patient drugs, alternative arrangements apply and the county councils play a significant role. At regional level, county councils are free to purchase and provide whichever drugs they deem appropriate for their populations in addition to those they are recommended to provide based on TLV's decisions. All drugs are financed from the county council budget. The Association of county councils (Sveriges Kommuner og Landsting, SKL) has a special board for New Drug Therapies (Nya Läkemedelsterapier, NLT) which assesses and makes recommendations on drugs not recommended by TLV, which county councils are free to implement or not [67].

Most MEAs in Sweden are part of a conditional reimbursement scheme, which means that reimbursement is granted with restrictions on the indication or the patient sub-group. In certain cases TLV may request manufacturers to provide additional clinical and cost-effectiveness data in order to obtain definitive coverage after the initial period of conditional coverage. TLV focuses mostly on cost-effectiveness and real-life use including compliance, but some agreements also look at long-term effects

on morbidity and mortality [26]. Other MEA types include discounting and pay-for-performance schemes (or a combination of these) and in recent years such schemes have been concluded at county council level.

During an ongoing enquiry on the Swedish pricing system, an extensive ethical discussion on ODs was undertaken. The enquiry did not lead to an official position on the issue, but this is expected in the next report due in 2014 [68]. The existing legislation is almost ten years old and does not mention ODs. As a result, without legislative support it is difficult to use different criteria for ODs.

DISCUSSION

There is considerable variation in the general methodology of value assessment as well as the way this applies to ODs across countries. In some cases prices are based on added clinical benefit, which is the case in France (ASMR rating) and indirectly in Germany, where pricing is free, but reimbursement is determined by the level of added benefit. By contrast in Sweden, a broad societal perspective is adopted when performing economic evaluations. England and Scotland apply a narrower approach to cost effectiveness and consider benefits and costs to health and, if applicable, social care. In Sweden, Scotland and England, the value assessment and, consequently, the price of a new therapy is an integrated consideration over the costs and benefits viewed as a whole. Poland and England are the only countries that use an explicit cost-effectiveness threshold, which is based on a multiple of the GDP per capita and a range between £20,000-£30,000/QALY respectively. In Sweden, a 'derived' WTP threshold has been identified through meta-analysis and stands at €100,000/QALY. In Sweden, Spain and Italy, the devolved healthcare systems leave less of a role for HTA, though this is beginning to change or is likely to change in the future with new legislation. Finally, national regulatory/HTA bodies may have partial competence over the totality of drugs consumed in the country (e.g. TLV in Sweden is responsible for out-patient drugs mostly).

In England there are no specific policies for RDs or ODs, although a UK-wide new strategy has been launched recently, triggering debate and reaction in England and Scotland. According to ongoing reforms, NICE in England will handle the appraisal of drugs and the NHS Commissioning Board will handle the appraisal of services. For drugs that are not reimbursed, patients have the option of an Independent Funding Request. France is currently in the process of implementing a new therapeutic index rating using some criteria particularly relevant to ODs. Existing policies like the Authorisation for Temporary Use, Temporary Treatment Protocols and fast-track HTA procedures also help in making new technologies available with no delay. Despite the absence of a specific RD policy, Germany has implemented some criteria for HTA which apply to ODs: higher p-values for small sample sizes; use of surrogate endpoints; and additional benefit considered proven at MA if the budget impact does not exceed the €50 million per year. In Italy, the first National Health Care Plan for Rare Diseases is currently under development. Half of the fund "Fondo AIFA 5%" is devoted to providing access to ODs before MA and additional policies exist that help patients access ODs (fast-track mechanisms and single patient access to specific drugs). Though there are no specific HTA measures for ODs in Poland, the therapeutic programmes provide access to expensive medicines (including ODs) and there is also the option of direct funding through the MoH. In Scotland, the SMC applies the same procedure for ODs as it does for all other drugs, although it accepts lower levels of evidence from clinical trials, as well as more uncertainty in economic evaluations. Other policies relevant to ODs include Individual Patient Treatment Requests, a specific non-formulary process and higher cost-per-QALY. There is no OD policy implemented in Spain, but pricing and reimbursement takes into account, among other things, severity of indication, needs of patient groups and therapeutic options. Finally, in Sweden TLV is flexible and accepts a higher willingness-to-pay threshold for treatments for severe conditions. County Councils can decide to reimburse drugs independently of TLV.

Risk-sharing or MEAs, whether financial, outcomes-based or a combination, are frequently used in England, France, Italy, Poland, Scotland and Sweden and in order to address uncertainties about the clinical value and the high cost of medicines including ODs. The outcome of risk sharing is greater certainty for the health system, for example, based on pay-for-performance or a lower price for an expensive drug through a confidential discount or conditional reimbursement through additional data generation.

The above leave little room for a common approach to the value assessment of ODs. The question is if individual country value assessment methods offer flexibility to the appraisal of ODs, or if the countries have set up specific policies to enable patients to gain access to these drugs. Indeed, most study countries have some mechanisms in place to increase access to ODs. Some countries recognise the limited evidence available for ODs and accept lower statistical significance of clinical benefits. This is the case of Germany and Scotland, where lower levels of evidence are accepted for clinical trials. Scotland accepts lower thresholds on efficacy and safety evidence, but other areas may require additional information, such as surrogate markers and quality of life data. Germany also considers the drug's additional benefit proven at MA if the budget impact is less than €50 million per year and France has a similar budget impact threshold of €30 million. Sweden does not have an explicit policy for ODs, but, according to a key informant, tends to be "pragmatic" in their approach, usually accepting a higher ICER for orphan drugs than for non-orphans and a greater degree of uncertainty for diseases with fewer patients.

In what concerns the threshold of £20,000-£30,000 per QALY in England, a closer examination suggests that this may not be rigidly adhered to for orphan and cancer treatments. In some cases, drugs with base case ICERs up to £59,000 per QALY were recommended even if the drug was considered not to be cost-effective, although this suggests that, for some medicines, greater weight is

placed on other factors (patient need, ethics and lack of alternative treatments), like in the case of sunitinib for advanced renal cancer [1]. England has no explicit remit for ODs unless it is for cancer indications; cancer drugs have a prioritisation in the selection process. Even in the case of being rejected by NICE, these drugs have still the chance to be included in the list of the NHS Cancer Drugs Fund (CDF) [69], which provides an additional £200 million per year to help cancer patients accessing treatments that are not routinely funded by the NHS. It also takes into account Individual CDF Requests (ICDFRs) for drugs that treat rarer types of cancers, including those affecting children. The creation of the fund was justified on the basis that: ". . .it is possible that society values health benefits to patients with cancer more highly, all else being equal, than benefits to patients suffering from other conditions" [70].

Two other countries, Scotland and Italy, have specific provisions for the funding of orphan drugs; in the former, a £21 million fund has been made available for the funding of ultra-orphan drugs whereas, in the latter, the "Fondo AIFA 5%" aims at facilitating access to ODs, in general [71].

Other regulatory mechanisms are not specifically intended for ODs, but may be well suited to facilitate patient access nonetheless. This is the case for Authorisations for Temporary Use (ATU), Temporary Treatment Protocols and fast-track HTA assessment in France. ATUs are considered for severe diseases with no treatment alternatives, while fast-track assessment is considered for drugs that are innovative, cover unmet need and have demonstrated efficacy and safety. Seventy two percent of ODs with a MA have been administered to patients via an ATU, 34 months on average before the MA [72].

When ODs do not receive a positive value assessment from national agencies, there are still a number of options for patients. Some countries consider individual patient requests, such as the Individual Funding Request in England and the Individual Patient Treatment Request in Scotland. The legal framework in Italy provides access to innovative treatments for conditions where no alternative therapy is available. However, these are tools that apply in exceptional circumstances, rather than for systematically gaining access to a medicine for a group of patients with a rare disease. In addition to the above, risk sharing and managed entry schemes are increasingly implemented across the surveyed countries. In circumstances where there is significant uncertainty about the therapeutic benefit and the cost of the treatment, a variety of managed entry schemes are found to be implemented, ranging from pure discounting schemes to conditional coverage and pay-for-performance.

CONCLUSIONS

Though there are certain similarities across countries with regards to the Health Technology Assessment and reimbursement of ODs, significant differences exist, which are likely to continue to cause variations in access to ODs across EU MS. Although special considerations seem to be in place in most of the study countries, in principle enabling access to ODs, it is likely that there are equity implications within the EU as citizens may be treated differently across countries; some countries place ODs rapidly on the market after MA is granted, others are considering faster access prior to MA being granted, whereas in other cases access is slower. An important implication that emerges from this study is that conventional HTA probably fails to address the precise specificities of and requirements posed by ODs and in so doing forces countries that use it to apply special considerations, often on an ad hoc basis, enabling their coverage by health insurance. Future research should attempt to quantify these special considerations and include them explicitly in value assessment methodologies. Future research should also explore ways of approximating structures for OD coverage, access and, potentially, procurement across EU member states.

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