

Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries

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EXECUTIVE SUMMARY

OBJECTIVES

This study compares the pricing and reimbursement (P&R) arrangements implemented in selected EU countries to make coverage decisions on orphan medicinal products (OMPs) and investigates whether these measures have had an impact on their availability.

METHODS

We collected evidence on P&R systems and specific OMPs policies in France, Germany, Italy, Spain, Sweden, the Netherlands and the UK (differentiating where relevant between constituent countries) through a literature review and a consultation of national experts.

We also collected data on coverage decisions on the first 43 OMPs approved by the European Medicines Agency (EMA) in the first eight years of the Orphan Drug Legislation, which has been in force since 2000. Data sources for this analysis included an IMS database, health care bodies' websites and a consultation of national experts.

RESULTS

Criteria informing coverage decisions vary substantially across countries. However, the most recurrent factors deemed important when making decisions on OMPs were the severity of the illness and the lack of an adequate alternative treatment. The main concerns among decision-makers were around the limited evidence base available for OMPs at the time of their evaluation and the high cost per patient associated with OMPs.

We found that in six of the selected countries, the large majority (or all) of the EMA-designated OMPs were considered eligible for reimbursement or prescribed within the National Health System (NHS). In countries where a formal health technology assessment (HTA) process is in place, OMP

1. The authors are grateful to Phill O'Neil and Qing Wang for their contribution to the data collection.

deliberations were varied. Within the UK, a large proportion of the Scottish HTA body's decisions were either rejections (46%) or involved some restricted use (11%) i.e. recommended for use only in some subgroups of the licensed population. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) has to date appraised only one OMP, which was recommended in both its indications.

Sweden is the country with the highest rate of rejection where almost 30% of the OMPs launched in the country were not reimbursed.

Specific policies for the implementation of post-launch studies for OMPs were identified in all countries but Germany. However, Italy and the Netherlands were particularly active in adopting innovative schemes to allow early access and evidence generation in real-world settings.

DISCUSSION

With an increasing demand for HTA by health care decision makers, OMP manufacturers will have to provide an expanded evidence package to show the value for money of their products. This might be problematic given the high level of uncertainty around clinical evidence of OMPs, particularly near the time of launch. As more OMPs will obtain regulatory approval on an accelerated or conditional licensing basis by licensing bodies such as the EMEA, this issue is likely to exacerbate. Also, additional pressures on national health care budgets will present a challenge in terms of the affordability of these drugs in the medium to long term.

Given the low and patchy distribution of rare diseases across regions/countries, more cooperation at the European and international level is required to develop robust evidence. Post-marketing data collection to inform subsequent re-assessment can represent the way forward to address uncertainty and knowledge gaps.

1 Introduction

1.1 Context

It is estimated that there are between 5,000 and 8,000 distinct rare diseases today, affecting between 6% and 8% of the population in total (between 27 and 36 million people in the EU, approximately) (DG for Health and Consumers, 2008).

Products targeting more prevalent diseases provide a greater reward for firms' research and development

(R&D) investment than products intended for small populations. This issue, coupled with the fact that patients with rare diseases have fewer, if any, medications available for their conditions, led the European Commission to set up a package of economic incentives for the research, development and marketing of orphan medicinal products (OMPs) which would not be developed under normal market conditions.

The EU OMP regulation (Regulation (CE) N°141/2000) combines a 'pull' incentive of increasing the effective size of the market (i.e. market exclusivity for 10 years during which similar products targeting the same indication cannot be approved) with some 'push' incentives aimed at reducing costs (i.e. fees reduction, protocol assistance, possibility for a single, EU-wide marketing authorisation and eligibility for research grants). In the US, where the Orphan Drug Act was introduced in 1983, prior to the EU regulation, evidence suggests that the provision of market exclusivity (the pull element) has been the key incentive for firms to invest in R&D for rare diseases (Peabody et al., 1995; Grabowski, 2005). Indeed, the EU OMP legislation was inspired by the US regulation.

In Europe, where the market is more segmented than in the US, the role of the market exclusivity incentive has not been assessed. However, it is true that, as in the case of other non-orphan medicines, EU market approval represents a necessary but not sufficient condition for the widespread and consistent use of these new products. As individual Member States remain responsible for funding and running their national health care systems, they can adopt different approaches to the provision of OMPs and the management of rare diseases within their boundaries.

The high prices generally associated with treatments for rare diseases have made it challenging for payers to make new OMPs available within their health care systems. They have to make sure that aggregate benefits generated by these interventions are large enough to justify their costs. From an efficiency perspective, the issue is around the opportunity cost of funding these treatments (i.e. what are the health benefits foregone in other disease areas as a result of providing these treatments?). From an equity perspective, there are concerns related to how these health benefits are distributed and the extent to which particular disease areas deserve special considerations because of their characteristics, such as seriousness and lack of effective treatment (it may be argued that it is unfair to deny access to new treatments to patients affected with rare diseases with no alternative therapy).

The UK policy on OMPs provides some useful insights that highlight these issues. The policy debate in this country has focused on the question as to whether health technology assessment (HTA) adopted by bodies such as the National Institute for Health and Clinical Excellence (NICE) should be used for coverage decisions for OMPs. McCabe and colleagues (2005) argue that payers should not pay a premium price for rarity, and therefore should not provide treatments for rare diseases that fail to meet the requirements for evidence-based cost effectiveness. Others are less prescriptive. Hughes (2006) argues that decisions on the provision of expensive treatments should be based not only on clinical and cost effectiveness but also on principles of equity. The final judgement as to what is equitable should be established by taxpayers. Drummond and colleagues (2007) reinforce the idea that cost effectiveness should not be the only criterion informing health care decision-making as there may be circumstances under which it does not reflect society's preferences.

The purpose of this study is to investigate what criteria drive individual EU Member States' decisions on OMPs, and to see whether these criteria are in line with the incentives created at the EU level to encourage R&D for rare diseases. In other words, whether health care policies established at the national level may restrict the access to orphan-designated medicines and thus limit the value of the market triggered by the EU OMPs regulation

1.2 The EU Regulation and the OMPs Landscape

In order to be granted orphan status, a product has to meet the following criteria: severity (i.e. they are for life-threatening or chronically debilitating conditions) and unmet need (i.e. they are for conditions for which no satisfactory method of diagnosis, prevention or treatment is authorised or, if such method exists, the product will be of significant benefit). In addition, products have to meet either the prevalence criterion (i.e. the target condition affects no more than five in 10,000 people in EU) or the financial return criterion (the expected product sales do not cover the initial investment associated with its development) (EMA, 2007). The latter has been a rarely invoked alternative basis for awarding orphan status.

Orphan designations have been granted to products targeting a variety of conditions, including cancer, metabolic disorders, immunology, cardiovascular diseases and respiratory disorders. To date, more than 40 interventions designated orphan status by the European Medicines Agency (EMA) have reached the market. Appendix 1 provides a complete list of those products as at March 2008.

It is worth noting that for seven conditions, more than one product have been orphan-designated and reached the market. Acute lymphoblastic leukaemia, chronic myeloid leukaemia, Fabry disease, malignant gastrointestinal stromal tumours, renal cell carcinoma have two products, and pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension have three products. Another, Alpha-Galactosidase A, was marketed by two distinct manufacturers. Also, one medicine, imatinib, has been approved for two orphan indications (treatment of malignant gastrointestinal stromal tumours and chronic myeloid leukaemia). This reflects a trend observed also in the United States, where a study published in 1997 reported that 15 drugs were approved for more than one orphan indication (Shulman and Manocchia, 1997). An earlier study discusses cases where either two different drugs obtain approval to target the same condition or the same drug is marketed for the same condition by two different sponsors (Peabody et al., 1995). This clearly indicates that although OMPs regulation provides some market exclusivity protection to first-in-class products, the possibility that "clinical superior" drugs can obtain approval has led to some form of limited (or controlled) competition within orphan disease indications. In other words, the market of OMPs to some extent mimics features of the market for treatments for more prevalent diseases.

1.3 Objective and Methodology of the Study

This paper analyses and compares current P&R arrangements for OMPs in seven EU Member States: France, Germany, Italy, Spain, Sweden, the Netherlands and the UK. Within the UK, and as highlighted later, we describe the situation in England and Wales on the one hand and the different situation in Scotland on the other. In particular, we explore whether OMPs are treated differently from other drugs, and if so, how. The choice of countries is driven by a number of factors. France, Germany, Italy, Spain and the UK represent the five largest markets in Europe and different approaches for decision making are in place in these countries. Sweden provides an example of an HTA-driven country, while the Netherlands has had a significant involvement in the OMPs policy arena.

To support our qualitative analysis, we extracted and examined evidence on decisions about reimbursement, listing and prescribing of OMPs within the health systems of the seven EU countries considered. The set of OMPs included medicines which were designated as orphans by the EMA and obtained marketing authorisation in Europe between January 2000 and March 2008 (see Appendix 1 for the complete list).

The qualitative analysis of P&R arrangements was informed by the following sources: a structured workshop (organised by OHE²) where speakers directly involved in health care decision making in selected EU countries addressed a list of questions, outlined in Appendix 3; and a search of published literature including grey literature (this included manual searches in Scrip and Pharma Pricing & Reimbursement, and original language policy documents available on health bodies' websites).

For each country, we collected evidence on: specific national institutions/committees dealing with OMPs; the types of evidence considered to determine the price and/or the reimbursement status of OMPs; and criteria underpinning P&R decisions. The main findings were combined into overarching themes in order to derive some policy recommendations.

We used the IMS Lifecycle Database to collect data on product launches in each country. Data on HTA bodies and other health care bodies' decisions were extracted from their websites; if information on reimbursement decisions was not available in the public domain, we consulted health care bodies or national experts.

The Briefing is structured as follows. Section 2 provides a country-by-country description of national P&R practices and specific arrangements for funding OMPs and the management of rare diseases. Section 3 compares access mechanisms for OMPs in the selected countries identifying their key characteristics, which are summarised in Table 4 at the end of the section, and presents the evidence on OMPs coverage decisions. Section 4 provides a summary of the issues raised and draws some policy recommendations.

2 Pricing and Reimbursement (P&R) Systems of Selected EU Member States³

2.1 France

In France the introduction of new medicines into the national health care system takes place in two steps. In the first, the Transparency Committee, a scientific committee of the High Authority for Health (*Haute Autorité de Santé - HAS*), assesses the medical value (*Service Médical Rendu - SMR*) and the incremental medical value (*Amélioration du Service Médical*

Rendu - ASMR) for each medicine. On this basis the Transparency Committee develops an opinion which is passed onto the HAS. In the second step, the Economic Committee for Healthcare Products (*Comité Economique des Produits de Santé - CEPS*) determines and negotiates the price of the new drug with the manufacturer.

There are three possible SMR levels: 'major', 'moderate' or 'insufficient'. It is usually 'efficacy' and 'disease severity' that determine the medicine's SMR classification. Normally, the cost of the drug is not considered in determining reimbursement status (Sorenson et al., 2008). There is a link between the product's SMR classification and the degree of co-payment borne by the patient, which ranges from 35% to 65% of its retail price.

The ASMR criterion is based on the degree of innovation of a new medicine relative to the existing treatments. There are five ASMR grades, ranging from 'Major' to 'No improvement'.

The ASMR rating is based on comparative studies of the reference product, although indirect comparisons are allowed. Pharmacoeconomics can influence decision-making but it is not an official criterion. Although there is no requirement for companies to submit any pharmacoeconomic evidence, it is expected that the role of economic evaluations will increase in the near future. HAS's remit has recently been expanded to include the provision of information "on the potential efficiency and economic consequences of a diagnostic or therapeutic procedure or of a public health initiative" to health authorities (HAS, 2008).

The CEPS negotiates the price with companies and regulates drug expenditures. Factors taken into account by CEPS for price setting include the ASMR level and the product's market size. This put manufacturers of OMPs in a relatively strong position when negotiating the price with CEPS, given the low volumes generally associated with these drugs.

There are no special criteria or exemptions formally applied by HAS to assess OMPs. However, it is reported that clinical evidence used for the assessment of the SMR of these medicines relies on data submitted to the EMEA for licensing purposes, hence it reflects all the limitations associated with that. Table 1 shows that in some cases HAS's assessment was only based on the results of Phase II trials and of literature reviews because a Phase III trial had not been conducted.

2. The Office of Health Economics organised and hosted the workshop "Accommodating orphan drugs: balancing innovation and financial stability" on 25th February 2008. Presenters included: François Meyer (Haute Autorité de Santé, France); Pietro Folino Gallo (Agenzia Italiana del Farmaco, Italy); Dr. Joakim Ramsberg, (former Läkemedelsförmånsnämnden (LFN), now called TLV, Tandvårds- och läkemedelsförmånsverket, Sweden); Dr. Sonja van Weely (Steering Committee on Orphan Drugs, the Netherlands); Martina Garau and Deven Chauhan (Office of Health Economics, UK); Professor Mike Drummond (University of York).

3. For more detailed information on most of the countries, see Garau and Mestre-Ferrandiz (2006).

Table 1: Number and type of studies included in manufacturers' dossiers for OMPs

	Bibliographic	Cohort studies	Phase II studies	Phase III studies (placebo as comparator)	Phase III studies (active drug as comparator)
Product A	3	1	1	-	-
Product B	3	-	4	2	-
Product C	3	1	-	-	-
Product D	3	1	1	1	-
Product E	3	-	1	-	-
Product F	3	-	3	1	-
Product G	3	-	-	2	-
Product H	3	-	-	1	-

Source: Adapted from a HAS slide presented at the OHE workshop

In France there are a number of fast-track procedures to ensure timely access of new treatments. They include:

- Authorisations for Temporary Use (ATUs), which provide access to drugs (either for compassionate use or reimbursement) prior to their marketing authorisation when the disease is severe and there is no alternative intervention available. ATUs are granted by the HAS;
- Temporary Treatment Protocols (TTP), which are implemented as extensions of licensed indications of medicines or devices. Also in this case, HAS can decide to reimburse a new treatment before marketing authorisation and the standard assessment process;
- Other fast-track procedures for products deemed "a priori innovative", which allow HAS to start the assessment of new medicines earlier, before they are launched on the market, thereby accelerating HAS's decision making process.

Although these schemes are not specific to OMPs, it is likely that many OMPs have met the requirements and have been made available through these channels.

More generally, there has been a strong political commitment to rare conditions in France, which has led to the development and adoption of a "National Plan for Rare Diseases" (French National Plan for Rare Diseases 2005 – 2008). When introduced in 2005, it was the only example in Europe of a plan providing a comprehensive national approach to address different aspects and issues related to the treatment and management of rare diseases in a national health care system. Its main goal is "to ensure equity in the access to diagnosis, to treatment and to provision of care for people suffering from a rare disease through ten strategic priorities:

- Increase knowledge of the epidemiology of rare diseases
- Recognise the specificity of rare diseases
- Develop information for patients, health professionals and the general public concerning rare diseases
- Train professionals to better identify them
- Organise screening and access to diagnostic tests
- Improve access to treatment and the quality of healthcare provision for patients
- Continue efforts in favour of orphan drugs
- Respond to the specific needs of accompaniment of people suffering from rare diseases and develop support for patients' associations
- Promote research and innovation on rare diseases, notably for treatments
- Develop national and European partnerships in the domain of rare diseases".

The French National Plan set a benchmark for other countries. Indeed, several plans in the process of being introduced in other European countries have been inspired by the French Plan.

2.1.1 Summary

Overall, it seems that there is a favourable environment for OMPs in France. As far as P&R negotiations are concerned, although no special exemptions are in place for OMPs, manufacturers have been in a relatively strong position given the characteristics of these products. However, HAS's new remit of considering economic evaluations when assessing the ASMR of new products may represent a new challenge in terms of demonstrating the value of OMPs.

2.2 Germany

In Germany, medicines are automatically reimbursed after marketing authorisation, with the exception of products for minor illnesses and the so-called 'lifestyle' drugs.

The degree of reimbursement is defined by a reference price system, which was first introduced in 1989. On-patent drugs have to exhibit significant additional therapeutic benefits or fewer serious side effects than comparable medicines in order to be excluded from the reference price system. There are three reference price groups: products with the same active ingredient (group 1), products with therapeutically and pharmacologically similar active ingredients (group 2) and compounds with comparable therapeutic effects (group 3).

Given the nature of most OMPs, it is unlikely that they fall into any of these groups and are therefore generally granted reimbursement status with no price limit.

No formal pharmacoeconomic evaluation is required to set reference prices. However, the 2004 health care reform saw the formation of the Institute for Quality and Economic Efficiency in Health Services (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen - IQWiG*), which is responsible for assessing the costs and benefits of pharmaceuticals and providing treatment clinical guidelines for certain diseases. The decisive body, the Joint Federal Committee (*Gemeinsamer Bundesausschuss - G-BA*), which consists of representatives of Social Health Insurers (*Krankenkassen - SHI*) and Accredited Office-based Physicians, makes decisions based on the Institute's recommendations on therapeutic guidelines, limitations of and/or exclusions from reimbursement of medicines.

Since April 2007, German law has stipulated that one of IQWiG's tasks is to conduct evaluations of cost-benefit ratio of pharmaceuticals which are not included in the reference price system based on their demonstrated therapeutic improvements. In January 2008, IQWiG issued a draft of its 'Methods' as a result of a consultation process with an international Expert Panel (IQWiG, 2008). This paper mainly focuses on the concept of an efficiency frontier. To compare costs and benefits in a particular therapy area, the paper argues that a diagram should be constructed with 'costs' on the x-axis and 'value' on the y-axis. The idea is then to plot the existing therapies as points on the graph so that comparisons can be made⁴. In those situations where no alternative therapy exists, the new intervention will be the first point to plot

onto the efficiency frontier graph. This may be particularly relevant to many OMPs given that they target disease areas with hitherto unmet clinical needs.

2.2.1 Summary

Overall, it seems that the German health care system does not treat rare diseases differently from other diseases. OMPs are automatically reimbursed and, because of their characteristics, it is unlikely that they are included in reference price groups. As far as HTA is concerned, according to the current draft of IQWiG methods, the Institute will not conduct economic evaluation when the new medicine has no comparator. Therefore, if there is no alternative therapeutic option, a new OMP will not be assessed by IQWiG. If this is not the case (say, when an old drug for the treatment of the disease in question is available), then IQWiG will conduct a cost benefit analysis accordingly and will formulate a recommendation on the maximum reimbursement price.

2.3 Italy

The main decision making body in the field of pharmaceutical care in Italy is the Italian Pharmaceutical Agency (*Agenzia Italiana del Farmaco - AIFA*) which operates in the following areas: marketing authorisation, pharmacovigilance, pricing and reimbursement, information to health professionals and patients and governance of pharmaceutical expenditure (Folino-Gallo et al., 2008).

There are two committees, the Technical Scientific Committee (CTS) and the Pricing and Reimbursement Committee (CPR) which work together within the same organisation. The remit of the CTS is to examine the dossiers submitted by manufacturers and to provide the CPR with an assessment of the efficacy of the new drug. The CPR, in turn, sets the price of new medicines and chooses their reimbursement class. There are two reimbursement classes in Italy: Class A (fully reimbursed medicines) which include a subclass H (for hospital use only) and Class C (non-reimbursed medicines).

Over the last few years Italian authorities have been using budget ceilings to control pharmaceutical expenditure. Since 2001 a series of changes in the payback mechanism were introduced in order to make the regional authorities as accountable as possible with regard to their deficit. With the latest scheme put in place in 2003, overall pharmaceutical expenditure, including both community and hospital expenses, cannot exceed 16% of regional health care expenditure. Overspending in general practice is refunded by pharmaceutical companies via a payback system whilst in the hospital sector it is

4. For a more detailed analysis of the new methodological guidelines issued by IQWiG see Drummond and Rutten (2008).

refunded by regions, which are responsible for managing pharmaceutical expenditure through a proportional reduction in hospital spending.

There are three channels through which OMPs have been made available in the Italian National Health Service: (i) the standard P&R process; (ii) the Law 648/96; and (iii) the 5% AIFA special fund established in 2005.

Under the 'standard' process, medicines authorised either by the EMEA centralised procedure or the national procedure have to go through the standard assessment of clinical value performed by AIFA. The reimbursement status is defined by AIFA based on the following criteria, which are employed for both OMPs and non-OMPs:

- Whether the new product is indicated for a disease with no alternative or adequate therapy;
- Whether the new product provides a better benefit-risk ratio than existing therapies;
- Whether the new product generates socio-economic benefits, which mainly refers to a lower price relative to the comparator(s).

Most of OMPs fall in class H, which consists of fully reimbursed medicines to be prescribed only in hospitals or specialist centres. Some OMPs are dispensed subject to patients being entered into a national disease registry and data being then collected to record treatment response and clinical outcomes in real world settings.

The second mechanism (Law 648/96) relates to a national law supporting the provision of treatments for conditions that have no valid alternative therapy available (BIF, 2000). The law allows the Italian National Health Service to reimburse medicines for which results of Phase II trials are available and which meet one of the following characteristics: they are authorised in other countries; they are being tested in a Phase III clinical trial; and they are marketed for another therapeutic indication.

The third mechanism (the 5% AIFA fund), which is the only one specific to OMPs, is a contribution paid by pharmaceutical companies to AIFA to be reinvested for the promotion of independent research and access to treatments for rare diseases. According to the regulation, half of the fund should be devoted to providing access to medicines for rare diseases before marketing authorisation. The other half of the

fund should be devoted to promoting independent research and other correlated activities (for example, pharmacovigilance programmes, communication and promotion of appropriate use of available medicines) (Istituto Superiore della Sanita, 2006).

2.3.1 Summary

The Italian National Health Service provides access to licensed OMPs through standard P&R processes, as most of them are fully reimbursed and provided in hospitals. In addition, special mechanisms, including a special fund promoted by AIFA, have been established to make OMPs available prior to marketing authorisation.

2.4 Spain

The Spanish Ministry of Health sets the maximum ex-factory price product by product after a negotiation with the manufacturer. Formally, the price is set according to a cost plus system which states that a drug's price must cover all costs (raw materials, production, administration, promotion, management, research and development, general costs) plus a profit margin. The price must be consistent with the therapeutic utility of the product and with the price of alternative treatments.

The following factors determine whether or not a medicine is reimbursed by the Spanish Ministry of Health (and thus included in the positive list⁵):

- the seriousness, duration and consequences of the various disorders;
- the needs of certain groups;
- the medicine's therapeutic and social utility;
- the limits of public expenditure allocated to pharmaceutical benefits;
- the existence of medicines or other product alternatives for the same conditions;
- the medicine's degree of innovation.

In addition, another criterion included in the same Article of the Law (but not as a listed point) is the price or cost of comparable medicines available in the market.

The 2006 Medicines Act is the latest key piece of legislation in Spain. Among other things it sets out the characteristics of the pricing and reimbursement system in Spain, replacing the 1990 Law. The 2006 Act incorporates for the first time the medicine's degree of innovation as a factor to determine a medicine's reimbursement status. However, in the 2006 Act there

5. The positive list includes all the publicly reimbursed medicines in Spain.

is no discussion as to what factors will be considered when assessing a product's degree of innovation.

The use of health economics is currently not compulsory, but the possibility of the *Agencia Española del Medicamento y Productos Sanitarios* (AEMPS) (the agency responsible for granting marketing authorisations) applying a 'fourth hurdle' to marketing authorisation has been introduced by the new Medicines Act. Overall, pharmacoeconomics currently plays a small role in the Spanish P&R system. There are nevertheless some initiatives at the regional level.

If a new medicine is not available in Spain, either because it has not been licensed in Spain but is available in other countries, or because it is still undergoing clinical studies alternative mechanisms exist. For the former, the medicine could be made available as a '*medicamento extranjero*' (foreign medicine) when authorised by the AEMPS. For the latter, the patient will have access to the medicine either if he or she is enrolled in the clinical trial or if the AEMPS authorises its use via '*uso compasivo*' (compassionate use). These mechanisms are not specific to OMPs although some OMPs have been funded through this route.

One key milestone regarding OMPs in Spain was the introduction of the "*Estrategia Nacional de Enfermedades Raras*" (National Strategy for Rare Diseases) by the Spanish government in January 2008. This strategy aims to encourage R&D in the area of orphan medicines via direct funding for R&D, improving the training and education system of healthcare professionals at all levels of care, and improving access to OMPs. It was inspired by the French National Plan.

Other initiatives in the field of rare diseases have been introduced at the regional level. A report by FEDER (*Federacion Española de Enfermedades Raras*⁶) on inequalities in policies on rare diseases in Spain explores the social and health policies directed towards rare diseases in the regions of Andalusia, Catalonia, Valencia, Extremadura and Madrid (FEDER, 2007). Andalusia and Extremadura were indicated as the regions with the best situation in terms of health policies implemented over the last years. Andalusia was the first region to create an integrated plan of action for rare diseases, developing coordinated assistance for patients suffering from rare diseases in the region. Extremadura announced their regional rare Diseases

Plan in December 2008, although it is not fully operational until January 2009. This strategy will be based on the data that have been collected since 2004 in the regional rare diseases' patient registry. The objective underlying this registry is to analyse the incidence, prevalence, survival and all other aspects related to those patients that have been diagnosed with and/or treated for diseases classified as rare within this region.

2.4.1 Summary

The P&R system does not treat OMPs any differently relative to conventional medicines but the criteria used are likely to result in approval. However, Spanish health authorities have promoted research programmes and supported improvements in the management of rare diseases through the introduction of the National Plan early in 2008. Some regions have been more active than others in the area of rare diseases, which might ultimately lead to differentiated access to orphan drugs in the near future.

2.5 Sweden

The Swedish decision making process is led by an agency that until recently was called the Pharmaceutical Benefits Board (LFN)⁷. The main remit of the LFN is to undertake a centralised review process and to make decisions on reimbursement status of pharmaceuticals (i.e. whether or not they should be included in the positive list). The agency is not involved in price negotiations with manufacturers, which have to provide an application demonstrating that the medicine in question is cost effective at the set price.

The law establishes the criteria which have to be fulfilled for a medicine to be reimbursed. These include the principles of human value, solidarity (those in greatest need take precedence in medical care) and cost-effectiveness (Jansson, 2007).

The review process is product-oriented and its outcomes can be grouped as followings: reimbursement for all indications; limited reimbursement (which restricts the use to subgroups of patients); and rejection.

There are 21 county councils in Sweden, each with a population ranging from around 50,000 to 2 million people. They can levy an income tax in order to finance health care services, including drugs. In principle, they pay for all drugs, both outpatient and inpatient, but in practice it is the central government which funds all reimbursed drugs (i.e. those included

6. FEDER is a not-for-profit organisation created in 1999 representing now more than 140 patient associations in Spain. For more information, please refer to: www.enfermedades-raras.org.

7. At the time of writing the paper the agency changed its name to 'Dental and Pharmaceutical Benefits Agency', with the acronym TLV. We have not considered any modifications in the process that may have occurred as a result of this.

in the positive list by the LFN) via money transfers to the county councils. This system is continuously under review in an attempt to avoid geographic differences in access to health care but also to make the county councils more cost-aware and responsible for their health care expenditure.

In Sweden, there is no specific policy for rare diseases but reimbursement decisions made by the LFN are generally driven by considerations of cost effectiveness, clinical need and solidarity. This approach has a direct effect on reimbursement decisions on OMPs due to their characteristics, particularly the severity of the target condition. The LFN in effect has different cost effectiveness thresholds for different characteristics of disease-linked severity (e.g. symptoms, patient autonomy). A study presented by the LFN in 2008 showed that “for more severe conditions the LFN has accepted costs per quality adjusted life year (QALY) in the area of €90,000” and observed a correlation between disease severity and willingness to pay for a QALY (Hugosson and Engstrom, 2008).

The other element considered in the LFN decision making process which is relevant in the context of OMPs is their overall budget impact. Based on standard HTA methods, greater uncertainty in clinical and cost effectiveness evidence can be accepted when the target population is small, because the cost of making wrong decisions is lower as compared to treatments for more prevalent diseases. Expenditure on OMPs makes up a small proportion of total pharmaceutical expenditure - less than 1% in Sweden. On this basis, LFN tends to accept more a limited evidence base for decisions on OMPs.

2.5.1 Summary

The national HTA body seems to accommodate the use of orphan drugs and reimburses products with a cost effectiveness ratio above the normally accepted level. However, this approach has started to be questioned and criticised (Ramsberg et al., 2004). On the local funding side, a fractionated system is under review in order to avoid an uneven access to treatments.

2.6 The Netherlands

The P&R system in the Netherlands differentiates between extramural (non-hospital) and intramural (hospital) treatments.

The Minister of Health, Welfare and Sport decides whether a medicine for extramural use will be reimbursed, based on the advice given by a committee of the Dutch Health Care Reimbursement Board (*College voor zorgverzekering* - CVZ). This committee assesses the contents of the reimbursement

dossier submitted by the manufacturer, which consists of clinical and pharmacoeconomic evidence and budget impact analysis. Medicines are then classified either as List 1A or List 1B. List 1A contains medicines which are deemed to be interchangeable and are thus subject to direct price controls (i.e. the price of a product on a therapeutic list cannot exceed the average ex-manufacturer price in Belgium, France, Germany and the UK).

Economic evaluation of health care programmes has become increasingly common in the Netherlands. In 1999, the CVZ published guidelines for pharmacoeconomic submissions which recommended the use of a societal perspective, including all associated medical and non-medical costs. Since 2005, pharmacoeconomic studies and budget impact analyses are formally required for reimbursement applications of new drugs to be included in List 1B and which seek a premium price.

In line with a parliamentary motion which invited the government to explicitly support adequate access to treatments for rare diseases, a slightly modified reimbursement procedure has been implemented for OMPs. For reimbursement dossiers of extramural treatments, manufacturers of an OMP can ask the Minister of Health for a dispensation from the submission of pharmacoeconomic evidence. In case of approved dispensation, the manufacturer’s dossier has to provide a budget impact analysis estimating how many patients can be treated and the expected costs of provision in the near future.

For intramural treatments, a new instrument (the diagnosis/treatment combinations - DBCs) for the performance-based costing system for hospital care and for mental health care was introduced in 2005. For rare diseases, if there is no DBC, treatments are provided through hospital budgets or through funding via one of the two policy rules described below.

The so-called ‘policy rule on orphan drugs’ was introduced in 2006 in order to secure provisional funding for new OMPs for three years to university hospitals that are expert centres, conditional on obtaining additional data on the clinical and cost effectiveness of the medicines being assessed. The CVZ is involved in this process as it appraises the available evidence, following the submission of the “value” dossier, and gives advice on the temporary listing. After a maximum of three years, the CVZ re-appraises the evidence that has been collected and on this basis it reviews its decisions on the product listing.

The other important initiative in the field of OMPs has been the establishing of the Steering Committee of

Orphan Drugs in 2001. It was appointed by the Minister of Health as a multidisciplinary committee, consisting of members of patient groups, academia, industry, insurance companies and representatives of the Dutch Medicines Evaluation Board and the CVZ (the registration and reimbursement agencies, respectively). The remit of the Steering Committee on Orphan Drugs is to encourage the research and development of orphan drugs and to improve the management of rare diseases, particularly by creating or improving scientific knowledge.

2.6.1 Summary

In the Netherlands, a number of policy mechanisms specific to OMPs are in place. For reimbursement purposes, similar procedures have to be followed for all medicines, although for OMPs there is a dispensation from submitting cost effectiveness evidence when there is limited data available. Furthermore, expensive OMPs that are used in hospitals may be provisionally listed via a policy rule with the condition of collecting further evidence and having a re-appraisal in no more than three years time.

2.7 The United Kingdom (UK)⁸

Prices of new medicines are not directly controlled at launch in the UK. Companies can fix the price of their new products provided that: any subsequent price increase is first approved by the Department of Health, and the rate of return limits imposed by the Pharmaceutical Price Regulation Scheme (PPRS) agreements are not exceeded. Most of new drugs launched in the UK are automatically reimbursed as they can potentially be prescribed by clinicians and are funded within the National Health Service (NHS).

The National Institute for Health and Clinical Excellence (NICE) produces guidance on the most appropriate use of selected health technologies within the NHS in England and Wales. NICE's recommendations are based on evidence submitted by key stakeholders, e.g. manufacturers and independent assessment centres. In Wales, the All Wales Medicines Strategy Group (AWMSG) "appraises new high cost, cardiac and cancer medicines for which no NICE guidance is expected for at least 12 months" (AWMSG, 2008). Given the relatively small population covered by AWMSG, we do not consider it in the rest of the Briefing.

NICE's decisions are driven by a decision-making principle based on an incremental cost-effectiveness ratio (ICER), with the threshold varying between £20,000 and £30,000 per QALY (NICE, 2008b). Other considerations may play a role, including the

degree of (un)certainty around the ICER and the innovative nature of the technology, both of which are not adequately captured in the QALY measure. NICE emphasises that when the cost effectiveness ratio is above £30,000 per QALY, the case for these additional factors has to be stronger.

Within the NICE process described above, no specific arrangements for OMPs were identified. According to the latest guidance on Social Value Judgements, the Institute's current position is that OMPs should be treated in the same way as medicines for more prevalent diseases, so standard HTA methods can be applied to assess and appraise OMPs (NICE, 2008a). However, its Methods Guide specifies that, although the potential budget impact is not one of the factors determining NICE's decisions, the larger the impact on NHS resources, the more robust will be the evidence base required (NICE, 2008b). Since OMPs target small populations and therefore have a relatively small budget impact, NICE should in principle accept higher uncertainty around the clinical and cost effectiveness evidence of these treatments as compared to those for more common diseases.

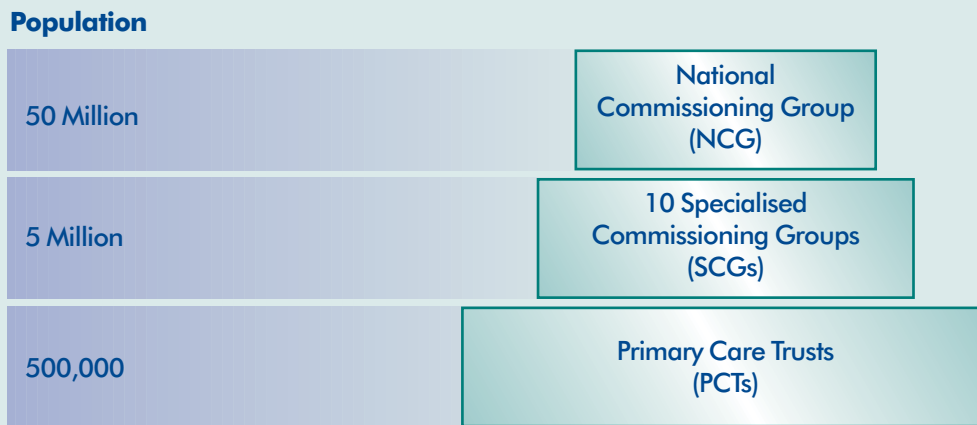
NICE has recently issued supplementary advice which recognises the need to give special weight to life-extending treatments licensed for terminal illnesses affecting small populations when deciding whether or not they should be made available within the NHS (NICE, 2009). The document provides a number of criteria used to identify cases in which new medicines with an ICER exceeding the threshold of £30,000 per QALY can be recommended for use. The advice will apply to treatments for rare diseases which result in improved survival, hence excluding a number of OMPs for chronic and long term conditions. It will also not cover medicines for very rare conditions - the so-called 'ultra-orphans' - instead targeting diseases with a prevalence of less than one in 50,000. These are dealt by the National Commissioning Group (NCG), as explained later in this section. The document indicates that a treatment approved according to this advice should undergo a programme of data collection on outcomes achieved in practice, which can then be used to inform a successive NICE guidance review.

In Scotland, the Scottish Medicines Consortium (SMC) has a role similar to NICE, although a different process is in place whereby all new medicines are assessed.

The SMC adopts the same assessment process for OMPs, although it recognises that it may be more

8. At the time of writing this report, the UK was going through a change in pharmaceutical pricing and reimbursement policy, by means of negotiations between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI). We have not considered here any changes that might occur as a result of these negotiations.

Figure 1: Levels of commissioning in England



Source: Adapted from a figure on the Department of Health website

difficult to have well-developed trials in the context of rare diseases. The cost per QALY still matters but some additional factors ('modifiers') may be taken into account. These include "whether the drug treats a life threatening disease; it substantially increases life expectancy and/or quality of life; it can reverse, rather than stabilise, the condition; or bridges a gap to a 'definitive' therapy" (SMC, 2007a).

With regard to the commissioning processes, there are many challenges related to local decision-making. One of those comes from the geographical concentration of rare diseases with a genetic component which can lead to uneven distribution of financial burden among primary care organisations. The responsibility for decision-making around the commissioning for rare conditions is distributed across different bodies, although responsibility of funding ultimately lies with primary care organisations. England, Scotland and Wales have developed specific funding mechanisms individually. They are broadly similar and we focus on the arrangements in England for illustrative purposes⁹.

As shown in Figure 1, at the top level there is the National Commissioning Group (NCG) which oversees the commissioning of health care services for very rare diseases with an incidence of less than 400 cases. NCG operates across the whole country for a population of 50 million. At the next level, there are ten regionally based Specialised Commissioning Groups (SCGs), each responsible for a population of five million, followed by the Primary Care Trusts (PCTs) with a population load of 500,000 each.

Specialised services are usually referred to the NCG for assessment by clinicians if they appear to be receiving referrals from geographical areas outside their usual 'expected areas'. The NCG evaluates the application received from the clinician, mainly based on clinical desirability. Although there is an implicit examination of costs associated with services, cost-effectiveness or opportunity costs are not criteria formally used to reach decisions. This is often criticised by fund-holding PCTs, as it seems that these specialised services are protected from the more rigorous assessments that other health technologies have to undergo (such as the NICE process).

When making local purchasing decisions, PCTs take into account national guidance, including NICE guidance (which has to be implemented within three months of publication), and health policy directives from the Department of Health.

There are circumstances where a new drug has not been evaluated by NICE or has been rejected for use in the NHS, and has not been referred to either the SCGs or the NCG. In these cases, individual clinicians have to request funding on a case-by-case basis directly from PCTs. PCTs treat each request as a special case and can approve the funding provisions based on the so-called "exceptional circumstances". The process is very resource-intensive, as it involves panel decisions from a number of clinicians and managers and does not ensure consistency across different areas of the country.

9. For a description of different funding arrangements in the UK see Moberly (2007).

2.7.1 Summary

In the UK, OMPs reviewed by HTA bodies have to go through the same process as treatments for more prevalent diseases. Although the incremental cost per QALY remains one of the main drivers of decision-making, the recent supplementary advice allows NICE to attach greater weight to QALYs achieved by terminally ill patients when the treatment is for small populations and shows an extension to life. This will have an impact on the approval of treatment for rare cancers but will have no effect on other OMPs, such as those for chronic conditions which do not occur at the end of life.

At the local level, PCTs have to take account of NICE's guidance, if available, when making funding decisions. Those OMPs which are not appraised by NICE have to be considered on a case-by-case basis at PCT level through a resource-intensive process that allows approval of these treatments "under exceptional circumstances".

Funding arrangements for health care services and treatments intended for very rare diseases are usually determined by commissioning bodies at the central level.

3 Overarching Themes

Based on the collected evidence on the national health care systems in France, Germany, Italy, Spain, Sweden, the Netherlands and the UK, a number of overarching themes were identified with the purpose of comparing the different policy arrangements for OMPs created at the national level and to ascertain how OMPs have been evaluated in practice using evidence on coverage decisions.

In this section we focus on the themes (six in total) that are directly relevant for the provision of OMPs. Table 4 at the end of the section provides a summary of the selected countries against the six themes.

3.1 Standard of Evidence for P&R Decisions

There are several issues concerning the collection of clinical data which is needed to obtain marketing authorisation and then reimbursement status in the context of rare diseases.

The WHO report on "Priority Medicines for Europe and the World" (van Weely and Leufkens, 2004) identified the following factors which have a negative impact on data availability:

- lack of epidemiological data, due to the difficulties in registering people with rare diseases in current databases (e.g. the International Classification of Diseases (ICD) code is not appropriate in many cases)¹⁰;
- lack of data on burden of disease, although it is generally recognised that the severity of rare diseases may be very high (e.g. WHO has not quantified the DALY burden of a number of rare diseases such as Crohn's disease and cystic fibrosis);
- lack of appropriate diagnostic systems;
- lack of trained health professionals;
- limited number of patients with a specific rare disease, which are often distributed in various parts of the world. This makes it more difficult to conduct randomised and placebo controlled double blinded studies.

In many cases it might be impossible to conduct clinical trials using orthodox endpoints as small patient populations may result in observations of health benefits that are not statistically significant. However, due to a lack of registration, few if any reports on the natural history of rare diseases are available and consequently it is difficult to identify valuable endpoints for clinical trials. Given the nature of some life-threatening conditions, there may also be ethical concerns about the use of placebo controlled studies.

Joppi et al. (2006) pointed out that 10 out of the 18 OMPs approved during the first four years of the EMEA legislation were approved "under exceptional circumstances" where additional follow-up studies were required in order to maintain the marketing authorisation (MA). More recently, Denis et al. (2009) show that as of December 2008, there was one orphan drug with a conditional MA and 16 with an exceptional MA (Denis et al., 2009). This means that regulatory bodies such as the EMEA are willing to accept a lower benefit-risk ratio for OMPs as compared to non-orphan products and allow them to be used in real-world settings while collecting additional evidence for future reviews. This is because OMPs meet the criteria of seriousness (they are for life-threatening or chronically debilitating diseases) and rarity (they are intended for a low-prevalence condition).

The key question is whether national health care decision makers have followed the same approach and accepted a more limited evidence base with the condition of collecting further data, or whether they have delayed the adoption until more information

10. Of more than 5,000 rare disorders currently known, only 250 have a code in the ICD (Orphanet, 2009)

becomes available. We collected evidence on how national decision makers have dealt with this issue to date, and have summarised the findings in the first row of Table 4.

Some countries (France, Italy and Spain) focus on clinical efficacy and rely on data available in the dossier submitted by manufacturers to the EMEA for marketing authorisations. Although there is a general concern around the limited clinical evidence available for OMPs, decision makers operating in these countries have occasionally relied on sources of evidence other than randomised clinical trials (RCTs), including literature reviews, cohort studies and Phase II clinical trials results.

In Germany, the current draft of the IQWiG guidelines states that the evidence base should not change for OMPs, hence the RCT is still regarded as the gold standard. However, it acknowledges that for some rare diseases it might not be possible “to include enough patients in a clinical study to statistically detect even moderate effects with sufficient power” (IQWiG, 2008). In these circumstances the guidelines indicates that it may be necessary to accept wider confidence intervals (i.e. p-value greater than 5%).

In Sweden, the Netherlands and the UK, where formal HTA processes are in place, cost effectiveness evidence is usually required. Only in the Netherlands is there dispensation for OMPs from submitting cost effectiveness evidence due to insufficient data. Manufacturers, provided that their product fits the OMP definition, have to submit a budget impact analysis estimating the expected number of patients and total costs associated with the implementation of the treatment within the country.

On the other hand, in the UK and Sweden, HTA bodies focus on health gains, defined by indices such as the quality-adjusted life year (QALY), and asks the manufacturer to model long-term health outcomes based on available surrogate or intermediate endpoints. HTA bodies have not lowered the evidence requirement for OMPs as compared to non-OMPs and their current position is that existing tools to handle uncertainty can be used to assess these medicines. This issue is discussed in more detail in the following section on criteria for P&R decisions.

This can lead to inconsistencies between the approach adopted by the regulatory body, which can grant conditional approval to OMPs, and HTA bodies’ requirements at the time of launch. For example, betaine anhydrous for the treatment of homocystinuria was approved by the EMEA based on data from a literature review showing biochemical

efficacy and associated improvements regarding the disease symptoms of betaine compared with historical data of untreated patients. When the drug was reviewed by the Scottish HTA body, SMC, although the difficulties in assessing clinical efficacy in this disease area were recognised, it was not recommended for use because the clinical data available was not deemed sufficient (SMC, 2007b).

In summary, it is generally recognised that one of the main challenges for OMPs is to develop clinical evidence that meets state-of-the-art standards. In particular, this is due to the lack of natural history of rare diseases, which makes it difficult to identify valuable endpoints and to run large-scale clinical trials. We found that countries whose main focus is on clinical evidence, namely France, Italy and Spain, have been flexible with regard to the evidence provided by manufacturers, and their approach seems to be in line with that taken at the central level by the EMEA (i.e. accept lower benefit-risk ratios when assessing OMPs due to lower evidence base available). However, as discussed in the country profiles in Section 2, it seems that concerns related to sustainability and budget pressure are leading these countries, particularly France and Spain, to increase the evidence base required to grant reimbursement, including pharmacoeconomic evidence to demonstrate the economic value of these new drugs. This is likely to raise new hurdles for reimbursement and delay access to new OMPs with limited data available.

Countries with formal HTA processes, such as Sweden and the UK, have not lowered the evidence base requirements and have therefore not always followed the EMEA approach. The Netherlands represents an exception to this, as its HTA body has allowed OMPs manufacturers not to submit cost effectiveness evidence and to rely exclusively on budget impact analysis.

3.2 Criteria for P&R Decisions

Criteria informing national health care bodies’ decisions largely depend on their remit, i.e. whether they are responsible for determining the coverage/listing status and/or the price, and, in turn, on the type of evidence required for making those decisions, as discussed in the previous section. The question to address here is whether OMPs have been formally treated as special cases by health care bodies in their decision making process, which would signal that they have a higher willingness to pay for health gain, however this is measured, for treatments for rare diseases.

In countries where no formal cost effectiveness analysis is requested (France, Italy and Spain), reimbursement decisions are based on a number of indicators, including whether the medicine in question

provides a clinical improvement as compared to existing treatments, whether it addresses an unmet need (i.e. no alternative treatment is available) and whether it generates any socio-economic benefits. In these countries, although P&R systems do not explicitly seek to treat OMPs differently, it seems that due to their characteristics, OMPs have met the criteria normally adopted by health care decision-makers and have therefore received positive reimbursement/listing decisions. Although decision makers were concerned about the high cost per patient of many OMPs, the relative low budget impact of these drugs has generally led to positive decisions.

This situation might change in the near future, as these countries have shown some interest in introducing formal HTA requirements. In France, for example, pharmacoeconomic evaluations have recently been incorporated into the remit of HAS, the health authority making reimbursement decisions. As a result, the role of cost effectiveness becomes a more important factor in determining the reimbursement status of OMPs.

In Germany, current IQWiG guidelines focus on the so-called 'efficiency frontier' although for innovative therapies which do not have an alternative technology to be compared with, no efficiency frontier can be built. This rule is not specific to OMPs but, considering that many OMPs are first-in-class, it means that cost-benefit analysis, as designed by IQWiG, will not be used for many OMPs, which should therefore be automatically reimbursed.

In countries where formal HTA processes are in place, there is a general agreement that the level of uncertainty that should be accepted depends on the cost of making a wrong decision. Given the low budget impact associated with OMPs, the current HTA framework suggests that it is possible to accept a limited, more uncertain evidence base as the impact on health care resources needed to fund the drug decrease. Within the UK, NICE supports this principle in its current guide to methods although only where the expected cost per QALY does not exceed £30,000 (NICE, 2008b), and to date we have found no examples of OMPs where less strict criteria on this ground have been applied.

The cost per QALY cut-off point used by HTA bodies as the cost effectiveness benchmark tends to vary from country to country. In Sweden, OMPs with high cost effectiveness ratios (up to €90,000 per QALY) have been accepted on the ground that they target severe diseases (Hugosson and Engstrom, 2008).

In the UK, NICE, covering England and Wales, applies standard criteria when appraising OMPs, including a cost per QALY threshold varying between £20,000 and £30,000. NICE states that in some circumstances (applying for both OMPs and non-OMPs) it may be appropriate to consider some additional factors, such as the innovative nature of the technology. However, it is not generally possible to tell whether and how this principle has been applied in practice. This may be because the system of incorporating "other considerations" in the context of formal HTA process has not reached maturity, or because the use of that system is not adequately reported. There is no agreement yet as to which additional criteria should be taken into account, and how explicitly (for example, using a formalised mathematical formula or informal discussion when the Appraisal Committee develops its recommendation). The recent NICE supplementary advice may represent a way forward in this respect, as it indicates some circumstances under which it may be appropriate for the Institute to approve new treatments with a cost per QALY exceeding the threshold. According to the advice (NICE, 2009), more weight will be attached to health gains generated by end of life treatments targeting relatively small populations, mainly including OMPs for rare cancers. However, this will not apply to OMPs with any survival benefits and targeting long-term conditions.

In Scotland, the SMC states explicitly that:

"The assessment process for orphan drug submissions is the same as for all other drug submissions. However, in addition to the usual assessment of clinical and cost-effectiveness, SMC may consider additional factors, such as whether the drug: treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; or bridges a gap to a "definitive" therapy."

(SMC statement on orphan drugs:
<http://www.scottishmedicines.org.uk/smc/3869.html> accessed
2nd October 2009)

In the Netherlands, pharmacoeconomic evaluation and budget impact analysis are part of the evidence package that has to be provided for products to be included in List 1B, where no maximum reimbursement price is fixed. However, the Minister of Health has refused to identify an explicit cut-off point for reimbursement decisions in order to have a more flexible system where other criteria, such as the

principles of justice and solidarity, can be applied. This raises issues relating to the transparency of the decision making process, which are relevant for OMPs as well as non-OMPs.

Overall, it is only in the Dutch system that less stringent criteria are formally implemented to appraise OMPs. In other five countries (France, Germany, Italy, Spain and Sweden), although there is no formal exemption for OMPs, if they have fulfilled certain criteria deemed important by decision-makers, such as the seriousness of the disorder, they may be considered to be worth paying for.

In the UK, NICE applies standard cost effectiveness threshold with exemptions to the rule made on a case-by-case basis. The SMC lists potential modifiers which it may apply to its cost effectiveness evaluations of orphan drugs. The outcomes of these processes are discussed in section 3.6 below.

3.3 Pre-Licence Access

Four countries (France, Italy, Spain and the Netherlands) have introduced special mechanisms to promote the collection of additional data and the uptake of medicines prior to their formal marketing authorisation. These channels have been established to provide access to drugs for unmet clinical needs which are either available in other countries or still under clinical trial testing (and made available for compassionate use). Although these mechanisms have not been created specifically for OMPs, there is evidence that many OMPs have been provided within national health care systems through them.

The Dutch system allows for off-label use of medicines authorised in other countries outside Europe (mainly the US) if the target population is less than one patient in 150,000 inhabitants. This approach allows the provision of medicines already available in other countries and provides an opportunity to start collecting data at an early stage that can be used subsequently for a more comprehensive assessment.

In the UK, there is an ongoing policy debate around the possibility of developing similar early access channels. In particular, the government-commissioned Cooksey review (Cooksey, 2006) recommended the establishing of conditional licensing programmes “at an earlier stage in the drug development pathway (e.g. at the end of Phase II testing)” (Cooksey, 2006). This would allow new drugs to become available much earlier and would enable the collection of safety, efficacy and economic data in the period following conditional approval, which can inform the review for full registration.

3.4 Post-Launch Studies

In some countries, decision makers are willing to accept a more limited evidence base with the condition of collecting further post-launch data to inform a re-assessment in the near future. Evidence on these initiatives was identified in all countries but Germany.

In the Netherlands, there is a formal process of coverage with evidence development followed by a review of the new data. This policy has been introduced specifically to accommodate new OMPs and so far, seven OMPs have been provided through this route.

In France, HAS can grant reimbursement status subject to the performance of post-marketing studies meeting certain requirements. Until January 2008, HAS requested only three studies for OMPs. This is because in some cases the sponsor had to conduct additional studies requested by the EMEA (which approved the product “under exceptional circumstances”). In other cases, it was not possible to conduct post-launch studies, given the insufficient number of patients in France.

In Italy and Spain, specific registries for OMPs have been established to improve knowledge on the use of new drugs in clinical settings.

In the UK, the supplementary advice on end of life treatments recognises the need to collect further evidence after NICE recommends the use of a new medicine with a cost per QALY exceeding the threshold of £20,000 to £30,000. However, the advice has been introduced only recently and no examples of implementation are yet available. In addition, the advice will apply only to drugs for rare cancers showing improvement in survival.

3.5 Other Specific Policies for OMPs

We found three countries where policy initiatives specific to OMPs, in addition to those identified above, have been implemented. These include:

- National plans for rare diseases in France and Spain, which provide a comprehensive approach to addressing different aspects and issues related to rare diseases, including research activities, diagnosis and providing access to available treatments;
- Steering Committee for orphan drugs appointed by the Dutch Minister of Health, which is intended to collect and disseminate information on rare diseases to create awareness; to develop interfaces and informal networks at a multidisciplinary level; and to encourage research programmes targeting rare diseases both at national and international level.

Table 2: Summary of decisions on reimbursement of 43 EMEA-granted OMPs

	France	Germany	Italy	Spain	Sweden	The Netherlands	England and Wales	Scotland
Potentially available	43	43	43	43	43	43	43	43
Launched	38	35	34	30	35	40	39	39
% of those potentially available	88%	81%	79%	70%	81%	93%	91%	91%
of which reimbursed	38*	35	32	30	24**	39	See Table 3	
% reimbursed of potentially available	88%	81%	74%	70%	56%	91%		
% reimbursed of those launched	100%	100%	94%	100%	69%	98%		

* Estimate based on SMR rating and new reimbursement category for treatment for severe and chronic diseases which are fully reimbursed.
** Three of those were reimbursed with some conditions (e.g. second-line use).

3.6 Coverage Decisions

We collected evidence on decisions about coverage and reimbursement of EMEA-designated OMPs in the seven countries considered. Appendix 1 lists the 43 products which were granted orphan drugs status as at March 2008. Appendix 2 provides more details on the sources used to extract information and additional country-specific information. Table 2 summarises some aggregate figures of the collected evidence. As outlined above, products assessed by NICE and/or SMC can be recommended, or not, for use within the English and Welsh and the Scottish health care systems respectively. NICE does not appraise all medicines launched and so far has appraised only one OMP for two different indications. SMC considers all new medicines including 28 OMPs to date. Table 3 summarises the decisions taken by NICE and SMC on those OMPs (out of the 43 that were potentially available by March 2008) that were appraised by them.

The second row of Table 2 (“Launched”) indicates the number of OMPs which were marketed by the manufacturer in each country after obtaining licensing approval from the EMEA. On average, 36 products out of 43 were launched in each country. Spain is the country with the lowest number of launches (30) and the Netherlands the country with the largest (40). We note that one product, 5-aminolevulinic acid hydrochloride, was not launched in any of the seven countries. There are various possible reasons underpinning manufacturers’ strategy of not launching a product in certain countries: one may be related to the expected low number (absence of) patients with a

specific rare condition in a country which does not justify the cost of the reimbursement application. However, it is unclear why Italy and Spain, which represent large European markets, are the countries with the lowest launch rate (out of the 43 OMPs analysed, 20% and 30% are not available in Italy and Spain, respectively) whilst a small country such as the Netherlands has the highest rate.

The fourth row (“of which reimbursed”) provides information on the reimbursement status of the selected OMPs. Given the significant variation in P&R approaches across the countries, these figures should be interpreted taking into account the context in which the decisions were made. For example, in France all 38 available OMPs were considered eligible for reimbursement (i.e. classified as medicines with an ‘important’ medical value using the SMR rating). In addition, data on the five-level ASMR rating (i.e. added therapeutic value) were collected and presented in Appendix 2 (Table A1, Appendix 2). We found that the majority (53%) of OMPs were considered to bring major or important added value (i.e. ASMR I or II). In France, pharmaceutical prices are negotiated on a product-by-product basis between the economic committee and the manufacturer, based on the ASMR rating and expected volumes, among other elements. Although there is no data in the public domain about the price negotiation, we infer that OMPs manufacturers were in a relative good position, given the ASMR rating and the low number of patients associated with their products.

In Spain, no OMPs launched have been rejected for

Table 3: SMC and NICE decisions on selected OMPs

	Yes*	Restricted**	No***	Total
SMC	12 (43%)	3 (11%)	13 (46%)	28
NICE	2	0	0	2

* 'Yes' category includes products fully recommended and those recommended for specialist use, which effectively represent a 'yes' given the nature of the products in question.
** 'Restricted' category includes products recommended for restricted use in subgroup population within the licence indication.
*** 'No' category includes products not recommended for use within the health care system.

reimbursement by the relevant health authority but, as noted earlier, a large proportion of OMPs are not available because they were not marketed.

In Italy, only two medicines out of the 34 launched were not reimbursed. It is worth noting that out of the 34 OMPs available, three were reimbursed through Law 648 and one through the 5% AIFA fund. Seventeen were subject to registries, three of which were provided via a risk-sharing scheme (data presented in Appendix 2, Table A2). Based on the data collected, Italy and the Netherlands have been the most active in terms of establishing innovative access schemes allowing for early uptake of new OMPs coupled with collection of real-world data informing subsequent review.

In Germany, where there are no direct restrictions of price at launch, most new medicines are automatically funded within the national health service. In particular, in Germany OMPs qualify for reimbursement with no price limit and our data confirm that this is the case.

In the Netherlands, a large proportion of OMPs (around 45%) was provided either through the policy rule or hospital funding (for intramural treatment as described in Section 2.6); the remaining 55%, classified as extramural treatments (21 OMPs), were assessed by the Dutch HTA body (see Table A4 in Appendix 2). The vast majority (80%) were deemed 'breakthrough' therapies with no interchangeable products and were therefore reimbursed with no price limit.

Sweden presents the second highest (less than Scotland – see below) proportion of OMPs that have not been reimbursed despite being launched in that country (slightly over 30% - 11 out of 35), although the HTA body adopts a higher willingness to pay for treatments for severe diseases. In some cases OMPs might not be included in the positive list because the manufacturer either withdrew or did not submit its application for reimbursement as noted by Wettermark et al. (2008). This is usually due to the manufacturer's expectation that its product was very unlikely to meet the cost effectiveness criteria.

In the UK, OMPs are made available after launch and can be prescribed by clinicians operating within the NHS. This applies unless a medicine is appraised by the relevant HTA body, which issues guidance on its appropriate use within the NHS. Table 3 presents summary statistics of the guidance issued by NICE and SMC. Using IMS data on sales, we assumed that every product not so far appraised by SMC or NICE is being provided within the NHS in Scotland or England and Wales respectively.

We checked whether any of the 39 OMPs launched in the UK were appraised by either NICE or SMC to see if there was any variation in their access due to HTA bodies' decisions. Table 3 summarises the results (which is also included in Annex 2 for completeness).

We found that up to March 2008 NICE had issued guidance for only one EMEA-designated OMP, imatinib for the treatment of gastro-intestinal stromal tumours and of chronic myeloid leukaemia. In both indications, imatinib was given positive recommendation. This shows that in England, NICE's impact on access to OMPs has to date not been very substantial – but this could change, as noted below.

The picture is very different in Scotland where SMC reviewed 28 OMPs. Almost half of those reviewed have been rejected (13 out of 28), while 12 were recommended and 3 were recommended only for restricted use, i.e. for patient sub-groups within the licensed indication. The larger number of OMPs evaluated by SMC as compared to NICE is due to the fact that the Scottish body produces guidance on all new medicines launched in Scotland whilst NICE only appraises health technologies selected by ministers. Also, unlike SMC, at the time of our analysis NICE's remit explicitly excluded the appraisal of ultra-orphan drugs (medicines for very rare diseases). On the other hand, SMC has reviewed three ultra-orphan drugs, laronidase for mucopolysaccharidosis-1, miglustat for Gaucher's disease and Carglumic acid for hyperammonaemia, which have a UK prevalence of less than 1 in 50,000. This shows that when HTA

processes are systematically used to review OMPs, they can lead to a high rate of rejection.

It is expected that NICE will increase the number of appraisals, especially for cancer medicines - and a significant proportion of orphan drugs are used to treat different types of cancer. This implies that limited access to orphan drugs could in future become more

of an issue in England and Wales. There might be, however, some flexibility for orphan (and non-orphan) drugs indicated for patients with a short remaining life expectancy, normally less than 24 months, as NICE recently announced in its 'end of life' advice in health technology appraisals (NICE, 2009).

Table 4 presents a summary of the overarching themes.

Table 4: Summary of overarching themes

	France	Germany	Italy	Spain
Standard of evidence required	Clinical therapeutic value No formal cost-effectiveness analysis required	Efficacy and effectiveness data	Clinical therapeutic value and innovation No formal cost-effectiveness analysis required	Clinical therapeutic value No formal cost-effectiveness analysis required
Criteria for P&R decisions	Medical value (SMR) and incremental medical value (ASMR) based on clinical efficacy	IQWiG will use efficiency frontiers to set ceiling price (only if there are alternative treatment/s)	<ul style="list-style-type: none"> No alternative or adequate therapy Better benefit-risk ratio than existing therapies Socio-economic benefits 	<ul style="list-style-type: none"> Seriousness Needs of certain groups Social utility Limits of drugs expenditure Alternative treatments Degree of innovation
Pre-licence access	<ul style="list-style-type: none"> Authorisation for Temporary Use Temporary Treatment Protocols Fast track procedures for products "deemed a priori innovative" 	Not identified	<ul style="list-style-type: none"> Law 648/96 5% AIFA special fund established in 2005 	Authorised by AEMPS: <ul style="list-style-type: none"> for use in clinical trial as "foreign medicine" compassionate use
Post-launch studies	Via standard HAS channels (only three requests between 2005-08)	Not identified	<ul style="list-style-type: none"> Disease registries (17 OMPs, so far) Risk sharing schemes (2 OMPs out of 17 with registry) 	Registries were established in one region (Extremadura)
Other policies for OMPs	National Plan for Rare Diseases	Not identified	Not identified	National Plan for Rare Diseases
Coverage decisions	100% of launched OMPs were reimbursed	100% of launched OMPs were reimbursed	94% of launched OMPs were reimbursed	100% of launched OMPs were reimbursed

Sweden	The Netherlands	England and Wales	Scotland
Clinical and cost effectiveness	<ul style="list-style-type: none"> Clinical efficacy and effectiveness Cost effectiveness (dispensation) Budget impact analysis 	Clinical and cost effectiveness	Clinical and cost effectiveness
<ul style="list-style-type: none"> Cost/QALY threshold correlated with severity Higher degree of uncertainty accepted 	No explicit cost effectiveness threshold has been identified	<ul style="list-style-type: none"> Threshold of £20-£30,000/QALY Special consideration for end of life treatments targeting small populations Other factors on a case by case basis 	Additional factors ('modifiers') may be taken into account on a case by case basis
Not identified	Medicine authorised in other countries with a population of < 1/150,000 in the country	Not identified Cooksey review recommends earlier conditional licensing	Not identified Cooksey review recommends earlier conditional licensing
Yes, but only two cases identified	Policy rule requiring collecting more evidence for re-appraisal	New NICE policy requires evidence collection for approved end of life medicines with high cost/QALY	Not identified
Not identified	Steering Committee of Orphan Drugs appointed by the Minister of Health	Not identified	Not identified
69% of launched OMPs were reimbursed	98% of launched OMPs were reimbursed	100% of launched OMPs are currently funded by the NHS in England and Wales, but so far only 1 (for 2 indications) has been appraised by NICE	67% of launched OMPs are funded by the NHS in Scotland

4 Summary

4.1 Summary of Findings

The EU-wide legislation in operation since 2000 has provided a package of economic incentives for the research, development and marketing of OMPs. The package includes cost-reducing measures such as protocol assistance and centralised marketing approval, and a market-enhancement measure in the shape of a ten-year market exclusivity. The aim of the legislation was to assist companies with their development programmes and to reward innovation in the field of rare diseases which, due to their low prevalence, have tended to lack appropriate treatments to offer to patients.

EU Member States have each faced rising expenditures on pharmaceuticals and have tried to contain costs by controlling their use, price and volume. This study has reviewed how these measures have varied across seven European countries (France, Germany, Italy, Spain, Sweden, the Netherlands and the UK) and has examined whether they have impacted on the availability of OMPs.

We found that decision-makers are aware of the difficulties in collecting relevant and robust data in the context of rare diseases, which include a lack of epidemiological data, natural history of the diseases, limited number of patients and variable distribution of disease incidence across countries. More specifically, the countries where no formal HTA evidence is required (France, Germany, Italy and Spain) have normally accepted a more limited evidence base compared to treatments for more common conditions. Thus their approach seems to be consistent with that adopted at the regulatory level by bodies such as the EMEA which has accepted OMPs on an accelerated basis (i.e. approval conditional to the provision of additional evidence to maintain marketing authorisation).

In the countries where HTA processes are in place (Sweden, the Netherlands and the UK), higher level of uncertainty as compared to non-orphan drugs should be in principle be accepted, as the cost of making a wrong decision (i.e. endorsing a cost-ineffective medicine) is also smaller given the size of the patient population. The Netherlands recognises this and is the only one of the three to accept a more restricted evidence package, including only budget impact analysis. Although the Swedish and the UK HTA bodies seem to accept this principle (NICE supports it in its current method guide), we did not find any evidence of its practical application.

Given the available evidence, national health care bodies make coverage decisions based on a set of criteria which are usually predefined to ensure consistency in the decision making process. We investigated whether OMPs have been treated as special cases by health care bodies, and found that the criteria informing coverage decisions vary substantially. In countries with no formal HTA, OMPs have tended to meet the criteria usually adopted by decision makers and have therefore been reimbursed within the national health system. The most recurrent factors deemed important when assessing OMPs were the severity of the illness and the lack of an adequate alternative treatment. Among the countries with HTA processes, Sweden has a cost effectiveness threshold which varies depending on the degree of severity, which will have a direct effect on the appraisal of OMPs that target serious diseases. HTA bodies operating in the UK (NICE and SMC) have identified a number of 'modifiers' that could be considered alongside cost effectiveness evidence (e.g. substantial improvement in survival). However, it does not seem that, to date, these factors have been applied in many instances.

Some countries have introduced special mechanisms to promote the collection of additional data and the uptake of medicines, either prior to their formal marketing authorisation or at the time of launch. Four countries have funded OMPs which are either available in other countries or still under clinical trial testing - in most cases, these were made available for compassionate use. In all countries but Germany we identified specific policies supporting post-launch studies/evidence generation. However, we found evidence of wide application of these policies only in Italy and the Netherlands. In the other countries the low prevalence of the disease was often mentioned as a barrier to conducting these types of studies.

With regard to the actual coverage decisions issued by national health care bodies on OMPs, the available evidence showed little variation across most of the selected countries. We found that in France, Germany, Italy, Spain, the Netherlands and England and Wales, the large majority (or all) of the EMEA-designated orphan drugs launched in the country were considered eligible for reimbursement or provided within the NHS. In some cases, no price ceiling was imposed by the relevant health care authority (for example in Germany and in the Netherlands). Within the UK however, deliberations of the SMC, the Scottish HTA body responsible for appraising all new medicines, were more varied, with many cases of rejections and some recommendations for restricted use in subgroups of the licensed population. Sweden also has a relatively high rate of rejection of OMPs: slightly over 30% of the OMPs launched there were not reimbursed.

Italy and the Netherlands are adopting a mix of innovative schemes to allow early access to and evidence generation of new OMPs. In Italy, for example, half of the OMPs available were subject to registries and three were provided through a risk-sharing scheme, where companies have to refund the Italian NHS for those patients for whom the treatment does not achieve the expected clinical outcome. In the Netherlands, around 45% of the OMPs launched were provisionally reimbursed conditional on the collection of further evidence which will inform an appraisal review in three years' time.

EU Member States have implemented P&R arrangements for controlling the use of pharmaceuticals provided within their health care systems. However, there are significant differences between countries in terms of HTA requirements for all drugs, including orphan drugs. Our study shows that, to date, measures not based on HTA have not substantially impacted the availability of OMPs which were considered eligible for reimbursement or provided within the national health system in the large majority of cases. Although P&R systems do not explicitly seek to treat OMPs differently, they have met the criteria normally adopted by health care decisions-makers, based on their characteristics, such as severity of the diseases and lack of alternative treatment. Thus we have found no evidence of specific barriers to access to new OMPs in countries with no formal HTA process which may reduce the value of the incentives introduced at the European level by the Orphan Drug Legislation. In Scotland and Sweden, though, HTA processes have led to a large minority of OMPs not being recommended for reimbursement.

However, these results have to be considered with some caveats. We analysed aggregate data on coverage decisions taken by decision makers at the national level which do not reflect any possible issues relating to the actual provision of medicines at the local level (by hospitals and trusts for example), and do not capture the possible gap between the time of launch of medicines and their coverage determination. Also, we did not collect data on the proportion of patients treated in each country or compare national data across borders. In order to test the impact of key policy mechanisms and to isolate other factors influencing the availability of OMPs across Europe, there is a need to collect reliable data on national uptake of these medicines on a systematic and comparable basis.

4.2 Future Directions and Some Recommendations

Our analysis provides some insights on the possible future directions for the orphan drug policy

environment. Some of the trends observed are likely to amplify going forward. In particular, it is expected that more treatments for life-threatening and severe diseases will be approved by regulatory bodies on an accelerated basis or conditional on additional data collection (the so called "exceptional circumstances"). This means that more OMPs will be approved for marketing with a relatively high level of uncertainty around their benefits/risk ratio.

This is expected to clash with the increasing demand for HTA by health care decisions makers to inform coverage decisions of new medicines (for example in France and Spain). The provision of cost effectiveness evidence might be more problematic for OMPs as compared to non-orphan drugs as in most cases they cannot meet HTA evidence requirements, particularly near the time of launch. This problem, combined with manufacturers' desire to charge relatively high prices in order to ensure an adequate return on their investment when patient numbers are small, is highlighted by our evidence on coverage decisions in countries where formal HTA processes are already established. We found that two HTA bodies evaluating all new marketed drugs (in Scotland and Sweden) presented a lower rate of acceptance as compared to other decision makers. In the case of NICE in England and Wales, an increasing number of new drugs will go through the accelerated appraisal process (the Single Technology Appraisal) near the time of launch which is likely to lead to a situation similar to the one observed in Scotland.

Due to a lack of evidence at launch and possible prolonged negotiations between health care decision makers and companies, it is likely that access to OMPs will encounter substantial delays.

There is therefore a conflict between the regulatory policy, which attempts to accelerate market introduction of innovative products for severe diseases, and the policies of HTA bodies which block access when available evidence does not meet their standards.

Different policy approaches can be pursued, some of which have already been emerging. For example, risk sharing, already widely used in Italy, and other similar innovative schemes to ensure early access and monitoring of expected clinical outcomes, are likely to play an increasingly important role. The uncertainty issue is expected to increasingly be addressed by means of temporary provision of new OMPs subject to data collection in real-world settings, which can then be used to inform subsequent re-review (such as the system observed in the Netherlands).

Given the low and patchy distribution of rare diseases across regions and countries, more cooperation and

networking at the European and international level will be required in order to develop more reliable evidence after marketing authorisation. It is crucial that all key stakeholders, including clinicians, are involved in the development of Europe-wide registries and processes for data collection around treatment pathways (a fundamental area of research for rare diseases).

To address the potential conflicts between data requirements for licensing and for reimbursement purposes, an early engagement between licensing bodies, HTA bodies and companies should be facilitated in order to identify the potential evidence

issues and to explore possible ways forward. In many cases there is no “second chance” to conduct an additional clinical study if the available data prove inadequate due to the limited number of patients and ethical considerations of further randomisation. It might be appropriate to develop common guidelines for setting an “acceptable minimum dataset” for licensing and reimbursement to be considered as a benchmark by developers/manufacturers and decision-makers at the European level. This might involve, for example, specifying clinically significant endpoints in clinical trials and identifying acceptable alternative options to RCTs.

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APPENDIX 1. LIST OF EMEA-GRANTED OMPS AS AT MARCH 2008

Product	Designated Orphan Indication	Designation date	Tradename	Authorisation date
1,5-(Butylimino)-1,5-dideoxy, D-glucitol dideoxy, D-glucitol	Treatment of Gaucher Disease	18/10/2000	Zavesca	20/11/2002
3-(4'-aminoisoindoline-1'-one)-1-piperidine-2,6-dione	Treatment of multiple myeloma	12/12/2003	Revlimid	14/06/2007
2-chloro-9-[2-deoxy-2-fluoro-β-D-arabinofuranosyl]adenine	Treatment of acute lymphoblastic leukaemia	05/02/2002	Evoltra	29/05/2006
4-(3,5-bis-(hydroxy-phenyl)-1,2,4 triazol-1-yl)-benzoic acid	Treatment of chronic iron overload requiring chelation therapy	13/03/2002	Exjade	28/08/2006
5-aminolevulinic acid hydrochloride	Intra-operative photodynamic diagnosis of residual glioma	13/11/2002	Gliolan	07/09/2007
Alpha-Galactosidase A	Treatment of Fabry disease	08/08/2000	Fabrazyme	04/05/2001
Alpha-Galactosidase A	Treatment of Fabry disease	08/08/2000	Replagal	04/05/2001
Anagrelide Hydrochloride	Treatment of essential thrombocythaemia	29/12/2000	Xagrid	16/11/2004
Arsenic trioxide	Treatment of acute promyelocytic leukaemia	18/10/2000	Trisenox	05/03/2002
Betaine anhydrous	Treatment of homocystinuria	09/07/2001	Cystadane	15/02/2007
Bosentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	14/02/2001	Tracleer	15/05/2002
Busulfan (Intravenous use)	Conditioning treatment prior to hematopoietic progenitor cell transplantation	29/12/2000	Busilvex	09/07/2003
Celecoxib	Treatment of Familial Adenomatous Polyposis	20/11/2001	Onsenal	17/10/2003
Cladribine (subcutaneous use)	Treatment of indolent non-Hodgkin's lymphoma	18/09/2001	Litak	14/04/2004
Dasatinib	Treatment of chronic myeloid leukaemia	23/12/2005	Sprycel	20/11/2006

APPENDIX 1 (CONTINUED)

Dexrazoxane	Treatment of anthracycline extravasations	19/09/2001	Savene	28/07/2006
Ecteinascidin 743	Treatment of soft tissue sarcoma	30/05/2001	Yondelis	17/09/2007
Eculizumab	Treatment of paroxysmal nocturnal haemoglobinuria	17/10/2003	Soliris	20/06/2007
Hydroxyurea	Treatment of sickle cell syndrome	09/07/2003	Siklos	29/06/2007
Ibuprofen	Treatment of patent ductus arteriosus	14/02/2001	Pedea	29/07/2004
Iduronate-2-sulfatase	Treatment of Mucopolysaccharidosis, type II (Hunter Syndrome)	11/12/2001	Elaprase	08/01/2007
Iloprost	Treatment of primary and of the following forms of secondary pulmonary hypertension: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease, chronic thromboembolic pulmonary hypertension	29/12/2000	Ventavis	16/09/2003
Imatinib mesilate	Treatment of malignant gastrointestinal stromal tumours	20/11/2001	Glivec	27/08/2001
Imatinib mesylate	Treatment of chronic myeloid leukaemia	14/02/2001	Glivec	27/08/2001
Laronidase	Treatment of Mucopolysaccharidosis, type I	14/02/2001	Aldurazyme	10/06/2003
Mitotane	Treatment of adrenal cortical carcinoma	12/06/2002	Lysodren	28/04/2004
N-acetylgalactosamine-4-sulfatase	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome)	14/02/2001	Naglazyme	24/01/2006

N-carbamyl-L-glutamic acid	Treatment of N-acetylglutamate synthetase (NAGS) deficiency	18/10/2000	Carbaglu	24/01/2003
Nelarabine	Treatment of acute lymphoblastic leukaemia	16/06/2005	Atriance	22/08/2007
Nilotinib hydrochloride monohydrate	Treatment of gastro intestinal stromal tumours	13/04/2007	Tasigna	19/11/2007
Nitisinone	Treatment of tyrosinaemia type I	29/12/2000	Orfadin	21/02/2005
Pegvisomant	Treatment of acromegaly	14/02/2001	Somavert	13/11/2002
Porfimer sodium (for use with photodynamic therapy)	Treatment of high-grade dysplasia in Barrett's Esophagus	06/03/2002	PhotoBarr	25/03/2004
Recombinant human acid alpha-glucosidase	Treatment of Glycogen Storage Disease type II (Pompe's disease)	14/02/2001	Myozyme	29/03/2006
Rufinamide	Treatment of Lennox-Gastaut syndrome	20/10/2004	Inovelon	16/01/2007
Sildenafil citrate	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	12/12/2003	Revatio	28/10/2005
Sitaxentan sodium	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	21/10/2004	Thelin	10/08/2006
Sodium oxybate	Treatment of narcolepsy	03/02/2003	Xyrem	13/10/2005
Sorafenib tosylate	Treatment of renal cell carcinoma	29/07/2004	Nexavar	19/07/2006
Stiripentol	Treatment of severe myoclonic epilepsy in infancy	05/12/2001	Diacomit	04/01/2007
Temsirolimus	Treatment of renal cell carcinoma	06/04/2006	Torisel	19/11/2007
Ziconotide (intraspinal use)	Treatment of chronic pain requiring intraspinal analgesia	09/07/2001	Prialt	21/02/2005
Zinc acetate dihydrate	Treatment of Wilson's disease	31/07/2001	Wilzin	13/10/2004

Source: EMEA website <http://www.emea.europa.eu/htms/human/orphans/opinions.htm>

APPENDIX 2. COUNTRY SPECIFIC DATA ON P&R DECISIONS AND RELATED SOURCES

Table A1: ASMR rating by HAS (France) on selected OMPs					
Total reimbursed OMPs	ASMR I	ASMR II	ASMR III	ASMR IV	ASMR V
38*	3	17	7	8	2

* The ASMR rating was not available for one product.

Table A2: Provision of selected OMPs in Italy					
Total reimbursed OMPs	Included in class A/subclass H	Subject to patient registry	Subject to risk sharing	Funded via Law 648	Funded via AIFA 5% fund
32	28	17 (out of 28 in class H)	3 (out of 17 with registry)	3	1

Table A3: SMC and NICE decisions on selected OMPs				
	Yes*	Restricted**	No	Total
SMC	12 (43%)	3 (11%)	13 (46%)	28
NICE	2	0	0	2

**'Yes' category includes products fully recommended and those recommended for specialist use, which effectively represent a 'yes' given the nature of the products in question.
 ** 'Restricted' category includes products recommended for restricted use in subgroup population within the license indication.

Table A4: Reimbursement decisions and funding arrangements of selected OMPs in the Netherlands				
Total reimbursed OMPs	Policy Rule	Hospital budget	List 1A	List 1B
39	10	8	4	17

Data sources:

IMS Lifecycle: for sales data on OMPs launched in the selected countries.

France: Data on SMR and ASMR rating collected for internal use by the Association of Research-Based Pharmaceutical Companies in France (LEEM).

Germany: Data collected for internal use by the Association of Research-Based Pharmaceutical Companies in Germany (VFA).

Italy: For OMPs included in class H: http://www.agenziafarmaco.it/PREZ_RIMB_MER/section1c12.html?target=&area_tematica=PREZ_RIMB_MER&§ion_code=AIFA_PREZ_RIMB_MER&entity_id=111.82243.1172659031689

For OMPs subject to registries: <http://monitoraggiofarmaci.agenziafarmaco.it/>

For OMPs provided via risk sharing schemes :
AIFA "Rapporto Nazionale 2007"
Presentation AIFA (for OMPs provided via law 648/96 and AIFA 5% fund)
http://www.agenziafarmaco.it/TARGET_MED_OPE/rapporto_rfom_2008.html

Spain: Press launch of the Spanish Department of Health (Ministerio de Sanidad y Consumo):
<http://www.msc.es/en/gabinetePrensa/notaPrensa/desarrolloNotaPrensa.jsp?nivel=3&cat=gabinetePrensa&id=1421>

Sweden: Data collected for internal use by the research-based pharmaceutical industry in Sweden (LIF)

The Netherlands: data collected for internal use by the Dutch Health Care Reimbursement Board (CVZ)

The UK: IMS Dataview (for data on sales);

For NICE decisions: <http://www.nice.org.uk/guidance/index.jsp?action=ByType&type=6&status=3&p=off>

For SMC decisions:
http://www.scottishmedicines.org.uk/smc/CCC_FirstPage.jsp

APPENDIX 3. TEMPLATE FOR THE WORKSHOP “ACCOMMODATING ORPHAN DRUGS: BALANCING INNOVATION AND FINANCIAL STABILITY”

Orphan drugs are used for the diagnosis, prevention or treatment of life-threatening or very serious conditions. Although there is EU orphan medicine legislation in place to provide incentives for researching, developing and marketing, access to such treatments across Europe is likely to be variable. In this conference we explore the extent to which pricing and reimbursement arrangements accommodate orphan medicinal products.

The focus of the seminar is twofold. First, we want payers in selected European countries to describe the P&R and decision making processes around orphan drugs if they exist. In particular, we are interested in understanding whether they treat them differently from other drugs and, if so, how. Second, we want to generate a constructive discussion about affordability of orphan drugs in the medium/long term with key stakeholders including third party payers.

For the first objective in particular, we are interested in learning about the following issues regarding orphan drugs, with case studies where appropriate:

- Is there any specific national policy in favour of orphan drugs e.g. creation of specific programmes or institutions dealing with orphan drugs?
- What type of evidence (clinical and/or cost effectiveness) is currently being used to determine the price and/or reimbursement status of orphan drugs? Are there any other criteria required for the decision-making process?
- What type of special reimbursement controls, if any, are currently targeting orphan drugs when launched (e.g. are they included in national reimbursement lists or reimbursed on a case by case basis)?
- Are there any market access issues regarding orphan drugs in particular? Are there any additional barriers to entry such as specific budgetary constraints?
- Are third party payers requiring post-launch studies for orphan drugs?

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