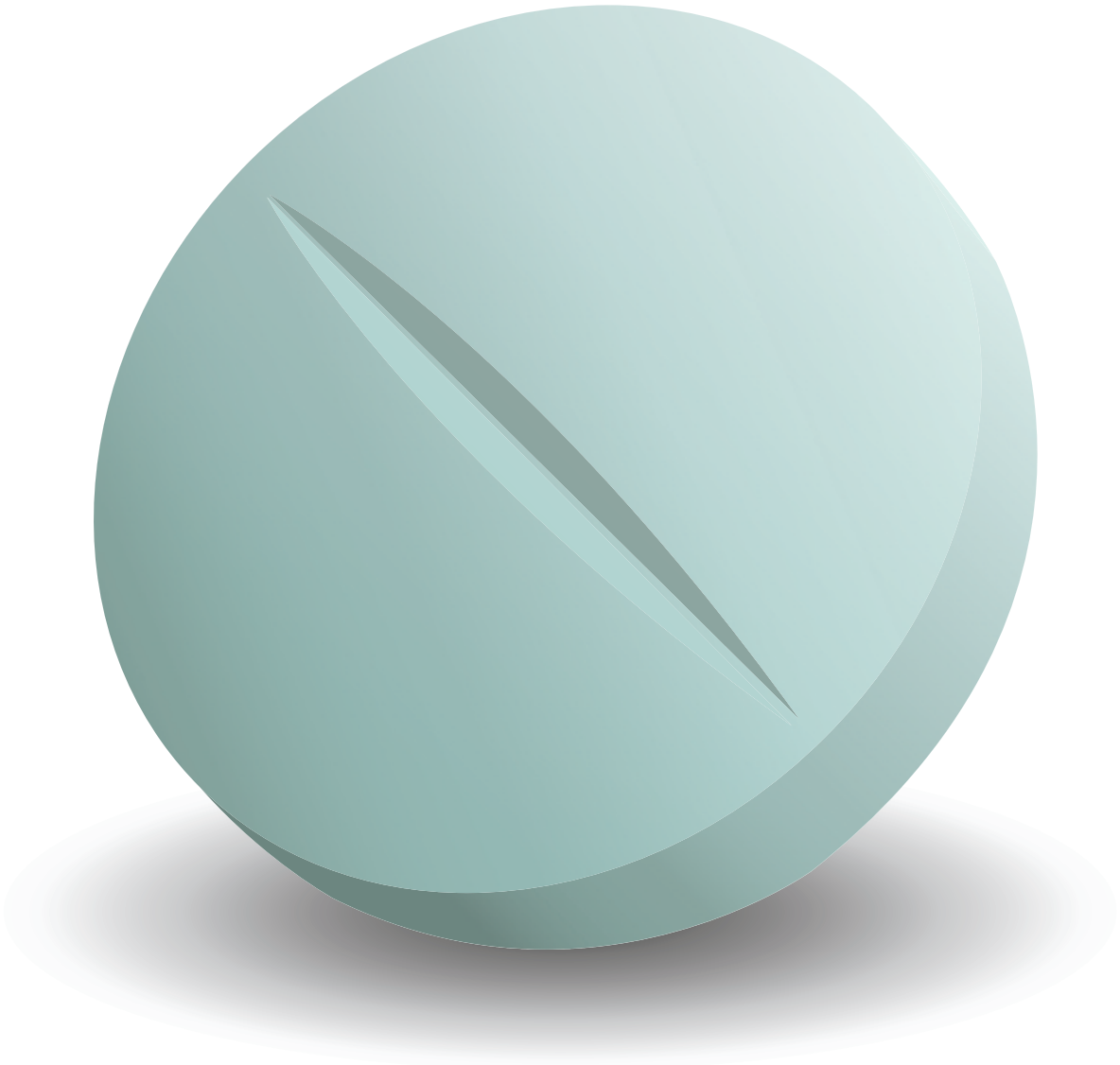
Orphan Medicines

Special treatment required?

Leela Barham

November 2012



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About this publication

This report was prompted by our concern that patients and their clinicians are not always able to access medicines for those with rare diseases. The ongoing reforms to the NHS and development of a strategy for rare disease offer an opportunity to explicitly consider access to medicines for those with orphan or ultra-orphan conditions. As the commissioning of services for those with rare diseases moves to be undertaken by the new National Commissioning Board we hope that this report will be timely.

We analyse the complex framework that influences patients' access to orphan drugs, in particular focusing on the role of R&D, regulatory and payer/commissioner decisions and the links between decision making along the pathway to access. In doing so we seek to make suggestions for better decision making and how to improve access for all to orphan drugs.

We draw on examples from the literature, explore several case studies in detail and take lessons from the situation in other countries. During this project we also benefitted from a mix of telephone and face to face interviews and discussions with patient representatives, clinicians, commissioners, pharmacists, health economists and companies. 2020health would like to thank all those who freely gave us their data, knowledge and expertise.

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November 2012

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Interviewee comments do not necessarily represent the view of others within the same stakeholder group (for example, comments from individuals from different pharmaceutical companies do not necessarily reflect the views of sponsors of this work).

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Whilst we are grateful for all of the insights from these experts, the content of this report is independent and may not reflect the views of experts, and represents only the views of the 2020health project team.

Executive Summary

This report examines the evidence to see if there are ways of improving decision making on treatments for people with rare diseases in the NHS. At the moment, access to medicines is inconsistent across the UK because of regional variation in decision making, and some approved drugs are routinely available to some patients, but not others. People with rare diseases are utterly dependent on the NHS and they deserve a fair deal.

Rarity, orphan drugs and inconsistent access

A disease is considered rare when it affects fewer than five in 10,000 people in Europe. For a small minority of these rare diseases there are drugs approved for treatment. When a product is approved it means that it offers more clinical benefits than harm and at an acceptable risk. Products are designated as 'orphan' drugs in the European Union (EU) when they are used for treating less than five in 10,000 people. Some products are produced for very rare diseases and these are often termed 'ultra-orphan drugs'. There is no formal definition for ultra-orphan drugs, but treatments for a rare disease with a prevalence of less than one in 50,000 population has been put forward as a possibility.

Not all of the approved orphan drugs are available to patients in the UK. In 2010, 48 out of 61 approved orphan drugs (at that time) were described as 'available'. Access in the UK has also been described as 'slow' compared to other European counterparts. Within the UK, there are different recommendations made by agencies such as the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC), and the All Wales Medicine Strategy Group (AWMSG) (see table below). They have not assessed all orphan drugs, leaving a gap which must be filled by regional and/or local decision makers about whether or not to pay for an orphan drug on the National Health Service (NHS).

Table: *Approved orphan products subject to appraisal and recommendations, NICE, SMC, AWMSG, 2000 - 2011*

Agency	NICE	SMC	AWMSG
Orphan products by indication subject to appraisal	18 (26%)	56 (82%)	51 (75%)
Of those:			
Recommended	7 (39%)	14 (25%)	12 (24%)
Restricted	5 (28%)	14 (25%)	9 (18%)
Not recommended	6 (33%)	27 (48%)	30 (59%)

Notes: We separately identified indications for each product, with a total of 75 indications for 68 approved orphan drugs. NICE: Further 5 products considered but not prioritorised for appraisal, 4 where the appraisal is suspended, 1 outside of NICE remit. SMC: Further 1 product withdrawn, 2 forthcoming. AWMSG: Further 1 product forthcoming.[3] *Some are indirect recommendations by AWMSG reflecting the decision to either appraise or not depending on when NICE guidance is likely to be published, and the superceeding of AWMSG guidance following NICE guidance publication.*

Those we spoke to raised their concerns about the lack of equity from different decisions being made between the devolved nations of the UK, and between different regions in England.

Both the lack of and inconsistent access to medicines is a real concern for patients and clinicians and prompted this report. This report also takes a wide view of access: access means a product is approved, reimbursed and available to be prescribed.

Planned and ongoing reforms offer an opportunity to explicitly consider access to orphan drugs

These issues are timely both because there are plans to reform pricing and reimbursement in the UK through Value Based Pricing (VBP) from 2014, and because of reforms to the NHS in England. These reforms mean that commissioning of services for those with rare diseases will be undertaken by the new National Commissioning Board (NCB) in the future. The UK is also developing its strategy for rare disease. We believe that jointly these present an opportunity for making changes that can improve access to orphan drugs. We also know that the NHS is facing significant problems: lower growth in funding, rising demand, attempts to increase efficiency and to dis-invest in services in order to free up resources. This is no easy task; funding orphan drugs will likely add financial pressure (because projections for other countries suggest rising expenditure, but we did not find projections for the UK) but will improve the health of those with rare diseases. The policy questions are how to make these decisions, and what is a reasonable cost to achieve these health improvements?

We found that:

Research and development is difficult for orphan drugs, even more so for treatments for those with very rare diseases because of small sample sizes

Research and development (R&D) is difficult for all drugs, but the difficulties are intensified when developing products to treat those with rare diseases. These include: high cost, high risk and difficulties conducting trials (for example recruiting patients from a small pool, and choice of outcome markers). This is the rationale for offering additional incentives to develop products for rare diseases in Europe through free advice from the regulator (the European Medicines Agency, EMA) and a longer time period for intellectual property (IP) protection to allow companies to re-coup high R&D costs.

Small patient numbers require developers to work across multiple countries in order to build up sample sizes. This allows them to explore safety and efficacy. But in some cases it is simply not possible to reach sizes sufficient sizes to be able to carry out these tests fully, particularly for very rare diseases. There is often then more limited evidence for the regulator to draw upon in making their decision, and the end result is that success rates for orphan drugs achieving authorisation are lower than for non-orphan drugs, based on US approval rates* for orphan versus non-orphan drugs.

Regulatory approval takes a pragmatic approach with different options for approval, and allowing for the specific context of drug and the rare disease

The EMA can respond to the more limited evidence base using:

- a conditional marketing authorisation. This permits a move to normal authorisation following provision of further evidence;

- a marketing authorisation under exceptional circumstances. This is where comprehensive data cannot be provided. This is annually reviewed, but is not normally expected to move to normal authorisation.

With 38% of marketing authorisations for orphan drugs between 2000 and 2010 classed as exceptional and 6% conditional, these signal the real limitations for developers to provide comprehensive data. But it is not always a constraint: the remaining 56% of those approved achieving a normal marketing authorisation. This means context matters: the disease, the drug, and the clinical benefit supported by the evidence.

The different types of marketing authorisation judged appropriate by the EMA provide some flexibility. Those we interviewed and the literature suggests that some would like this judgement to become more patient focused, as opposed to clinically focused. This includes scope for patients to (knowingly) take on more risk than perhaps EMA believes is acceptable.

* Our research did not find comparable statistics for the European Union.

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There are inconsistent approaches to decision making across the UK which influences Payer/Commissioner funding decisions locally

The way that agencies in the UK make recommendations on orphan drugs differ, as set out in the table below. The Advisory Group for National Specialised Services (AGNSS) provides the widest framework partially applying the multi-criteria decision analysis approach.

It can be very difficult for manufacturers of orphan drugs to provide cost effectiveness assessments, if at all. Agencies such as the SMC do not recommend products when there is no cost effectiveness assessment submitted. In assessing value for money there also remains debate about what is reasonable in terms of evidence to inform payer approval and in terms of evidence required for re-reviews (e.g. outcome markers that are acceptable for use).

Table: *Key features of UK agencies who make recommendations on orphan drugs*

Feature	NICE	SMC	AWMSG	AGNSS
Geographical coverage	England and Wales	Scotland	Wales	England
Scope of remit: technologies	Wide: drugs, devices, public health	Narrow: new medicines	Narrow: new medicines	National specialised services (generally services that affect <500 people across England)
Coverage	Selected medicines	All new medicines	Selected medicines	(Ultra*) orphan drugs
Core criteria	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	12 criteria based on 4 domains: Does it work? Does it add value to society? Is it a reasonable cost to the public? Is it the best way of delivering the service?
Different criteria for orphan drugs?	No (but suggested different approach in 2006 but not fully acted on)	Yes (from 2007)	Yes (from 2011)	Only considers orphan drugs (<500 patients in England)
Status of guidance	Positive recommendations from Technology Appraisal must be funded by commissioners in England	Input to local decisions, but no requirement for the NHS in Scotland to follow recommendations	NHS in Wales expected to follow guidance	Recommendations to Ministers, with Ministers taking final decisions. Funding is top-sliced

Note: QALY = Quality Adjusted Life Year, a generic measure which aims to capture the impact of a technology in terms of both survival and quality of life.
**Although this is not a formal term used by AGNSS*

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Some of those we spoke to are concerned that the weight that different factors are given in these processes, such as maximising health gain for all over concerns about distribution of those health gains. The latter is essentially a concern about equity or fairness, such as whether those with rare diseases will be 'left behind'.

Commissioners/payers must also balance cost effectiveness with budget impact. The budget impact of orphan drugs tends to be much lower than for treatments for more common diseases, because there are fewer patients who will be prescribed treatment. And that is also a key driver of the price: developers have to re-coup R&D (including failures) across a small patient population. However, the precise price that is charged will reflect the specific circumstances, and what price is 'reasonable' is always likely to remain a controversial subject. The evidence of public support for priority being given to those with rare diseases is mixed, and does not currently provide a clear recommendation for policy.

There are also a whole host of factors that influence how recommendations translate into access for patients, and we recognise that new efforts have been made to improve access through initiatives such as the NICE Compliance Regime as set out in Innovation, Health and Wealth.

Evidence generated by companies needs to inform both regulatory and HTA/payer decisions

The evidence available to inform both regulators and payers has a significant overlap. This has led to a number of international efforts to improve the evidence base, with the aim of helping all parties: more relevant evidence for decision-makers and a more efficient generation of that evidence for companies.

Recommendations

Based on our research we believe that improvements can be made to how decisions are reached on orphan drugs:

Patients should be involved in early decisions about R&D for orphan drugs: working with individual companies to identify targets and appropriate patient focused outcome measures. This work should also involve regulators.

EMA and Health Technology Assessment (HTA) agencies should continue to explore the concept of real world evidence generation (medicines being used outside of the clinical setting) via EUnetHTA. This should include a pilot using an orphan drug.

EU Member States (MS) should work together to explore the feasibility of sharing information arising from compassionate use monitoring, as part of individual MS strategies for rare disease.

Agencies should apply multiple criteria in informing their recommendations on use of orphan drugs in the NHS. There is scope to explore building more consistency across the agencies across the UK and build on approaches to patient involvement.

Full details of the approach to VBP are not yet known. It is too early to take a decision on whether VBP will be appropriate to consider orphan drugs.

Orphan drugs should be explicitly included in ongoing work to support access to NICE approved products.

Finally, in the longer term, there should be further research undertaken with the UK population to explore the presence and scale of a societal premium to treat rare diseases.

1 Introduction

1.1 Rare Diseases and Orphan Drugs

The European Commission (EC) considers a disease rare when it affects fewer than five per 10,000 people in Europe (EC, 2008). It has been estimated that one in 17 people will be affected by a rare disease at some point in their life. That would amount to 3.5 million people in the UK (Rare Disease UK, 2012a). Rare diseases together touch millions of lives, including those of carers. There are real opportunities to improve the lives of some of those with rare diseases through appropriate treatment, as the result of the continuing efforts of scientists, clinicians, universities, and commercial companies to identify, develop and deliver effective medicines.

By the end of 2011 there were 68 medicines with orphan drug designation in Europe approved for use (Committee for Orphan Drugs (COMP) and the European Medicines Agency Scientific Secretariat (EMASS), 2011 and Orphanet, 2012a).[1] A drug can receive an orphan drug designation in the European Union (EU) when it treats less than five in 10,000 people in the EU (EMA, undated a).[2]

1.2 Evidence on Access to Orphan Drugs

Our starting point for this work was a concern that there is inconsistent access to orphan drugs. We have interpreted access widely to encompass regulatory approval, reimbursement, speed of decision making and supply being available for patient use. Inconsistent access is a source of frustration and there is sense from those we spoke to of unfairness. We looked at the evidence base to help us understand access to orphan drugs.

Comparisons to explore availability of individual orphan drugs across countries has found that the UK has variously demonstrated lower availability than other countries (in 2007), and higher availability (in 2010) (see table below). Even when availability has been high, compared to other countries, it is still below that of approved products; 48 available from 61 approved.

1. 63 identified by COMP and EMASS, a further five identified by Orphanet.
2. Other conditions also apply, see later discussion in this report.

1 Introduction

Table 1: *Number of Orphan Medicinal Products (OMPs) available in 2006, 2007, 2010*

Country	2006	2007	2010
Austria		15-19	13
Belgium	15	5-9	40
Bulgaria			18
Czech Republic	14		30
Denmark	15	15-19	47
Estonia	4		
Finland	11	20-21	25
France		20-21	
Greece		5-9	42
Germany		20-21	
Hungary	6		18
Ireland	6	5-9	22
Italy	15	10-14	
Latvia	3		0
Luxembourg		5-9	
The Netherlands		10-14	48
Norway			47
Portugal		5-9	
Slovakia	11		
Spain		15-19	
Sweden		20-21	
UK	17	10-14	48

Sources:
1 Task-Force in Europe for Drug Development for the Young (TEDDY), 2007
2 EURODIS, 2007
Note: The latest EURODIS survey we identified was undertaken in 2010 but did not include the UK. See: http://www.eurordis.org/content/survey-patients'-access-orphan-drugs-europe
3 Habl and Bachner, 2011

Note: These surveys are not strictly comparable, in 1 and 2 there was a limited sample of approved orphan drugs assessed for their availability, in 3 there was a full sample of approved drugs as at the time the survey was completed (61 for the majority of countries).

1 Introduction

The UK has been characterised as having 'slow' access, in comparison to other European countries (see table below).

Table 2: *ORPHANET assessment of early access and access to orphan medicines in Europe*

Country	Early access [1]	Access [2]	Comments
Germany	No	Fast	Nothing particular
Austria	UC/NP	Slow	Nothing particular
Belgium	UC/NP	Slow ++	Nothing particular
Denmark	UC/NP	Complex	Nothing particular
Finland	UC/NP	Complex	Nothing particular
France	TUA	Rapid	Co-ordination at OMA level
Spain	UC/NP	Classic	Nothing particular
Greece	UC/NP	Classic	Nothing particular
Ireland	UC/NP	Classic	Nothing particular
Italy	TUA	Classic	Nothing particular
Luxembourg	UC/NP	Classic	Nothing particular
The Netherlands	UC/NP	Classic	Improvements to be discussed
Portugal	Depends on the case	Depends on the case	Special funds awarded
UK	**UC/NP**	**Slow**	**Considered as expensive**
Sweden	UC/NP	East	Nothing particular

Notes: TUA = Temporary Use Authorisation
UC/NP = Compassionate use / Nominative base of patients
Source: Orphanet, 2012b [online]

1. Although not defined, we take this to mean before marketing authorisation.
2. Although not defined, we take this to mean after market authorisation.
Note: that comments are not from 2020health but those of Orphanet.

1 Introduction

Our own research finds that there are different recommendations made about orphan drugs according to which agency assesses the clinical and cost effectiveness of medicines (see table below). NICE recommends more orphan drugs than either SMC or AWMSG on a percentage basis, but far fewer products by indication overall. This research also highlights that many approved orphan drugs have not gone through a national assessment.

Table 3: *Approved orphan products subject to appraisal and recommendations, NICE, SMC, AWMSG, 2000 - 2011*

Agency	NICE	SMC	AWMSG
Orphan products by indication subject to appraisal	18 (26%)	56 (82%)	51 (75%)
Of those:			
Recommended	7 (39%)	14 (25%)	12 (24%)
Restricted	5 (28%)	14 (25%)	9 (18%)
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Notes: We separately identified indications for each product, with a total of 75 indications for 68 approved orphan drugs. NICE: Further 5 products considered but not prioritorised for appraisal, 4 where the appraisal is suspended, 1 outside of NICE remit. SMC: Further 1 product withdrawn, 2 forthcoming AWMSG: Further 1 product forthcoming.[3] *Some are indirect recommendations by AWMSG reflecting the decision to either appraise or not depending on when NICE guidance is likely to be published, and the superceeding of AWMSG guidance following NICE guidance publication.*

Research has also explored whether there are differences in access to orphan drugs versus non-orphan products. That pilot research, undertaken over two years ago, suggests that there is no larger variability in use than drugs without an orphan medicine status (Stolk et al, 2009). This suggests that variation in access stems from the systems, and not from the designation of the product. But that finding does not necessarily accord with the perception of those we recently interviewed, and of course the situation is dynamic; access is likely to change over time.

There are also access issues beyond decisions relating to marketing approval and funding, as there can be challenges when there is a supply problem (an example is provided in Deegan and Cox, 2012).

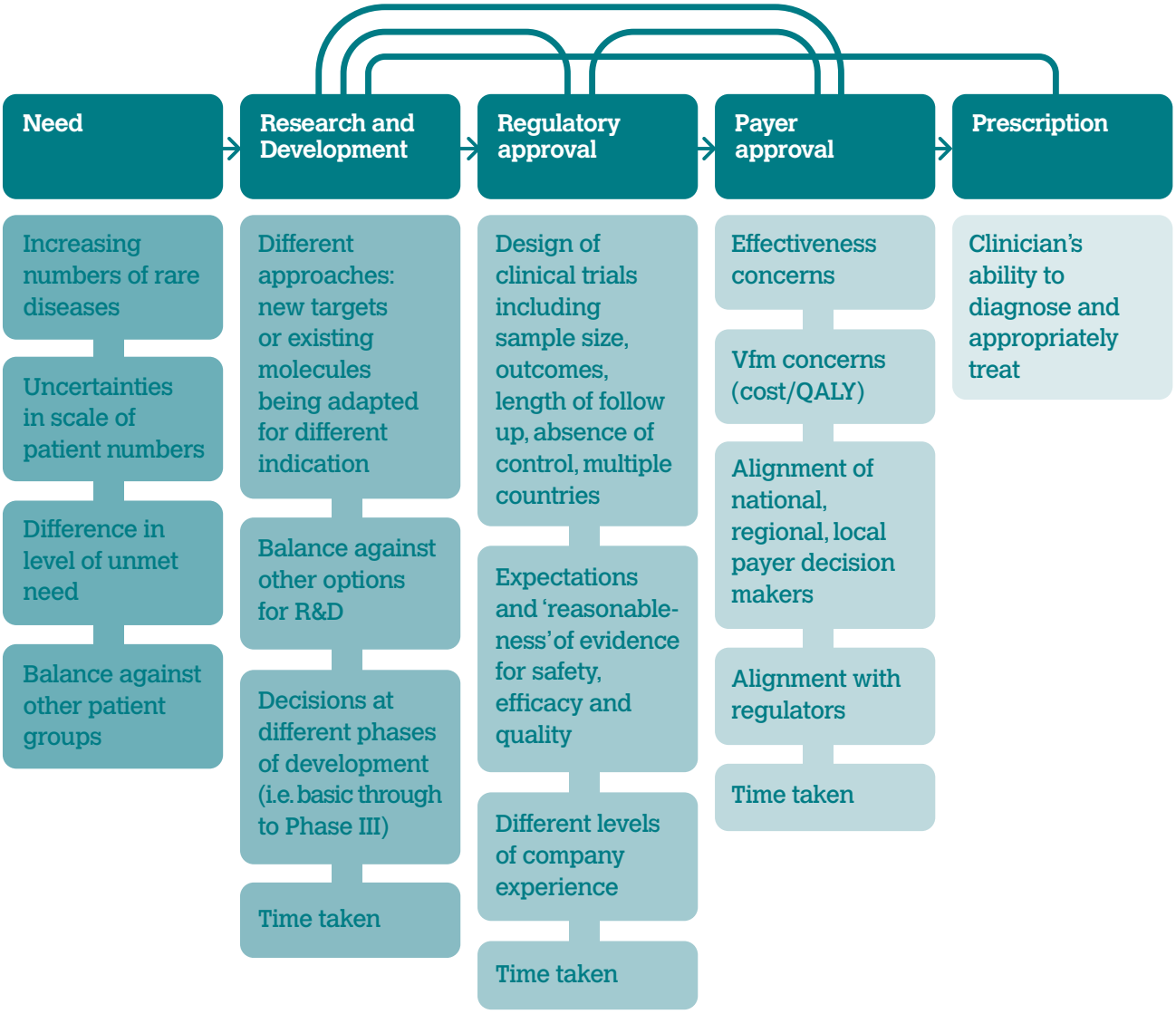
3. This compares to 55 decisions by SMC for 74 indications and nine indications by NICE in OHE analysis (http://news.ohe.org/2011/08/23/recent-statistics-on-orphan-approvals-in-scotland-and-england/ [Accessed May 10th 2012]). Differences in the counts could be a result of different timescales (with OHE looking up to May 2011). For example, since OHE undertook their analysis, Azacitine is now recommended by SMC, previously it was not.

1 Introduction

1.4 The pathway to access Orphan Drugs

Early on in our research we identified the pathway to access for orphan drugs, based on our reading of the literature, and discussions within our project team and steering group. The pathway includes the key decision points and issues at each stage. Although presented in a linear fashion in our figure below, the realities are complex interactions between each decision point.

Figure 1: *Pathway to access orphan drugs and underlying issues*



Notes: R&D = research and development.
Vfm = Value for money.
QALY = quality adjusted life year.

2 Wider NHS Context

2.1 Opportunities to improve access to orphan drugs as part of a strategy for rare disease in the uk

We believe that there are opportunities to improve patient access to orphan drugs in the UK. Changes could help to reduce the frustrations when patients cannot access products, whether that is in comparison to other countries or where access differs within the UK. These opportunities are also linked to broader efforts including the development of a strategy for rare disease in the UK, to improve diagnosis and access to treatment. The Department of Health (DH), on behalf of all the devolved nations, published their initial thoughts in February 2012 (DH, 2012a).[4] Although the strategy is wider than our scope in this report, it does include access to medicines to treat rare diseases. We hope that our report will be of relevance as the DH continue work on this.

2.2 Proposals for Value Based Pricing (VBP)

In addition to specific efforts focused on rare disease, there are proposals to change the way the UK approaches pricing and reimbursement of medicines, with a particular focus on access to medicines. Under proposals set out by the DH, Value Based Pricing (VBP) will include a wider assessment of the value that medicines can bring. Pricing is a reserved power and covers the whole of the UK (DH, 2010a).

VBP is intended to extend the approach to cover not just quality and length of life, but also the pioneering aspects of the new medicine, its societal benefits, and the burden of the disease it combats. The debate on what this means in theory and in practice (such as who will take on this wider assessment of value, value to whom and how that will link to a product's price) is continuing.

Orphan drugs could become part of the VBP approach as indicated by the UK's consultation on a rare disease strategy (DH, 2012b). However, this is not certain, with respondents to the VBP consultation suggesting that it may be appropriate to have a separate process for treatments for very rare diseases (which we take to mean ultra-orphan drugs although this is not explicitly stated) (DH, 2011). The Government has yet to determine whether and how separate processes might exist for assessing and pricing treatments for rare diseases, and our understanding is that this remains a policy decision to be made (DH, 2011).

2.3 Reform in the English NHS

VBP proposals are not the only reforms that could affect future patient access to medicines. The broader structural changes to the NHS, such as the move to new Clinical Commissioning Groups (CCGs) to replace Primary Care Trusts (PCTs) and the new National Commissioning Board (NCB) in England could also be either enablers or barriers to patient access. For example, the level at which commissioning decisions are made (at a national, regional or local level, or in some combination) and the incentives that commissioners face (such as budget constraints) will have an impact. As part of the reforms there are opportunities to consider the scope to use the new NHS Mandate, which sets out the objectives for the improvement of health and healthcare to the NCB, to also enable access. The draft Mandate includes an objective to:

"Objective 10: Uphold, and where possible, improve performance on the rights and pledges for patients in the NHS Constitution"

Consultations on the Mandate are ongoing at the time of writing.

2.4 Precision medicine can learn from approaches to orphan drugs

It is clear that as knowledge increases (for example, in genetics) that there will be more and more diseases that can be sub-divided. This trend towards precision medicine, also known as personalised medicine[5], will mean that decision-making processes increasingly need to respond to products that treat smaller patient groups. But with that comes the opportunity to focus on those who will be most likely to benefit from treatment, offering value for money (interviewee's comment). This makes the case for improving the decision-making processes for access to orphan drugs even more pressing, as it will provide useful lessons for the approach to precision medicines, which will be increasingly relevant in the future.

4. Others have produced reports that consider a wider range of issues affecting those with rare diseases. For example, Rare Disease UK, 2011
5. Other terms include personalised medicine, or stratified medicine. These were used interchangeably in our interviews with different stakeholder groups.

2 Wider NHS Context

2.5 Pressures on the NHS

There is no way to ignore the stress the NHS is under. The NHS across the UK is facing a context of rising demand (as people age, as expectations rise and new technologies become available) and falling growth in funding. For example, the NHS in England will receive a 0.1% real terms increase in funding in 2012/13 which compares to an average of 6.5% between 2000/1 to 2009/10 (Harker, 2011). This is leading to a renewed focus on what the NHS can afford, and within that, what it can afford for new medicines. Given that orphan drugs are often (but not always) high cost, they may add to the NHS budget, but that depends too on volume (typically very low) and other decisions (such as what activities to stop funding). We did not find projections for expenditure in the UK on orphan drugs, but a projection for Europe suggest orphan drugs will take up a greater share of expenditure on medicines (Schey et al, 2011), and will increase in Belgium (Denis et al, 2010b). It seems reasonable to infer that expenditure could rise in the UK too.

Finding the balance between what the NHS should pay (which could be less than manufacturers ask) and can afford to pay, and how those decisions are made (for example, how far cost effectiveness is considered of other non-drug activities), remains controversial. And that is in the absence of considering whether there are genuine efficiency savings or appropriate dis-investments that could provide the headroom for funding new medicines.

3 Methods

We adopted a multi-method approach to this project, reflecting the need to deliver within a relatively short period of time and with limited resources. We:

- conducted a review of the literature looking at papers identified by searching for the phrase 'orphan drugs OR medicines' in the title or abstract, in Pubmed on the 5th March 2012. We limited our search to papers published in the last five years and written in English;

- undertook a mix of telephone and face-to-face interviews with stakeholders across the system from patient representatives, clinicians, commissioners, pharmacists, health economists and companies. Their names are listed in the acknowledgements;

- focused on five case studies to explore in more detail the pathway to patient access to five specific products in five rare diseases.

Case studies were selected on the basis of an iterative application of the following criteria:

a. Products that have been through a formal assessment undertaken by NICE. NICE appraisals cover the largest proportion of the UK population. Next we looked at whether these NICE appraised products had been through Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) assessment.

b. A product for more 'rare' rare disease and a product for more 'common' rare disease (given the diversity within rare diseases).

c. A product which was assessed early on in the implementation of the orphan drug legislation (i.e. 2001) and a product assessed later on (i.e. 2010).

d. A product approved under exceptional circumstances, conditional approval and under normal approval (as this is a proxy for evidence available at the time of approval as well as confidence in the product from the regulators point of view).

We also had a steering group who provided their expert insights and helped us consider the approach and evidence and had advisors who commented on our draft report. Their names are listed in the acknowledgements.

We recognise that our approach has its limitations and that in practice we could not hope to cover all the issues that affect those with rare diseases and their access to orphan drugs, both today and in the future. With between 5,000 and 8,000 rare diseases in existence and 68 orphan medicines approved we could not possibly hope to be comprehensive. That also leaves aside those medicines that are being used before marketing approval or outside of their license. However we hope that this report provides the evidence needed to support improvements to decisions that determine patient access to orphan drugs. We also hope that this report will be seen as a working report, and the issues re-visited over time.

4 What does having a rare disease mean for the medicines that treat them?

4.1 About Rare Diseases

Between 5,000 and 8,000 rare diseases exist (Ayme and Schmidtke, 2007). Some 250 new rare diseases are described each year (Heemstra et al, 2011). Rare diseases collectively are likely to affect some 3.5 million people in the UK (Rare Disease UK 2012a) but prevalence of rare diseases is relatively under-researched (Tambuyzer, 2010). This results in uncertainties for the number of people with a rare disease, and within that the numbers who may benefit from specific orphan drugs.

Many rare diseases have a genetic origin but many are related to environmental factors (Taruscio et al, 2011). It is estimated that around half of rare diseases manifest themselves at birth or during infancy, the rest appearing in adulthood. Their impact can be severe: premature mortality or longstanding and severe disability. There is also diversity within the spectrum of rare diseases: Buckley (2008) notes that rare diseases cover those from low incidence and poor survival (e.g. severe combined immunodeficiency syndrome) through to those with a low incidence and relatively long survival (e.g. Duchenne muscular dystrophy, cystic fibrosis), to those with a relatively common incidence but short survival (e.g. pancreatic and renal carcinomas, myeloma, and glioma).

4.2 Needs of people with rare diseases

The needs of those with rare diseases are as diverse as the diseases themselves under the broad umbrella term of 'rare disease'. Based on our discussion with interviewees, successfully meeting those needs entails a complex set of interactions based on:

- appropriate diagnosis and the speed of diagnosis, as some treatment options will no longer be viable past a certain point of disease progression. This is the case in Gaucher's Disease (interviewee's comment);
- appropriate access to expertise to inform choice of treatment, and ideally in partnership with the patient; and
- appropriate access to services and technologies, including diagnostics and medicines.

There are widely held concerns about meeting the needs of those with rare diseases, both in the literature (Philipidis, 2001; Dunoyer, 2011; Kole and Faurisson, 2010) and from our discussions with interviewees. Kole and Faurisson (2010) suggest that some of those with rare diseases are denied the right to *"the enjoyment of the highest attainable standard of health [which] is one of the fundamental rights of every human being without the distinction of race, religion, political belief, economic or social condition"*, as set out in the World Health Organisation (WHO) Constitution.

The challenges are not just about money, but also how the system is structured and can either enable, or act as a barrier, to diagnosis, management and treatment, including access to orphan drugs. For example, delayed diagnosis can be a significant challenge for some rare diseases (Taruscio, 2011; Kole and Faurisson, 2010). The delay can be substantial. For 75% of patients surveyed in 2006 by EUORDIS, the delay in diagnosis for Ehler-Danlos syndrome was 28 years (Kole and Faurisson, 2010). This example illustrates a more general issue for rare disease, as Ehler-Danlos syndrome does not currently have an orphan drug treatment.

4.3 Orphan Drugs

Just as those diseases classified as rare are diverse, the medicines to treat them are also many and varied. We have focused on those products that have been successful in achieving orphan drug designation under EU legislation and marketing authorisation, but we recognise that there are others that can be used, including off license use of products for other indications or products not yet licensed.

Products that have been successful in achieving orphan drug status under EU legislation implemented in 2000 have met at least one of two criteria (EMA, undated a):

"It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10,000 people in the EU at the time of submission of the designation application.

It is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development."

In addition, there *"must also be either no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such a method does exists, the medicine must be of significant benefit to those affected by the condition."*

4 What does having a rare disease mean for the medicines that treat them?

The key characteristic for orphan drugs is the underlying small numbers of patients with the condition. In some diseases, this can be as low as two or three in a country like Wales (interviewee's comment).

Our case studies of five orphan drugs illustrate the range of patient numbers in the UK who may be eligible for treatment with an orphan medicine:

1. Less than 4,000 people potentially eligible for treatment with Afinitor for renal cell carcinoma (RCC). EU prevalence is estimated to be 4.2 per 10,000 population.

2. Approximately 75 children in Scotland, and between 10 and 25 in Wales, potentially eligible for treatment with Diacomit for severe myoclonic epilepsy in infancy (SMEI). EU prevalence is estimated to be 0.4 per 10,000 population.

3. Approximately 2,700 people diagnosed with chronic myeloid leukaemia (CML) in England and Wales[6] and potentially eligible for treatment with Glivec. EU prevalence is estimated to be 0.9 per 10,000 population.

4. Around half of the 5,000 people diagnosed with multiple myeloma (MM) in the UK will be eligible for Revlimid. EU prevalence is estimated to be 1.3 per 10,000 population.

5. Between 3,000 to 9,500 people in England will have chronic idiopathic thrombocytopenic purpura (ITP). EU prevalence is estimated to be <five per 10,000 population.

Those small numbers have particular relevance for a number of decisions that contribute to the pathway to access: from initial decisions for targets of research and development (R&D), because the return on investment can be challenging, all the way to prescribing where only limited numbers of experts may be available to diagnose, manage and prescribe orphan drugs. This is because few clinicians can see sufficient numbers of patients to build up their expertise. This has a knock on effect to patient access: in theory no R&D being undertaken because of a concern of limited profit can stop the development of a treatment. This is not necessarily the reality though, as breakthroughs in medicines to treat rare diseases can come from outside commercial companies and progress through later stages of R&D by a commercial company. Small patient numbers also introduce significant uncertainty in the assessment of products, for safety, quality and efficacy, and for clinical and cost effectiveness, reflecting small sample sizes in clinical trials.

The recognition of the poor incentives for R&D in rare diseases led to concerted efforts to encourage R&D through EU legislation. Those products that meet the criteria for orphan drug status can benefit from 10 years market exclusivity. This essentially allows a period for the manufacturer to re-coup R&D costs, not necessarily just on the successful product but also on failures which have arisen on the way. Manufacturers also benefit from direct access to the centralised procedure at the European Medicines Agency (which must be respected across European Member States). They also benefit from a reduction in fees and free scientific advice. Over time the provisions of the legislation have changed, offering from 2009 more generous fee reductions (Taruscio et al, 2011).

Similar efforts to encourage R&D into medicines for rare diseases were pursued earlier in the US. In 1983 the US introduced orphan drug designation for products that serve a maximum of 200,000 patients (around 7 per 10,000 residents). Brewer (2009) suggests that the figure of 200,000 patients represents the point beneath which R&D becomes unprofitable for manufacturers. Under the Orphan Drug Act (ODA) manufacturers can benefit from tax grants (Heemstra et al, 2008a) and 7 years exclusivity (Brewer, 2008). They can also benefit from exemptions from FDA fees for regulatory submissions and regulatory advice (Tambuyzer, 2010).

In the US, patient advocacy has been cited as a key driver for Government intervention (Davies et al, 2012). Patient advocacy has also been a key driver in Europe (Tambuyzer, 2010).

However, not all countries have agreed on the need for incentives for companies. For example, Health Canada decided against a specific Orphan Drug Policy in 1997 (Health Canada, 1997).

6. An interviewee has told us that this may be lower than is the case now

4 What does having a rare disease mean for the medicines that treat them?

As of 2011, 68 marketing authorisations have been granted in Europe for products with orphan drug designation. Details are set out in Appendix A. Just over half of approved orphan products in Europe are for diseases affecting fewer than 1 in 10,000 people (COMP and EMAS, 2011). Overall the average time between receiving orphan designation and marketing authorisation was 2.8 years (COMP and EMAS, 2011). There are over 400 products in the pipeline to treat or prevent rare diseases, as at 2011 (PhRMA, 2011).

Not all products will retain their orphan drug designation. For example, one of our case study products, Afinitor, for renal cell carcinoma, was removed from the Community Register of orphan medicinal products at the request of Novartis. This implies that, in some instances, it may make commercial sense not to be an orphan.

5 How are decisions made which affect patient access to orphan medicines?

In this part of the report we discuss the key decision points in the pathway for access to orphan drugs. We focus on the approaches taken across the UK, but also draw on insights from other countries. We also explore specific issues for treatments for rare diseases; inevitably there are some crossovers with treatments for common diseases as some of the issues are the same.

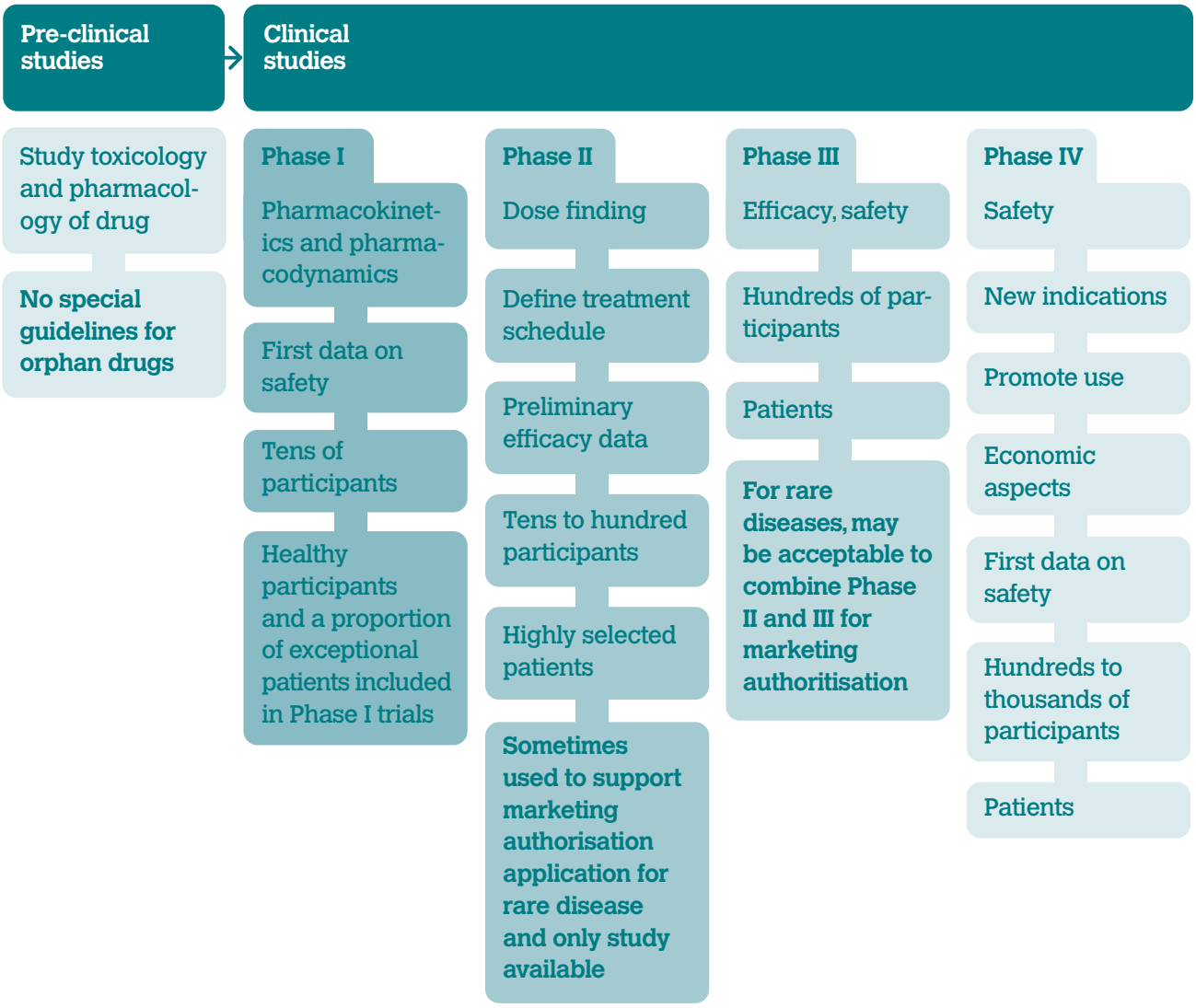
Although we focus on access, we also know that there are other policy objectives linked to elements of the pathway to access: for example, the contribution of the pharmaceutical industry to UK economic growth via expenditure on R&D, including employment (OHE, 2010). This is part of the broader discussion of the links between health and wealth. It is also recognised how difficult it is in general to balance health and industrial policy objectives and the tension that this can cause (Morgan et al, 2008). Further, some have expressed concern about a disconnect between health and industrial policy with Government departments such as DH and the Department for Business, Innovation and Skills (BIS) (interviewee's comments). There is evidence of a broader link between origin of orphan drug designation applications and general innovation policies in individual countries across Europe. Those countries with more 'supportive' innovative policies, such as support for small and medium sized enterprises, have a greater proportion of applications for orphan drug designation (Heemstra et al, 2008b). If there is a desire for more drugs for rare diseases, there is scope to build on both general innovation and specific areas of policy.

6 R&D Decisions

6.1 Introduction

R&D is a complex set of activities. An overview is provided in the figure below. It also highlights that there are some differences in the regulatory approach between treatments for rare diseases and more common diseases. We have included them here because commercial companies must consider the needs of the regulator when they make their R&D decisions. No approval means essentially no market access.[7]

Figure 2: *R&D for new medicines*



Source: Adapted from Llinares, 2010

7. With the exception of any earlier access and/or compassionate use which can allow access to some products for some patients.

6 R&D Decisions

Choices need to be made within R&D regarding the approach to exploring the potential clinical benefits and risks from a new active ingredient. Although not focused just on rare diseases, there are broader debates about the approach to development. Some have argued that high attrition rates for drugs in development are in part due to too much focus on target-based approaches to development, versus alternative approaches including phenotypic screening, modification of natural substances and biologic-based methods. There is scope to explore the potential of drug repositioning or re-purposing—essentially looking at the potential to use existing products, or modified versions, to treat other diseases (Swinney and Anthony, 2011; Sardana et al, 2011; Ekin et al, 2011).

Some have also suggested that the economic viability of the research-based pharmaceutical industry is uncertain (Davies et al, 2012). This reflects the underlying challenges in successful drug development, including using current revenues to fund future R&D. It appears that the productivity of R&D is declining with fewer successful products brought to market despite increasing expenditure on R&D (Pan et al, 2012; Swinney and Anthony, 2011). The solution to such concerns is also much debated, with interest in more collaboration (Golden, 2011) and, potentially, innovation prizes (Callan and Gillespie, 2007).

R&D decisions are taken by accounting for a variety of factors. Largely, they are influenced by experience (Schmid and Smith, 2004). However, underlying commercial R&D activities are the commercial realities that pharmaceutical manufacturers face, as Villa (2008) notes: *"pharmaceutical firms in a market-driven system respond mainly to economic and profit drivers rather than social or human imperatives"*.

The development of treatments for rare diseases faces challenges, perhaps intensifying some of the same challenges surrounding more common diseases. These include (Heemstra et al, 2008a; Llinares, 2010):

- high costs of R&D;
- risks of R&D;
- challenges of conducting trials in small patient populations; and
- small market size.

We discuss the difficulties of R&D in more detail below.

6.2 High costs of R&D

High costs of R&D are recognised as part of the overall poor incentives for commercial R&D in rare diseases (Heemstra et al, 2008a; Llinares, 2010). The cost of R&D for new medicine in general is substantial, with estimates ranging from US$800million (Pan et al, 2010) to US$1billion (Davies et al, 2012). It can take 10 to 17 years to bring a product to market (Pan et al, 2010).

For example, the development costs of alglucosidase α for Pompe disease were in excess of US$500 million by the end of 2004, excluding academic research costs and any later costs for post-authorisation monitoring (Tambuyzer, 2010). However, some companies do not provide transparency on the specific R&D expenditure on developing products for rare diseases (Philippidis, 2011). Davies et al (2012) also note that empirical estimates of the cost of bringing an orphan drug to market are not available.

Some interviewees thought that the costs may be slightly less than those for a common disease because of smaller sample sizes in clinical trials. Others felt that the added complexity of having to work across countries in order to recruit trial participants may offset the lower cost of smaller sample sizes.

Only companies know the true costs (although it may not be easy to attribute costs to specific products when companies have large portfolios), and cost generalisations are not straightforward given the diversity of rare diseases. But the costs are unlikely to be trivial and will be driving later pricing decisions by companies.

6 R&D Decisions

6.3 Risks of R&D

There are no guarantees that R&D will necessarily result in an effective medicine (leaving aside later questions of regulatory and payer approval and prescription). Eisenberg (2009) illustrates this by highlighting the lack of new treatments for systemic lupus erythematosus. He cites a number of reasons why no new novel compounds have been approved (as at 2008 and despite R&D being undertaken), including: complexity of the disease itself; the lack of reliable outcome measures; limited understanding of the pathogenesis of the disease (the mechanism by which the disease is caused); the propensity of lupus patients to have bad outcomes and to react to medicines in unusual ways; the heterogeneity of the patient population; the unpredictable course of disease in individual patients; and the lack of reliable biomarkers (indicator of a biological state, such as the level of a protein in the blood). However, by 2012 there was a product available and approved by the regulatory authorities. Now the challenge is proving cost effectiveness (Bosely, 2012).

A marker of success is achieving marketing authorisation. In the US marketing authorisation may occur in anywhere from 8% to 20% of all drugs that enter Phase I testing (Grabowski and Moe, undated). Tambuyzer (2010) cites a differential success rate of 62.9% for orphan products versus 70.7% for non-orphan products in the US.[8]

A variety of factors may underlie the failures. These can be general issues that apply equally to products to treat common diseases, such as the failure of investigators to secure funding to continue the development process (interviewee's comment). However, there may be particular challenges for development of orphan medicines because of a more general lack of understanding of why a rare disease occurs (Dunoyer, 2011).

Some have called for the EMA to play a role in helping to understand the discontinuation of R&D in orphan drugs and to be able to propose remedial action (EURORDIS, 2012).

6.4 Difficulties in conducting trials in small patient populations

The difficulty of running trials in small patient populations is a recognised disincentive for R&D in rare disease (Heemstra, 2008a; Llinares, 2010; Taruscio et al, 2011).

Buckley (2008) suggests that the most challenging element is patient recruitment, given the small patient population. He cites an example where there are only 42 patients from 28 families across the EU with a particular condition, hyperammonaemia associated with N-acetylglutamate synthase deficiency, which were identified during a 20-year period from 1980 to 2001.

Even where there are potential patients available for trial participation, they need to be recruited and stay in the trial over time. Shilling and Young (2009) highlight the challenges when recruiting children to clinical trials, including obtaining parental consent and allowing some tailoring to respond to different anxieties and concerns, both of children and parents. Whilst not applicable to all rare diseases, it is applicable in many and adds further complexity to recruitment. But there are some indications of a greater willingness among those with rare diseases in general to take part in clinical research (Philippidis, 2011). Companies must also consider the specific design of studies and trials, including the desired outcomes. Although not definitive, review of submissions to the regulator, the EMA, have found limitations in the evidence submitted, including (Taruscio, 2011):

- lack of dose finding studies;
- lack of controlled studies;
- insufficient exposure to the treatment; and
- use of surrogate endpoints or weak proof of clinical benefit.

The difficulty is identifying which of these, and to what degree, are a result of the inherent characteristics of rare diseases, the cost of research or insufficient effort on the part of manufacturers who bear the cost.

8. Although this is not defined further, so it is unclear what exactly is being referred to as a 'success rate'.

6 R&D Decisions

Small market size also creates poor incentives for R&D in rare diseases (Heemstra et al, 2008a; Llinares, 2010). Tambuyzer (2010) notes that even when there is a 'relatively high' estimate of prevalence that the actual number of treated patients can be very small. He cites the example of Gaucher's disease, where estimates suggest there are around 5,000 affected patients in Germany, with approximately 250 receiving treatment with an approved orphan drug. This implies that only 5% of patients with the disease have been found over the 15 years when the orphan product has been available.

The small market size, especially if there is uncertainty within the prevalence estimates, can reduce the revenue that companies can make in practice. The small market size is therefore a key driver of the cost per patient. Further, companies with products to treat the same indication have to compete for this market. This occurs even in rare diseases. For example, one of our case study products, Afinitor for renal cell carcinoma, is only one of at least two other options (Sorafenib and Sunitinib). Products may also only be suitable for some sub-groups or considered after other options have been used.

Together these factors could undermine the incentives of commercial companies to undertake R&D at all. That is the underlying driver of the EU legislation to provide more incentives for companies to take on the costs and risks.

In terms of how decisions are made to focus on rare diseases today, and in the context of EU legislation, interviewees highlighted that some commercial companies consider:

- the level of unmet need (essentially whether an existing effective treatment exists or not);
- disease severity; and
- size of patient population.

The size of the patient population may be greater when products are able to secure approval across different indications. For example, one of our case study products, Afinitor, was approved for use in renal cell carcinoma but is also used to treat a subependymal giant cell astrocytoma (a type of brain tumour). The manufacturer is also seeking approval for hormone receptor-positive HER2/neu negative advanced breast cancer.

Interviewees also stressed that breakthroughs can come from outside of commercial companies and be driven by academic research. However, interviewees told us it is likely that the decision to acquire new targets in rare diseases from academic research institutions are also driven by these factors.

Wherever the original source of the early research, commercial companies must make decisions about which targets to pursue and which to stop. Commercial companies with a varied portfolio of products across disease areas must make those decisions between starting/continuing R&D for rare diseases versus common diseases.

Davies et al (2012) use an example to demonstrate the challenges faced in bringing an orphan product to market. This is set out in the figure below.

Figure 3: *The challenges in bringing an orphan drug to market: case of Osteosarcoma*

Disease: Osteosarcoma

Prevalence: 2.5–4 cases per million total population ~<1,000 people in the UK

Prognosis: long-term event-free survival rate is less than 30%

Product: Mifamurtide

Time to bring to market: Granted orphan drug designation in 2001 in the US, 2004 in Europe. Initial application was not granted by the FDA, with a request for further trial. With recruitment for a separate trial in the same disease underway it was unlikely to be practical and would be very expensive. Subsequently a six year follow up of Intergroup Study 0133 was submitted to the European Medicines Agency (EMA) in 2009. Mifamurtide now has authorisation across Europe.

Clinical trial: Initial application for approval based on Intergroup Study 0133 (largest ever RCT in osteosarcoma). Trial took 5 years to gain sufficient numbers (800 US patients).

Benefit: Patients receiving Mifaurtide (alongside other treatments) survived longer than those without (70% to 78% at six years).

Source: Davies et al, 2012

7 Regulatory Decisions

7.1 Striking the appropriate balance of safety and risk

Decisions in the regulatory stage of the pathway are primarily concerned with safety, efficacy and quality. Regulators are charged with making decisions about the relative balance of benefits and risks. This is not necessarily easy or straightforward. They need to take a view about the level of uncertainty in both benefit and risk that is 'reasonable' or 'acceptable'. That balance is subject to debate, with some such as Saltonstall (2011) highlighting that in the case of orphan drugs, *"patients with such disorders are willing to accept reasonable risk in return for hope of effective treatment."*

Rare Disease UK (2012b) has used a citizens' jury approach to explore the balance that needs to be struck. According to their findings:

- regulators should include psychosocial factors in their decision-making;
- regulators should be more permissive for those treatments for people with rare and/or serious conditions;
- patients should be more involved in all stages of the process, from setting the research agenda to post-marketing authorisation decisions; and
- patients should be better supported to make their own decisions.

It was also suggested to us in our discussions that efforts to make clinical trials more relevant to patients by including patient-focused endpoints would also need regulators to be willing to consider those endpoints in their decision making.

Kesselheim et al (2011a) note that excessively lowering trial standards runs the risk of identifying benefits that are not real, or missing real risks. For example, gemtuzumab ozogamicin was approved in 2000 for acute myeloid leukemia but subsequently removed from the market in 2010. It was removed as a result of a confirmatory trial that found no improvement in outcome and a higher mortality risk (Kesselheim et al, 2011b). In part, concern about safety may be as a result of a different 'standard' accepted for clinical evidence (e.g. smaller trials with shorter follow up) and accelerated approval (AA) approaches in the US. However, analysis of orphan products under the AA process versus the normal FDA processes suggests that this may be less of a concern (Richer et al, 2009). Similarly the record of safety may be better for orphan than for other products; but vigilance is recommended (Heemstra et al, 2010).

Although the legislation may be widely considered a success, Heemstra et al (2008a) point to the fact that in April 2004, only 7.1% of EU designated potential orphan drugs received marketing authorisation. This suggests that more is needed to move from designation to successful approval.

7.2 European Medicines Agency (EMA) and orphan drug approval

In the European context, the EMA is responsible for taking a view on the risks and benefits of new medicines. EMA is specifically responsible for (EMA, undated b):

- scientific evaluation of applications for European marketing authorisations (centralised procedure);
- monitoring the safety of medicines through a pharmacovigilance network; and
- stimulating innovation and research in the pharmaceutical sector, including providing scientific advice.

EMA has six scientific committees: Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT) (EMA, undated b).

Sponsors can apply for an orphan drug designation for their product. They need to notify the EMA of their intention to submit two months before the planned submission date. EMA encourages sponsors to request a pre-submission meeting, which are free of charge. EMA uses a common orphan application form with the US Food and Drug Administration (FDA). This application then goes to the COMP (EMA, undated c).

7 Regulatory Decisions

The COMP is made up of (EMA, undated d):

- a chair, elected by serving COMP members;
- one member nominated by each of the 27 Member States;
- three members nominated by the European Commission to represent patients' organisations;
- three members nominated by the European Commission on the Agency's recommendation;
- one member nominated by Iceland, one by Liechtenstein and one by Norway;
- one European Commission representative; and
- general observers.

COMP can invite the sponsor to present orally, or invite other third parties as appropriate to inform their opinion (EMA, 2007c).

By May 2010, COMP has considered in excess of 1,000 applications for orphan drug designation, of which 728 had been designated as orphan drugs and over 60 given marketing authorisation (EURODIS, 2012).

Products with an orphan drug designation must go through the EMA centralised procedure (EMA, undated h). CHMP review the scientific evidence. Their opinion on marketing authorisation is then transmitted to the European Commission. The EC has the ultimate authority for granting marketing authorisations in the EU.

CHMP publish the European Public Assessment Report (EPAR) which provides details of the scientific evidence used to inform the application for marketing authorisation (EMA, undated i).

There have also been efforts to collaborate by the FDA and the EMA. For example, adoption of the same forms for orphan drug designation (COMP and EMASS, 2011). However, in general there may still be differences in the detail between regulators and a need for companies to 'negotiate' with the regulator (Seldrup, 2011).

COMP is also responsible for advising the EC on policy on orphan medicines in the EU. The Committee assists the EC in drawing up guidelines and liaising internationally on matters relating to orphan medicines (EMA, undated j).

7 Regulatory Decisions

7.3 Types of marketing approval

The EC can grant different types of marketing approval. These include conditional marketing authorisation and marketing authorisation under exceptional circumstances. This is particularly relevant for orphan drugs because an exceptional marketing authorisation can be granted when the indications are *"encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence"* (EMA, undated k).

However, it is also important to note that some orphan products can be authorised on the basis of well established use. This can mean a limited evidence base even where there may be reasonably widespread use (interviewee's comment).

Conditional marketing authorisation and marketing authorisation under exceptional circumstances are characterised by the following features:

Table 4: *Differences between exceptional circumstances and conditional marketing authorisation*

Conditional marketing authorisation	Marketing authorisation under exceptional circumstances
Demonstrate positive benefit-risk balance, based on scientific data, pending confirmation	Comprehensive data cannot be provided (specific reasons foreseen in the legislation)
Authorisation valued for one year, on a renewable basis	Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure
Once the pending studies are provided, it can become a 'normal' marketing authorisation	Will normally not lead to the completion of a full dossier and become a 'normal' marketing authorisation

Source: EMA, undated k

By the end of 2010, 38% of all orphan products approved had been granted approval under exceptional circumstances (essentially where it was not possible to fulfil all the usual regulatory requirements) and 6% had been given conditional approval (where further data is required post approval) (COMP and EMASS, 2011). This illustrates that there are considerable difficulties in providing comprehensive data to the regulator on orphan drugs. The remainder were approved with a normal marketing authorisation.

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7.4 Access without a marketing authorisation

In Europe there is scope to provide access for patients when there is no/not yet marketing authorisation. Compassionate use is permitted when patients have an unmet medical need and there is a promising medicine that has not yet been authorised (licensed) for their condition.

Compassionate use programmes may provide access to patients outside of clinical trials (EMA, 2012 j).

Compassionate use programmes are a national responsibility. National competent authorities can decide what use is permitted. They also keep a register of the patients treated with the medicine and record any side effects reported by the patients or their doctors (EMA, 2012 j). CHMP can provide advice on compassionate use (EMA, 2012 j).

In the UK, there are ongoing discussions about earlier access to medicines. The MHRA are currently consulting on proposals (as at July 2012) (MHRA, 2012). We have also been told through our discussions that other countries provide early access.

7.5 Managing risk over time

There may still be unanswered questions or a need for continued monitoring of effectiveness and safety for newly authorised products. The EMA can require further studies from developers as part of their approval process. This will affect the cost for manufacturers in bringing products to market.

Over time this has changed from informal agreements to more formal legally binding requirements (Breckenridge, Woods and Walley, 2010). This can form part of the Risk Management Plan (RMP) of the manufacturer. EMA are implementing new requirements for RMPs (Blackburn, 2011). Within EMA, the Pharmacovigilance Risk Assessment Committee deals with the periodic safety update reports assessment (PSUR), post authorisation safety studies (PASS) and the RMP.

There is in general a high compliance with regulators' requests for post marketing surveillance (Blake, 2011). However, it may be less likely to be completed for orphan drugs than non-orphan drugs (Kesselheim et al, 2011a).

Registries can form part of the post-marketing surveillance requirements. Registries are often considered appropriate for rare diseases to answer a host of policy and practice questions (Dunoyer, 2011; Simeons and Dooms, 2011; OECD, 2010; Jones et al, 2011). However, Hollak et al (2011) have raised concerns about multiple 'product' registries (where patients are enrolled on the basis of a product that they are receiving as opposed to their disease per se) running in the case of Fabry disease and Gaucher's Disease. They note that with three new treatments now available for Gaucher's Disease, and a further two in the pipeline, this could lead to five separate product registries across Europe. They argue instead for the EMA to move to a single disease registry to prevent small numbers of patients in each of the separate registries.

Simeons and Dooms (2011) argue for flexible approaches to registries allowing the collection of a range of information as new treatments emerge or the disease evolves.

Registers are often, although not exclusively, industry paid for (interviewee's comments) and so they contribute to the cost of bringing a product to market.

7.6 Insights from case studies

Our case studies illustrate the type of evidence that EMA considers in deciding upon marketing approval.

- Afinitor for renal cell carcinoma was approved on the basis of an international, multi-centre randomized, double blind trial comparing Afinitor to placebo. 416 patients were involved in the trial. Those on Afinitor lived an average 4.9 months without disease progression compared with 1.9 months for those on the placebo.

- Diacomit for SMEI was approved based on a trial with 65 patients but full safety analysis was not possible. Those on Diacomit experienced fewer seizures. Reflecting the limited evidence base, it received a conditional approval, with a further trial required by EMA.

- Glivec for chronic myeloid leukaemia was approved on the basis of four trials including 2,133 adults and 54 children. It was approved on an exceptional circumstances basis, reflecting promising results on a surrogate outcome marker but the absence of overall survival data.

- Revlimid for multiple myeloma was approved on the basis of two trials, one of which included 704 patients. Results suggested an improvement in progression-free survival; combined results suggested that it took on average 48.3 weeks for the disease to progress in those taking Revlimid, compared to 20.1 weeks for those on placebo.

- Revolade for chronic idiopathic thrombocytopenic purpura was approved on the basis of two trials including 311 patients. In both trials, higher proportions of patients had higher platelet counts than those not taking Revolade.

This illustrates the range in sample sizes used in research; from tens in very rare diseases to thousands in more common rare diseases. It also illustrates that in some cases, such as Diacomit, it is not possible to fully assess safety, yet results are considered by EMA promising enough to permit conditional approval.

7.7 Success of the orphan drug legislation

Many of those we interviewed noted that the COMP has been pragmatic and willing to consider a range of evidence. There are some however who suggest that COMP should be more flexible and allow innovative trial designs and the use of biomarkers (Dunoyer, 2011) and be more clinically driven (Augustus, 2011). Buckley (2008) highlights that EMA has been 'eclectic' in their approach to evidence to support marketing authorisation applications for orphan products, with sample sizes as low as 12 and not always requiring new evidence. In part, this reflects the variety of the diseases within the rare disease area and the ability of the regulator to take a view based on the specific context.

Kesselheim et al (2011b) note that there may however be some nuances about the implementation of the incentives contained in the legislation. Questions have been raised about manufacturers selecting particular subgroups of non-rare diseases in order to achieve orphan drug designation. This is termed 'salami slicing' (Tambuyzer, 2010). Yin (2009) suggests that half of the total R&D response to the ODA in the US have been within rarer segments of common disease and that 10% of the innovation within this would have been conducted without the ODA.

Nistico (2011) reflects on his personal experience as a member of the CHMP, where he has been part of decision-making on marketing authorisation for orphan products. He suggests that there is scope to make changes to facilitate patient access, recommending that:

1) conditional approval or approval under exceptional circumstances should be granted more frequently;

2) the opinion of international societies for rare diseases should be taken into greater account by the EMA Committees;

3) the guideline's requirements should be interpreted more flexibly;

4) in comparison to the fulfilment of primary and secondary endpoints, the improvement of the quality of life should justify the approval of a new orphan drug;

5) the rigidity of guideline requirements should not prevail over the unmet medical need for severe and lethal rare disorders;

6) the statistical values of clinical data to the limit of significance should not prevail over the opinion of patients' associations and international scientific societies; and

7) the current legislation should be amended.

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7.8 Speed of regulatory decision making

The speed of decision making is also relevant, because this will affect how quickly patients can access products. There are differences across regulators for individual orphan drugs, as illustrated in the table below, with different decisions made on authorisation across the products. The EU can be either faster or slower than others and differ in their views. This may be a source of frustration for patients. It is also a risk for developers who may not be able to market their drug and make revenue in every jurisdiction.

Table 5: *Days for authorisation, selected orphan drugs in Canada, EU and US*

Drug name	Canada	EU	US
Pulomunary arterial hypertension			
Bosentan (Tracleer)	248	461	368
Iloprost (Ventavis)	Not authorised	635	182
Sildenfil (Revatio)	522	330	183
Treprostinil IV (Remodulin)	291	NA	285
Trepostinil INHS (Tyvaso)	Not authorised	NA	368
Sitaxentan (Thelin)	583	378	Not authorised
Ambrisentan (Volibris/Letairis)	352	416	184
Fabry disease			
Agalsidase alfa (Replagal)	1235	395	Not authorised
Agalsidase beta (Fabrazyme)	899	394	1035
Hereditary angioedema			
Icatibant (Firazyr)	Not authorised	350	Not authorised
Ecallantide (Kalbitor)	Not authorised	Not authorised	434
Complement C1s inhibitor (Berinert)	Not authorised	NA	581
Complement C1s inhibitor (Cetor/Cinryze)	Not authorised	NA	437
Chronic myeloid leukaemia			
Imitinib (Glivec/Gleevec)	202	251	72
Dasatinib (Sprycel)	362	312	182
Nilotinib (Tasigna)	644	410	395

Source: Blankart et al, 2011 *Note: NA = not available.*

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The approach that health care systems take to decisions on reimbursement are complex.[9] There is a growing trend for undertaking Health Technology Assessment (HTA) to help inform such decisions (Finn, 2012). HTA has been defined as: *"a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value"* (EUnetHTA, undated a).

HTA is now a well established tool used to a lesser or greater degree across Europe and further afield. Although HTA is not just economic evaluation (generally a comparison of the costs and benefits of one technology to another) it is one of the domains in HTA (EUnetHTA JA, 2011.) We have also been told through our discussions of the importance of the UK HTA agencies; particularly the Scottish Medicines Consortium (SMC) which we discuss in more detail later in this report. The SMC can be the first HTA conducted globally on a new medicine.

There are also different layers of decision makers: from national agencies, which either take the decision or inform those that do (such as politicians), to regional agencies, to local approaches reflecting individual clinician requests for reimbursement for individual patients and individual products. There are also multiple agencies which can contribute to decisions on access in practice. That is both those formally part of the health care system and also those outside, such as academic units completing assessments to support health care decision makers.

We have tried to identify whether there are specific approaches that are taken for orphan medicines but we have not sought to describe the approach to pricing and reimbursement of medicines more generally. Although relevant, we could not cover such a complex area across multiple countries within the time and resources available for this work.[10]

We focus on the UK and also draw on evidence from other countries where we have been able to identify a specific approach for orphan drugs.

8.1 Cost, pricing and budget impact of orphan drugs

It is relevant to focus here on the cost, pricing and budget impact of orphan drugs. Whilst regulators are concerned with safety, efficacy and quality, it is the payers/commissioners who have a remit to consider the costs of treatments. That includes not only the cost per patient, but also for those who are concerned with managing the overall budget impact.

8.1.1 Cost of bringing a product of market

The cost of bringing a product to market is a function of a range of factors: the decisions taken by the original investigators, the decisions taken by those seeking to commercialise the product (where there may be different levels of efficiency across developers and different expectations of shareholders and venture capitalists) and the need for the manufacturer to meet the demands of regulators as a first priority, and then payers, as a second priority. For payers, that can mean meeting the needs of many in the context of Europe, with arguably more than 27 payers given both national and regional payers across the Member States. That contrasts to a centralised regulatory approach.

9. This can also be termed 'approval', although that may be approval at a given price determined by the system.
10. There are a range of reports that can help provide further detail, including:
PPRI Report, 2008, and OECD reports including Health Technology and Decision Making 2005, Pharmaceutical Pricing in a Global Market 2009, Value for Money in Health Spending 2010, Value in Pharmaceutical Pricing 2012, and ISPOR Roadmap.

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8.1.2 Price of an orphan drug

Simeons (2011a) reviewed the literature to explore how orphan drugs are priced and reimbursed generally. He cites a number of economic factors which drive prices:

a. orphan drugs benefit from a period of marketing exclusivity (via a patent, companies can protect their revenue using the legal framework for Intellectual Property);

b. few alternative health technologies are available;

c. third-party payers and patients have limited negotiating power (essentially that health care expenditures are paid for by either general taxation or from an insurer, with the patient often paying little or nothing towards the cost of their health care);

d. manufacturers attempt to maximise orphan drug prices within the constraints of domestic pricing and reimbursement policies (essentially, commercial companies seek to make the most profit that they can reflecting their commercial imperative);

e. substantial R&D costs need to be recouped from a small number of patients.

Given that the costs of bringing a product to market will need to be recouped from a small number of patients, the price per patient will inevitably be high relative to products to treat more common diseases (Davies et al, 2012). There is some evidence of a link between price and prevalence within Italy (Messori et al, 2010), although the precise relationship is likely to differ according to the specific approach to pricing as well as national prevalence in each country. Orofino et al (2010), using 2007 data, suggest that the costs of orphan drugs vary across rare diseases, but those that treat more rare diseases tend to have higher prices suggesting a link between the number of eligible patients and per unit price.

Manufacturers may also be able to recoup R&D across a wider population over time, as some products go on to treat more indications (diseases). Some manufacturers may also be able to use the knowledge from developing a product to develop other products to serve wider populations than the original target, as has been suggested as a potential in the case of orphan drug development in cystic fibrosis (Dolgin, 2011).

Concerns have been raised in the literature about prices of some orphan drugs when they move from unlicensed to licensed status. Unlicensed use is where there is no marketing authorisation at all, or the marketing authorisation is for a different indication, however clinicians can still prescribe the product if they so choose. Examples of changes to prices as products have become licensed are:

- the product 3,4 diaminopyridine (3,4 DAP) to treat Lambert-Eaton myastenic syndrome and congenital myastenic syndrome has seen a price rise from £800 per patient per year on an unlicensed basis to £40,000 to £70,000 per patient per year (Taruscio et al, 2011);

- it costs £160 a year to treat a patient with sickle cell disease using 500 mg capsules of hydroxycarbamide (hydroxyurea) which is licensed for chronic myeloid leukaemia, but it costs £14,900 a year using 1 g tablets of hydroxycarbamide licensed as an orphan drug for sickle cell disease (Ferner and Hughes, 2010);

- N-carbamylglutamate where the price of the unlicensed product was £11 per g versus the licensed cost of £262.90per g. If the licensed preparation is used, the annual cost for a 10 kg child increases from £4,015 to more than £95,000 (Leonard and Richmond, 2009).

Such examples have led to debate about 'fair' prices for orphan drugs (Quartel, 2010; Rockley, 2010; Counsel, 2010; Bouvy; 2010). However, we have not fully explored the issues of unlicensed use and the move to licensed use which will affect pricing; for example, the costs and evidence generated for licensing which would not be present for unlicensed use.

The justification for a specific price is not transparent to all: some of our interviewees noted that there is not always clarity on how these decisions are made by companies. And as Simeons (2011a) notes in general, manufacturers have a vested interest and can try to exploit the system to secure high prices.

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8.1.3 Cost per patient

The cost per patient will also reflect any other clinical activities required to deliver treatment, such as diagnostic tests and management of any side effects or adverse events.

Illustrating the scale of expense, our case studies include the following costs:

- £9,771 per treatment for Afinitor
- £7,600 per patient for Diacomit
- £20,000 per patient for Glivec
- £40,000 per patient for Revlimid
- £10,000 to £30,000 per patient for Revolade

8.1.4 Budget impact

The budget impact for the health care system will depend on both the real price (given some products can be sold at a discount depending upon local circumstances) and the number of patients who are eligible for treatment. The number of patients who are eligible for treatment will be a result of a number of factors: prevalence (underlying number of people with the disease), diagnosis, clinicians' decisions to prescribe influenced by their own clinical views, clinical guidelines (which can come from various sources, nationally from Royal Colleges or international guidelines) and the views of patients.

Again, our case studies illustrate the scale of budget impact (we did not find UK estimates so present budget impact for devolved nations that we found in our research):

- £972,000 in the first year to £1.12million by year five in Scotland for Afinitor;
- £52,000 to £130,000 by year five in Scotland for Diacomit;
- £8 million to £11.8 million in England, rising to £15.8 million to £25 million by year five in England for Glivec;
- £920,000 in year one to £2.92 million in year in Scotland for Revlimid. £3 million in year one, to £4.2 million in year five in Wales.

To place these in context, the NHS across the UK spends approximately £13 billion on medicines (OHE, 2012). Linked to budget impact is pricing, and UK prices are low in comparison to many European countries (DH, 2012d).

We did not identify work to explore the budget impact of orphan medicines in the UK; however, work has been undertaken at a European level and for Belgium.

Schey et al (2011) have explored the likely budget impact of orphan products by looking at past trends in approvals of new orphan drugs and their costs. Their analysis suggests current costs of orphan drugs varying from €1,251 to €407,631 per patient per year, with a median of €32,242. The share of the European pharmaceutical market accounted for by orphan drugs is predicted to rise from 3.3% in 2010 to 4.6% in 2016, plateauing from then on to 2020. Schey et al argue that *"fears of an unsustainable cost escalation are unjustified."* They do note however the speculative nature of the forecast. And of course, this does not necessarily imply that such spending offers the greatest value for money, as that depends on a number of other factors—the cost of the disease without access to medicines, the willingness to pay for generating health etc.

Denis et al (2010a) forecast expenditure on orphan drugs in Belgium between 2008 and 2013. They found that spend on orphan drugs was €66.2 million (or 5% of the Belgian hospital drug budget) in 2008. This could increase to between €130–204 million in 2013. Denis et al suggest that this is likely to put pressure on the drugs budget. Some options they suggest to mitigate this include: pricing linked to return on investment (i.e. setting some amount of reasonable return given the scale of costs), risk-sharing arrangements (where the real price and revenue could vary according to a specific agreement, such as the change in health outcomes of patients) and re-appraisal of orphan drug status.

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8.2 Making decisions in the UK

Access to orphan medicines is part of the wider commissioning of services for those with rare diseases. We focus on England's approach to commissioning as this is where there are significant reforms.

8.2.1 Commissioning in England

In England, there is a national approach to commissioning around 70 highly specialised services. Specialised services are defined as *"services that help improve the lives of children and adults with rare diseases or disorder"*, and each of those commissioned at the national level generally affect fewer than 500 people across England or involve services where fewer than 500 highly specialised procedures are undertaken each year (NHS Specialised Services, undated a). This means that decisions are taken about which services to commission on a national basis (in England) and funds top-sliced (interviewee's comments).

Specialised services are set out in the Specialised Services National Definitions Set (SSNDS) (NHS Specialised Services, 2011). There are currently 38 nationally defined specialised services (DH, 2011a).These cover a variety of rare diseases and guidelines are available to support commissioning of some services. These can include orphan drugs; two examples are given below:

1. Guidelines for the Diagnosis and Management of Anderson-Fabry Disease (Hughes et al, 2010), discusses Replagal (agalsidase alfa) and Fabrazyme (agalsidase beta) and the place of these treatments in the patient's pathway.

2. UK National Guideline for Adult Gaucher Disease (Deegan et al, 2005), discusses Cerezyme (Imiglucerase) and the place of this treatment in the patient's pathway.

With the passing of the Health and Social Care Act 2012, changes are being implemented in the approach to commissioning of specialised services, both those commissioned nationally and those previously commissioned regionally (interviewee's comments). The National Commissioning Board (NCB) will commission prescribed services. Prescribed services are named in the legislation (e.g. services for the armed forces) and include some specialised services. Services to be commisioned by the NCB, as opposed to the Clinical Commissioning Groups (CCGs, which will replace Primary Care Trusts) have been declined with regard to four criteria.

These are (Clinical Advisory Group for Prescribed Services, 2012):

(a) the number of individuals who require the provision of the service or facility;

(b) the cost of providing the service or facility;

(c) the number of persons able to provide the service or facility; and

(d) the financial implications for clinical commissioning groups if they were required to arrange for the provision of the service or facility.

The Clinical Advisory Group for Prescribed Services provides advice to Ministers and has published its advice for future commissioning of specialised services. They have not however reviewed the list of services currently included in regulations and commissioned by the National Specialised Commissioning Team.

There will also be an Innovation Fund for Specialised Services. The fund will be piloted during 2012/13 and rolled out in April 2013 (Burns, 2012).

The Advisory Group for National Specialised Services (AGNSS) is currently part of NHS Specialised Services. AGNSS is a committee that currently advises Ministers on which services should be nationally commissioned and the centres that should provide them. AGNSS also commissions services at the national level in England. This essentially provides an end to end approach; AGNSS considers the evidence, makes a recommendation, and assuming that recommendation is accepted by Ministers can then commission the service nationally. Having a single agency responsible from assessment all the way to commissioning avoids a fragmented approach of looking at drugs in isolation, when orphan drugs are available to treat those conditions.

In July it was announced that the work of AGNSS on high cost, low volume drugs would go to NICE from April 2013 (DH, 2012c). From 1 April 2013 AGNSS will formally cease to provide advice to Ministers. We have heard that there are concerns about this move because it may result in a less holistic view of drugs as part of broader services.

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8.2.2 Agencies that make recommendations on orphan drugs in the UK

The UK has a number of agencies and approaches that inform decisions to fund orphan medicines. These agencies provide guidance that is often used by commissioners. At a national level these agencies include: the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC), the All Wales medicine Strategy Group (AWMSG) and AGNSS. AGNSS had developed a new framework when considering orphan drugs, but its application has not yet led to final decisions by Ministers at the time of writing (interviewee's comments).

In these agencies there is a strong overlap in the approach to decision making for orphan drugs and non-orphan drugs. Details are set out in appendices covering the ways that recommendations are made, but we highlight in Table 6 below the key features of the approaches taken. Table 7 presents in full detail the criteria applied to orphan drugs.

All of the approaches share features of multi-criteria decision analysis (MCDA). Devlin and Sussex (2011) define MCDA as *"a set of methods and approaches to aid decision-making, where decisions are based on more than one criterion, which make explicit the impact on the decisions of all the criteria applied and relative importance attached to them."* All the agencies apply more than one criteria. Arguably none yet (in the public domain) meet the latter elements of making explicit the impact on the decisions of all the criteria applied, and the relative importance attached to them.

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Table 6: *Key features of UK agencies who make recommendations on orphan drugs*

Feature	NICE	SMC	AWMSG	AGNSS
Geographical coverage	England and Wales	Scotland	Wales	England
Scope of remit: technologies	Wide: drugs, devices, public health	Narrow: new medicines	Narrow: new medicines	National specialised services (generally services that affect <500 people across England)
Coverage	Selected medicines	All new medicines	Selected medicines	(Ultra*) orphan drugs
Core criteria	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	Clinical and cost effectiveness, underpinned by opportunity cost (typically the cost per QALY)	12 criteria based on 4 domains: Does it work? Does it add value to society? Is it a reasonable cost to the public? Is it the best way of delivering the service?
Different criteria for orphan drugs?	No (but suggested different approach in 2006 but not fully acted on)	Yes (from 2007)	Yes (from 2011)	Only considers orphan drugs (<500 patients in England)
Status of guidance	Positive recommendations from Technology Appraisal must be funded by commissioners in England	Input to local decisions, but no requirement for the NHS in Scotland to follow recommendations	NHS in Wales expected to follow guidance	Recommendations to Ministers, with Ministers taking final decisions. Funding is top-sliced

Note: QALY = Quality Adjusted Life Year, a generic measure which aims to capture the impact of a technology in terms of both survival and quality of life.
**Although this is not a formal term used by AGNSS*

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Table 7: *Criteria applied to appraisal of orphan drugs*

NICE	SMC	AWMSG	AGNSS
Same as for non-orphan drugs	Additional factors: • whether the drug treats a life threatening disease; • whether the drug substantially increases life expectancy and/or quality of life; • whether the drug can reverse, rather than stabilise, the condition; or • whether the drug bridges a gap to a "definitive" therapy	AWMSG will consider: • The degree of severity of the disease as presently managed, in terms of quality of life and survival • Whether the medicine can reverse, rather than stabilise the condition • Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development • The innovative nature of the medicine. • Whether the medicine represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment) and; • whether it can plausibly generate substantial health gains over existing treatments for the individual	Core medicine criteria: **1. Does it work?** • Severity and ability of patients to benefit • Clinical safety and risk • Clinical effectiveness and potential for improving health **2. Does it add value to society?** • Stimulating research and innovation • Needs of patients and society **3. Is it a reasonable cost to the public?** • Average cost per patient • Overall cost impact and affordability including opportunity cost • Value for money compared to alternatives **4. Is it the best way of delivering the service?** • Best clinical practice in delivering the service • Economic efficiency of provision • Continuity of provision • Accessibility and balanced geographic distribution

Note: QALY = Quality Adjusted Life Year, a generic measure which aims to capture the impact of a technology in terms of both survival and quality of life

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These tables illustrate that there are a variety of factors or criteria or 'modifiers' that are used for considering orphan drugs. The widest framework, from AGNSS, was developed particularly for treatments for very rare diseases. Although some agencies share similarities in the modifiers used, such as whether the orphan drug bridges a gap to definitive therapy (SMC and AWMSG), they also differ. AGNSS has the largest number of criteria, and in particular includes an explicit consideration about society. This is largely absent for the others, although it has been applied for appraisal of other interventions, such as for public health interventions (Drummond et al, 2008).

While NICE does not currently have a separate process and/or modifiers for orphan products they have considered the issue (NICE, undated). NICE suggested in 2006 that there may be a need for a different approach when considering so-called 'ultra-orphan' drugs. NICE defined these as treatments for patients with a disease prevalence of less than 1 in 50,000. Such ultra-orphan drugs have particular features which pose special difficulties, including:

- high acquisition costs and correspondingly high incremental cost effectiveness ratios (ICERs);
- use solely for an ultra-orphan disease (i.e. not also indicated for non-ultra-orphan diseases);
- use in ultra-orphan diseases that are chronic, severely disabling, and/or life-threatening;
- use potentially life-long.

In these cases, NICE could draw on the ICERs from previously appraised ultra-orphan products and apply a different decision rule: allowing ICERs much higher than the usual range. NICE noted that this would not necessarily result in recommendation of all ultra-orphan products and that there could be scope for the Department of Health to enter into discussions with the manufacturers on possible price reductions. Then NICE could re-consider the product. The process would be seen as distinct and separate to that for non-ultra-orphan products.

As NICE prepare to take on the AGNSS remit in 2013, it remains to be seen how far they will draw on their earlier thoughts and on the AGNSS framework as they develop an approach for very high cost drugs.

8.2.3 Insights from the literature

Vegter et al (2010) found that SMC rejected 8 out of 11 orphan products up to May 2008 that had an unfavourable cost effectiveness ratio (i.e. over £30,000 per QALY). This implies that the cost per QALY ratio alone is not always a barrier to a positive recommendation, as they recommended use in 3 of the 11 orphan drugs considered.

Simeons and Dooms (2011) note that pharmacoeconomic evaluation can aid decisions but that there are value judgements which can place higher priority on anti-cancer medicines. Rosenberg-Yunger (2011) suggest that whilst clinical and cost effectiveness are used to inform priority setting for orphan drugs, other factors such as availability of alternative treatments are also relevant. Kirkdale et al (2010) highlight concerns about the approach to the costs of drugs which can influence the overall estimate of the cost per QALY and call for changes to be made to the NICE methodology.

Davies et al (2012) raise the concern that the approach taken by HTA agencies such as NICE could prove a barrier to future R&D because cost per QALY approaches may lead to negative recommendations for orphan products. However, NICE has been willing to recommend a product with lower levels of evidence and higher cost effectiveness threshold for orphan products (Denis et al, 2010b).

8.2.4 Local implementation of national recommendations

It is worth noting that it is not just agency recommendations that influence access, it is also how locally such recommendations are adopted (or not). For example, Bennie et al (2011) stress that the impact of the SMC on use is difficult to assess. Similarly it is difficult to track implementation of NICE guidance (Information Centre, 2011), but the NHS' implementation of positive appraisals appears to be increasing over time (NICE, 2009f). There are also a range of other mechanisms which either influence funding decisions and/or provide funding.

There are also products which may not go via any of these national agencies and hence will be considered regionally or locally. Those we spoke to expressed concerns over products ending up in this 'gap'. Although it will differ according to product, for some this can result in a vacuum with an absence of guidance for commissioners. This is

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the case for C1 Inhibitor and Icatibant for hereditary angioneurotic oedema (HAE) (interviewee's comment). This can be frustrating for both individual patients who must seek funding, but also for patient organisations to support them and who must duplicate their efforts with many commissioners. This is compounded when patient organisations also believe that there are cost savings that could accrue from timely and appropriate levels of access, as this could prevent more costly A&E attendances, which should be of relevance to commissioners when they make their funding decisions (interviewee's comment).

We next discuss some of the approaches to regional/local decision-making in the UK.

8.2.6 Orphan drugs and the Cancer Drugs Fund (CDF)

The Cancer Drugs Fund (CDF) is a special fund in England to pay for cancer products that have not been recommended by NICE, or have yet to have final NICE guidance. An interim fund ran between October 2010 and April 2011 of £50 million. The full fund of £200 million per year for 3 years began in April 2011 (DH, 2011b). The fund has also funded some off-label use of products (Macmillan Cancer Support, 2011a). Although a national fund, decisions on what the fund can be spent on are made via regional clinical panels (DH, 2011c).

Some products with an orphan indication have been funded from the CDF. For example, one of the products in our case studies, Afinitor, has been funded from the CDF. However, as Afinitor can be used for different indications this may not reflect access for the orphan indication but rather access for another indication.

We have heard from interviewees that the CDF has provided a route for access to orphan medicines, although it is unclear how consistent this is, or on what scale. There remains some debate about the future of the fund and hence it may, or may not, provide funding and support access beyond 2014.

8.2.7 Orphan drugs and Individual Funding Requests (IFRs)

There is scope for local decisions to be taken on funding and providing access under 'exceptional circumstances'. This is not focused on orphan drugs per se, but funding can be applied for on an individual basis, known as an Individual Funding Request (IFR). Such local decision making exists across the UK.

There is guidance to support local decisions on access to drugs for Primary Care Trusts (PCTs) in England (NHS, 2009). This guidance acknowledges that PCTs may not reasonably be expected to have the full range of expertise or resources to support decision making for rare or complex conditions. While recommending that PCTs should consider collaborative approaches, it also recognises variance in local approaches to decision making, including the use of different terminology. The guidance suggests that the criteria to inform decisions should include at the minimum:

1. patient safety;
2. clinical and cost effectiveness and strength of evidence;
3. place in therapy relative to available treatments;
4. affordability;
5. national guidance and priorities;
6. local priorities.

A generic process includes a number of steps, from the submission of the IRF through a triage process, before consideration by an IFR panel. An appeals process should be included where necessary.

Interviewees highlighted in our discussions that IFRs can be a source of frustration, particularly because they perceive a lack of specialist knowledge within commissioners about specific rare diseases. One interviewee also suggested that demonstrating exceptionality for a patient with very rare disease can be difficult because it is the disease that is exceptional, and not the patient within that small group of patients.

8.2.8 Broader policies which influence access

There are also broader policies which can/could influence access and funding. As with the main agencies, there are differences across the UK. We focus on some specific English policies.

The NHS Constitution in England

In England, the NHS Constitution (NHS, 2012) sets out a patient right to: *"drugs and treatments that have been recommended by NICE for use in the NHS, if your doctor says they are clinically appropriate for you."*

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Although orphan drugs are not explicitly referenced, where orphan products are supported by a positive NICE appraisal, they would then fall under this right. This is however unlikely to be a major enabler of access given that we already know that NICE has, to date, appraised few orphan products.

The Constitution also sets out the patient right to: *"expect local decisions on funding of other drugs and treatments to be made rationally following a proper consideration of the evidence. If the local NHS decides not to fund a drug or treatment you and your doctor feel would be right for you, they will explain that decision to you."*

The NHS Constitution has not (yet) been formally tested, so it is unclear how effective it is at influencing behaviour within the NHS.

As part of the reforms there are also opportunities to consider the scope to use the new NHS Mandate, which sets out the objectives for the improvement of health and healthcare to the NCB, to also enable access. The draft Mandate includes a link to the Constitution, with an objective to:

"Uphold, and where possible, improve performance on the rights and pledges for patients in the NHS Constitution" (DH, 2012e).

The Mandate is currently being consulted on (at the time of writing).

Innovation, Health and Wealth

Although not yet designed and implemented there are new proposals to enable access to medicines set out in 'Innovation Health and Wealth - Accelerating Adoption and Diffusion in the NHS' (DH, 2011d). They propose:

- the introduction of a NICE Compliance Regime, to reduce variation and drive up compliance with NICE technology appraisals;
- that all NICE Technology Appraisal recommendations are incorporated automatically into relevant local NHS formularies in a planned way that supports safe and clinically appropriate practice;
- a NICE Implementation Collaborative (NIC), established to support prompt implementation of NICE guidance;
- the development and publication of an innovation scorecard, designed to track of NICE Technology Appraisals at a local level.

This is unlikely to be a major enabler of access given that we already know that NICE has to date appraised few orphan products.

Dis-investment

Dis-investment has gained more interest in light of the reduction in funding growth for the NHS in England. What dis-investment means in practice is quite challenging to assess because there is not a single national list of activities which are considered low value, and hence appropriate for disinvestment (Audit Commission, 2011). This allows local approaches to be adopted that may differ across England. The approach taken to dis-investment could be via explicit lists or a more deliberative approach to identify what should be done less or stopped altogether (Moberley, 2012; Nuffield Trust, 2012).

Dis-investment is being supported by national work. This includes the NICE 'do not do' database (2012l). The Cochrane Collaboration has also set out in Quality and Productivity (QIPP) topics, activities which systematic reviews suggest could be targeted for disinvestment. Horizon scanning for new medicines is also intended to identify areas of disinvestment (National Prescribing Centre, 2011). The Audit Commission (2011) has also set up a tool to help PCTs make decisions on low clinical value treatments.

8.3 Making decisions outside of the UK

Like the NHS, other health care systems have to make choices about access to orphan drugs. We initially looked at a large number of countries, including Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand, Spain and Sweden. However, we often found it difficult to identify if there was a specific approach taken to orphan drugs and/or there was a language barrier based on searches of their respective HTA agencies websites. We focus on a smaller set of countries below.

8.3.1 Decisions in Australia, Canada, France and New Zealand

We looked at how decisions are made outside of the UK, and more detail is available in the appendices. Key features are outlined in the table below for Australia, Canada, France and New Zealand.

8 Payer/Commissioner Decisions

Table 8: *Key features of international agencies who make recommendations and/or funding decisions on access to orphan drugs*

Feature	Pharmaceutical Benefits Advisory Committee (PBAC)	Special Drugs Program	Trilium Drug Program	Exceptional Access Program
Geographical coverage	Australia	Province of Ontario, Canada	Province of Ontario, Canada	Province of Ontario, Canada
Scope of remit: technologies	All medicines	Special drugs	High cost medicines relative to household income	Specific medicines
Coverage	All medicines	Specific drugs: e.g. alglucerase for Gaucher's Disease	Specific individuals with prior approval	Specific individuals with prior approval
Core criteria	Comparative costs and benefits	Unclear	Unclear	Unclear
Different criteria for orphan drugs?	Implicitly via Rule of Rescue which includes: • no alternative treatment • Severe, progressive disease • Applies to small number of patients • Worthwhile clinical benefit	Implicitly, yes	Implicitly, yes	Implicitly, yes
Status of guidance	Affects reimbursement status	Products are funded	Products are funded for selected individuals	Products are funded for selected individuals

Note: QALY = Quality Adjusted Life Year, a generic measure which aims to capture the impact of a technology in terms of both survival and quality of life

8 Payer/Commissioner Decisions

Table 8 *(continued)*

Feature	Rare Diseases Drug Program	Haute Autorite de Sante (HAS)	Pharmaceutical Benefit Management Agency (PHARMAC)
Geographical coverage	Province of Alberta, Canada	France	New Zealand
Scope of remit: technologies	Treatment, including medicines	All medicines	All medicines
Coverage	Specific diseases covered: e.g. Gaucher's Disease, Fabry Disease	All medicines	All medicines including funding for exceptional circumstances
Core criteria	Ethical and compassionate reasons	Medical benefit and improvement in medical benefit vs alternatives	Cost effectiveness, typically using the cost per QALY For exceptional circumstances they consider seriousness and urgency
Different criteria for orphan drugs?	Implicitly, yes	No	Not explicitly, and recent moves away from rarity with rarity not considered to be an obligatory criteria for expectional circumstances
Status of guidance	Products are funded for selected individuals	Affects reimbursement status and reimbursement rate	Additional funding allocated for funding drugs in exceptional circumstances

This table illustrates a diversity in approach towards orphan drugs, where they can be included within the same processes as for non-orphans (as in France), or where specific criteria apply, although this can be implicitly via the Rule of Rescue (in Australia) or under exceptional circumstances (in Canada). It also illustrates that some agencies will go further than applying different criteria to decision making, and provided dedicated funding, as seen in provinces in Canada, although often on an individual or disease basis with requirements for prior approval.

8.4. Insights from case studies

Our case studies explored some more details about products and resulting recommendations; some key facts are included in the table overleaf.

8 Payer/Commissioner Decisions

Table 9: *Case study products and HTA/payer recommendations*

	Afinitor for renal cell carcinoma	Diacomit for severe myoclonic epilepsy in infancy	Glivec for chronic myeloid leukaemia	Revlimid for multiple myeloma	Revolade for chronic Idio-pathic throm-bocytopenic purpura
Prevalence	4.2 per 10,000	0.4 per 10,000	0.9 per 10,000	1.3 per 10,000	<5 per 10,000
Patient numbers	4,000 (England)	75 (Scotland) 10-25 (Wales)	2,700 (UK)	2,100 (England) 48-75 (Scotland) 106 (Wales)	3,000-9,500 + (UK)
Approximate yr of breakthrough in knowledge	Unknown	1970s	1960s	Before 1950s	Unknown
Clinical benefit	Survival	Reduction in seizures	Survival	Survival	Improvement in platelet counts
Clinical evidence base	416 patients in trial	65 patients in trial	2,187 patients in trial	704 patients in trial	73 patients in trial
Type of marketing authorisation	Normal	Conditional	Exceptional (later moved to normal)	Normal	Normal
Yr of marketing authorisation in EU	2009	2007	2001	2007	2010
Cost per patient	£9,771 (per treatment)	£7,600	£20,980	£43,680	£10,000-£30,000
Budget impact	£972k to £1.12m (Scotland)	£52k to £130k (Scotland)	£8m-£25m (England)	£862k-£3.75m (Scotland) £3m-£4.2m (Wales)	£237k-£2.9m (Scotland)
Cost per QALY	£51,375-£92,074 (Scotland)	Not available	£33,225-£301,500 chronic phase £21,800-£56,000 accelerated phase £22,275-£64,750 blast phase (England)	£46,865-£69,500 for 1 prior therapy £24,584-47,100 for 2 prior therapies £22,589-56,500 for prior thalidomide and 1 other therapy £22,589-43,600 for prior thalidomide and 2 other prior therapies (England)	£77,496-£545m splenectomised population £90,471-£200m in non-splenectomised (England) Overall savings (Scotland)

8 Payer/Commissioner Decisions

Table 9 *(continued)*

	Afinitor for renal cell carcinoma	Diacomit for severe myoclonic epilepsy in infancy	Glivec for chronic myeloid leukaemia	Revlimid for multiple myeloma	Revolade for chronic Idiopathic thrombocytopenic purpura
NICE recommendation	Not recommended (TA) in 2011	Recommended as 2nd line (clinical guideline) in 2012	Recommended in 2002 and 2012	Restricted recommendation in 2009 with PAS and EoL	Not recommended in 2010
SMC recommendation	Not recommended in 2010	Not recommended in 2008	Restricted recommendation	Not recommended in 2008 Restricted recommendation in 2010 with orphan drug modifier	Recommended in 2010
AWMSG recommendation	Not recommended (indirectly)	Not recommended in 2008	Recommended (indirectly)	Not recommended in 2008	Not recommended (indirectly)
Regional decisions	Funded via Cancer Drugs Fund (ongoing)	Unknown	Reviewed regionally	Funded via Cancer Drugs Fund (ongoing)	Unknown
PBAC recommendation	Not recommended in 2010	Not found	Recommended (individual requests) in 2002	Not recommended in 2011	Not recommended
Canada		Funding via Special Access Programme	Funding in all provinces	Funding in nearly all provinces	Not recommended in 2011
Alberta (Canada)	Funded via Genitourinary Tumour Group in 2011	As above	Funded via Alberta Cancer Board	Funded via Alberta Cancer Board in 2009	
British Columbia (Canada)	Funded via Genitourinary Tumour Group and Systematic Therapy Program in 2011	As above	Funded via BC Cancer Agency	Funded via BC Cancer Agency in 2009	Not funded
Ontario (Canada)	Funded via Exceptional Access Program in 2011	As above	Funded by Ontario Drug Benefit Program incl Trillium Drug Program	Funded by Ontario Drug Benefit Program Exceptional Access Program in 2009	Funded by Ontario Drug Benefit Program Exceptional Access Program

8 Payer/Commissioner Decisions

Table 9 *(continued)*

	Afinitor for renal cell carcinoma	Diacomit for severe myoclonic epilepsy in infancy	Glivec for chronic myeloid leukaemia	Revlimid for multiple myeloma	Revolade for chronic Idiopathic thrombocytopenic purpura
France	Listed for reimbursement in 2010	Listed for reimbursement in 2010	Listed for reimbursement in 2007	Listed for reimbursement	Unknown
Revenue	>€55m (incl other indications, sales in Europe in 2008)	Not available	$4.3bn (incl other indications, sales globally in 2010)	$1.28bn (sales globally in 2012)	Unknown
Likely date patent expires/expired	2016	Unknown	Between 2013 and 2015	2019	Unknown

Sources: See case studies in the Appendix.
Notes: Some are indirect recommendations by AWMSG reflecting the decision to either appraise or not depending on when NICE guidance is likely to be published, and the superceeding of AWMSG guidance following NICE guidance publication.
Yr = year, ma = marketing authorisation

The case studies suggest to us the following:

- There is a material difference in scale between very rare and rare diseases that affects the level of uncertainty in the evidence base that agencies consider. Diacomit had the lowest number of patients in a trial and no cost effectiveness estimates available, and has the lowest prevalence of our case studies. Glivec, next in line in terms of prevalence, had very wide ranges in cost effectiveness. Similarly the cost effectiveness ranges are vast for Revolade.

- There is limited tolerance for an absence of cost effectiveness evidence from companies. This results in an automatic 'no' from the SMC, as seen for Diacomit.

- All agencies have become more flexible over time and allowed for additional modifiers, applied in the case of Glivec by both NICE and SMC, perhaps signalling a greater honesty in the judgement required to make decisions, but perhaps also a greater level of transparency in how decisions are made.

8 Payer/Commissioner Decisions

8.5 Insights from the literature

Ernst and Young (2011) note in their review of European countries that many use the same approach to decisions on access as they do for non-orphan products. Specific challenges are encountered in assessing orphan drugs in comparison to non-orphan drugs including:

- low quality of evidence for clinical efficacy and safety;
- scarcity of knowledge on specific rare diseases and difficulties identifying regional clinical experts;
- important amount of time required given the dispersion of information;

Specific issues in terms of quality of evidence are set out in the table below.

Table 10: *Comparative quality of clinical evidence in reimbursement submission for orphan drug and non-orphan drug innovative medicines*

Quality criteria	Number of orphan submissions with:	Number of ATV submissions with:
At least 1 RCT	13(52%)	21(84%)
RCT active control	3(12%)	15(60%)
Dose finding studies	5(20%)	23(92%)
Use of clinical end-points	12 (48%)	14(56%)
Adequate trial sample size	4(16%)	23(92%)
Adequate duration of exposure	12(48%)	24(96%)

Source: Ernst and Young, 2011 who cite: 'Access to orphan drugs despite poor quality of clinical evidence'; AG Dupont, PB Van Wilder; accepted article to British Journal of Clinical Pharmacology

There are also studies that compare and contrast across a number of countries. Blankart et al (2011) looked at decisions made for a selection of orphan drugs across eleven countries. They found that many are not evaluated and there are differences across agencies in terms of recommendations made. The table overleaf illustrates some of their findings.

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Table 11: *Recommendations for agencies for selected orphan drugs in eleven countries*

Drug name	Australia (PBAC)	Canada (CEDAC)	England (NICE)	France (CT)	Germany (IQWiG)	Hungary (Tel)	Netherlands (CFH)	Poland (AOTM)	Slovakia (KKL)
Pulmonary arterial hypertension									
Bosentan (Tracleer)	+	NE	NE	+	NE	+	+	+	+
Iloprost (Ventavis)	+	NE	NE	+	NE	+	+	+	+
Sildenfil (Revatio)	+	+	NE	+	NE	+	+	+	+
Treprostinil IV (Remodulin)	+	+	NE	+	NE	NE	+	+	+
Trepostinil INHS (Tyvaso)	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sitaxentan (Thelin)	+	NE	NE	+	NE	NE	+	IP	+
Ambrisentan (Volibris/Letairis)	+	NE	NE	+	NE	+	+	IP	+
Fabry disease									
Agalsidase alfa (Replagal)	+	-	NE	+	NE	+	+	NE	NE
Agalsidase beta (Fabrazyme)	NE	-	NE	+	NE	+	+	-	+

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Table 11 *(continued)*

Drug name	Australia (PBAC)	Canada (CEDAC)	England (NICE)	France (CT)	Germany (IQWiG)	Hungary (Tel)	Netherlands (CFH)	Poland (AOTM)	Slovakia (KKL)
Hereditary angioedema									
Icatibant (Firazyr)	NE	NE	NE	+	NE	NE	NE	NE	+
Ecallantide (Kalbitor)	NE	NE	NE	NE	NE	NE	NE	NE	NE
Complement C1s inhibitor (Berinert)	NE	NE	NE	+	NE	+	NE	NE	NE
Complement C1s inhibitor (Cetor/ Cinryze)	NE	NE	NE	NE	NE	NE	+	NE	NE
Chronic myeloid leukaemia									
Imitinib (Glivec/Gleevec)	+	NE	+	+	NE	+	+	+	+
Dasatinib (Sprycel)	+	NE	IP	+	NE	+	+	+	+
Nilotinib (Tasigna)	+	NE	IP	+	NE	+	+	+	+

Source: Blankar et al, 2011

Note: + = positive recommendation. NE = not evaluated. IP = in progress. Agency abbreviations in brackets. Note: This work did not include SMC and AWMSG

The OECD (2005) note: *"Standard methodologies applied in health technology assessment may struggle to deal with such cases [of orphan drugs] and there is no agreed proven system in place that can assist the decision maker to make appropriate allocation choices for rare diseases."* In later work they also highlight that cost effectiveness thresholds may be ignored in the case of rare diseases and for products to treat life threatening diseases for which no alternative products exist (OECD, 2008).

OHE note that rarity may feature in decision making via other factors or 'modifiers'. Factors particularly relevant include severity of the illness and the lack of an adequate alternative treatment (OHE, 2009).

8 Payer/Commissioner Decisions

8.6 The value of rarity and its role in decision making

There is also some debate about the value placed on rarity, and its link back to the drivers of price. McCabe et al (2007) argue that the cost of development and production is entirely a matter for the private sector in making its investment decisions. The price that society ought to be willing to pay is based on whether society values the health outcomes more than the costs, including the opportunity costs. In some countries there is a premium attached to the price for orphan drugs, for example a 10% to 20% premium in Japan (OECD, 2008) (although we do not know how that was decided as an appropriate level for the premium and/or if this was widely supported by society in general). McCabe et al (2007) argue for clarity on whether there is a societal premium for drugs to treat rare diseases, and if there is, its scale. Simeons (2010) suggests that there may be a preference for rarity but more research is needed.

Others have explored whether there is a broader societal preference to treat those with rare conditions using surveys of the general population. Desser et al (2010) used a survey to explore preferences of Norwegians; they found that there is not necessarily a preference to treat those with rare diseases if this is at the expense of those with common diseases. Dolan et al (2008) used a survey to explore their method of measuring a range of societal preferences of the general public in the UK, including preferences of treating those who have a rare or extremely rare disease. They found that an 'extremely rare' condition is given 20% more weight than a 'slightly more common' condition. Other research in the UK does not support this. Hughes (undated) found that the general public place greater priority for medicines that treat severe disease, address unmet needs, bring wider societal benefits, medicines that work in a new way if they also bring considerable improvement to health. A priority for rarity was tested but was not supported by the results (Hughes, undated). The presence or absence of a higher preference to treat rare diseases versus common diseases remains a controversy (Philips and Hughes, 2009).

8.7 Speed of reimbursement/funding decision making

There are also concerns about the speed of decision making because this affects how quickly patients can access products. This is becoming an increasing concern generally across both orphan and non-orphan products. The time that decisions can take can be significant. For example, in Italy access to new oncology products (75% of which are orphan products from 2006 to 2008) can take some 2.3 years including both the regulatory decision and the pricing and reimbursement decision (Russo et al, 2010).

Kole and Faurisson (2010) suggest that delays in access are part of a 'dynamic' which is affected by company decisions on making their products available (perhaps less willing to do so in countries with low incomes) and/or competent authorities (i.e. agencies within countries that are formally responsible for pricing and reimbursement of medicines) where delays may occur as time is taken to agree prices. However, they also note that due to the lack of transparency across Europe, the precise drivers of delay seen across countries are not possible to attribute to a single cause.

9 Prescribing decisions

The final decision to prescribe rests with the clinician. Their decisions will be a result of a number of factors, and cost may be part of considerations (interviewee's comment). In some cases, they may need to act as an advocate for the patient to obtain funding for the treatment, including supporting IFRs and/or contributing to the various levels of decision making. They may also have a role in clinical trials, such as recruiting patients.

Based on our interviews it is clear that ensuring clinical expertise on rare diseases is particularly challenging. This includes issues of:

- basic training, where some have highlighted that training of clinicians tends to provide only a short introduction to rare diseases, and that in practice many clinicians (especially GPs) will only see someone with a rare disease once over several years. This can slow diagnosis and referral to specialists. Hence, indirectly, it can affect later prescribing options;

- peer support for those treating rare disease at a specialist level, because treatment is not necessarily straight forward, including the importance of consensus guidelines to support clinical decision making;

- sufficient time for expert clinicians to be part of decision making on funding.

The level of prescribing will directly inform the level of revenue for companies producing orphan drugs. The amount of revenue earned from orphan products is not usually the same order of magnitude as 'blockbusters' at over US$1billion. Instead, annual sales are estimated to be between US$50 million and US$300million (Villa et al, 2008). But there are a small proportion of products that have generated blockbuster sales (9% of US designated products) (Wellam-Labadie and Zhou, 2010).

10 The links between decision making along the pathway to access

The pathway that we set out in the beginning of this report, and which has been used to structure the previous discussion, is linear. We know however that there are a number of links and connections that make it much more challenging to understand how access decisions are made and on what basis.

Denis et al (2010b) review a number of interventions that influence access along the pathway to access in 6 countries. Key findings are summarised in the table below. Notable are the range of ways that Governments intervene and the lack of a single model in use for orphan drugs.

Table 12: *Regulation governing rare disease and orphan drug markets*

Features	Belgium	France	Italy	The Netherlands	Sweden	UK
Institutional context						
Existence of centres for rare diseases/orphan drugs	No	Yes	Yes	Yes	Yes	Yes
Policy measures to promote development of orphan drugs	No	Yes	Yes	Yes	No	No
Incentives for research on rare diseases/orphan drugs	No	Yes	Yes	Yes	No	No
Marketing authorisation						
Existence of domestic marketing authorisation procedure	No	Yes	No	No	No	No
Procedure for compassionate use of orphan drugs	Yes	Yes	Yes	Yes	No	Yes
Procedure for off-label use of orphan drugs	No	No	Yes	Yes	No	Yes
Pricing						
Free pricing	-	-	-	-	Yes	Yes
Fixed pricing	Yes	Yes	Yes	Yes	-	-

10 The links between decision making along the pathway to access

Table 12 *(continued)*

Features	Belgium	France	Italy	The Netherlands	Sweden	UK
Reimbursement						
Third party payer:						
National Health Service	-	-	Yes	-	-	Yes
Social insurance	Yes	Yes	-	Yes	Yes	-
Reimbursement based on cost effectiveness	No	Yes	Yes	Yes	Yes	Yes
Reimbursed based on budget impact	Yes	Yes	Yes	Yes	No	Yes
Reimbursement level						
Full reimbursement	Yes	Yes	Yes	Yes	Yes	Yes
Partial reimbursement	No	Yes	-	Yes	-	-
Distribution channels						
Hospital pharmacies	Yes	Yes	Yes	Yes	Yes	Yes
Community pharmacies	-	Yes	Yes	Yes	Yes	-
Health authorities	-	-	Yes	-	-	-
Prescribing process						
Prescription by specialist physician	Yes	-	Yes	Yes	Yes	Yes
Prescription by general practitioner	-	-	-	Yes	Yes	-
Existence of conditions for prescribing orphan drugs	Yes	Yes	Yes	Yes	No	Yes

Source: Denis et al, 2010b

Note: This work did not separate out ultra-orphan and orphan policies

10 The links between decision making along the pathway to access

Based on our research it is clear that a particular issue across the whole pathway is the evidence base: this is often geared towards achieving marketing authorisation but it is much of the same evidence (although with additional components such as economic modelling) that is also considered by HTA agencies and commissioners. This means that companies are trying to meet the needs of many agencies (e.g. EMA and other regulators, as well as numerous HTA agencies). They must also do that some time in advance given the lead time involved in setting up trials in order to generate evidence.

The evidence base is also shaped by prescribing: for example, clinical trials will be conducted using the current standard of care. If that is not available/widely used in a specific country then patients in that country may be precluded from a trial (interviewee's comments). Companies are trying to efficiently meet demands and choose their approaches and countries accordingly. This will have a significant impact on patients in countries that are out of step with the current standard of care, limiting access even on a trial basis (interviewee comments).

10.1 Efforts to explore improvements that will meet both regulators' and payers' needs

The shared interest in the evidence base between regulators and payers has led to a range of work to explore how each can meet their own responsibilities to the mutual benefit of both. There may also be broader lessons as work progresses on a lifecycle approach to managing the risk-benefit of medicines (Curtin and Schulz, 2011; Eichler et al, 2011; Walker et al, 2011). This is ongoing work by the EMA. This has included issues relating to inclusion of secondary as well as primary endpoints and non-pivotal trials. Discussions have also suggested that this work should be shared with HTA agencies (Cone and Lisinski, 2008).

Some relevant activities are set out below.

10.1.1 Clinical added value of orphan drugs (CAVOD)

There is naturally a shared interest amongst patients and industry and others to develop the evidence base to show the value of orphan drugs. EUORDIS (a European patient organisation collaboration), in collaboration with others, has asked for a working group to be set up to explore the Clinical Added Value of Orphan Drugs (CAVOD). The working group would *"facilitate collaboration amongst EU level authorities and Member States in order to make the most of already existing information at the EU level, to help national health authorities make their pricing and reimbursement decisions"* (Tejada, 2012).

There could potentially be two CAVOD reports produced if the approach was adopted: a CAVOD compilation report and a CAVOD relative effectiveness assessment report. These would be non-binding reports. This would provide a common format for agencies to consider across the EU in decision making, whether regulatory or for HTA purposes (Ernst and Young, 2011).

Different models are possible for implementing CAVOD, with one option being the adoption of a CAVOD process by EUnetHTA Joint Action (discussed below). EURORDIS is continuing their work to build on this proposal.

10.1.2 EUnetHTA Joint Action 1 and 2

The EUnetHTA Joint Action (JA) is a network *"focusing on scientific cooperation in HTA in Europe"* (EUnetHTA JA, undated a). The network builds on a long history of European work on HTA.

The first JA includes the development of a model for rapid relative effectiveness assessment and is being trialled. This includes pazopanib for the treatment of advanced renal cell cancer. Although this was previously an orphan drug, the orphan drug designation has been withdrawn (Orphanet, 2012d). The pilot report has been published, but EUnetHTA (2012) stress that *"results of this assessment are not suitable for drawing conclusions for decision making"*, because it is a pilot.

EUnetHTA JA is also working on a collaboration between payers and regulators on how the European Public Assessment Report (EPAR) could make a better contribution to the assessment of relative effectiveness by health technology assessment bodies in the EU Member States (EUnetHTA JA, undated b).

The second JA (JA2) from 2012 to 2015 will develop a general strategy, principles and an implementation proposal for a sustainable European HTA collaboration according to the requirements of Article 15 of the Directive for cross-border healthcare (EUnetHTA JA, undated c).

10 The links between decision making along the pathway to access

The network is therefore likely to be a key forum for the development of methods and for information sharing on relative effectiveness and HTA across Europe.

10.1.3 Early dialogue in the UK

There has been interest in early dialogue and engagement as part of helping companies meet regulators' needs for some time. There has also been the same interest for HTA. In the UK there are opportunities for engagement between companies and agencies, including:

- early scientific advice from the Medicines and Healthcare products Regulatory Authority (MHRA, 2011);
- early scientific advice from NICE (2012k);
- parallel scientific advice from NICE and MHRA in relation to clinical trial programmes through a pilot which started in March 2010 (MHRA, 2011).

Companies pay for the advice and it is non-binding. It is also likely that the advice would remain outside of the public domain and not open for wider comment, given the commercial implications.

Although it is too early to assess the success or otherwise of such approaches (particularly in the context of the time to conduct research) there is an example (announced in March 2012) of a new real world study that has been informed by the joint scientific advice from NICE and MHRA. The study will explore the real world benefits of a GSK late-stage investigational respiratory medicine before it has been licensed (Manchester Academic Health Science Centre, 2012).

10.1.4 Other work at European level

There are also a whole host of others who are involved in rare diseases at the European level and have insights that affect the way that information is exchanged, collected, etc, and who could inform the wider knowledge and evidence on rare diseases including orphan drugs. They include (Ernst and Young, 2011):

- EUCERD. This group is aiding the EC with activities in the field of rare diseases. This group will foster exchange of experience, policies and practices across Europe;
- EUROSCAN. This is a collaborative network to share information on new technologies, including drugs;
- Swedish EU Presidency Assessing Drug Effectiveness Project. A special meeting was held to explore approaches to assessing drugs and the role of registries during 2009. This includes a pilot on an orphan drug;
- Tapestry Networks Pilot of multi-stakeholder consultations in early stage drug development. This initiative includes EMA, HTA agencies, payers and pharmaceutical companies, patient associations and clinicians. The pilot includes representatives from six Member States (France, Germany, Italy, Netherlands, Sweden and the UK). The group is exploring alignment on the evidence required to demonstrate therapeutic value in Phase III;
- Europlan: European Project for Rare Diseases National Plans Development. This is a project to support delivery of MS national plans on rare diseases and over time to collect and disseminate best practices, develop indications for monitoring and evaluating national plans;
- Centres of Excellence for Rare Disease and European Reference Networks. This is mapping centres of excellence and exploring how European networks could be built;
- Orphanet. This is a reference database on rare diseases and orphan drugs.

11 Making better decisions

In this part of the report we consider what our descriptive work has revealed to us about the pathway to access to orphan drugs and the challenges that underlie that complex process. This sets the context for our suggestions for improvements to the decision-making processes.

11.1 Learning from current approaches

Our research has identified some general themes relating to decision making. We discuss these under each of the main stages of the access to orphan medicines pathway below.

Acceptance that there is a need for additional incentives for R&D…but some concerns about unintended consequences.

Many countries have implemented changes to the regulation of medicines to encourage the development of products to treat rare diseases. Although Canada is notable by its exception, it appears that there is broad consensus on the need to improve on the incentives for R&D in these areas. And many believe that such incentives are successful, citing the increasing number of products now available.

There are some who have questioned whether these incentives go far enough, citing the lack of effective drugs in some areas. There are also those who ask if they have perhaps gone too far, incentivising drugs that may not offer significant benefits. Others also cite concerns that some companies are using the legislation to charge higher prices, even on products where they have not necessarily borne the high costs and risks of their development.

Acceptance that there will be more limited evidence to inform regulatory decisions, especially for treatments to treat very rare diseases….but debate about what is reasonable.

There is evidence both from the literature and from our discussions with interviewees that there is a pragmatism applied at the regulatory level about the nature of the evidence that is feasible and reasonable in the context of rare disease. Treatments for very rare diseases are likely to face practical challenges in building the clinical evidence base because of the very small sample sizes. In some cases that translates into greater uncertainty of clinical benefit. There also appears to be an acceptance that there needs to be a case-by-case assessment. There is currently no formal distinction made between treatments for very rare diseases (ultra orphan drugs) and rare diseases (orphan drugs).

Perhaps inevitably there is some debate about what is feasible and reasonable in terms of the evidence base to be expected by regulators. The true costs of R&D, of which a large part are geared towards meeting the needs of regulators so as to obtain marketing approval, are not widely known for orphan drugs. They are perhaps only really understood by companies who bear them, and are a result of multiple factors, some but not all under the control of companies. Some say regulators could consider more creative approaches to evidence generation, which may be either more feasible and/or more efficient—perhaps even both.

The costs are also linked to the willingness of regulators to accept uncertainty. And the regulators themselves must pick up on the willingness of patients and carers to accept risks in return for benefit. Further, they must weigh up the time taken for more evidence generation, which in part drives different types of marketing approval. This recognises that there is a cost to patients from delay.

Acceptance that there will be a need for more evidence on safety and effectiveness over time… but debate about what the requirements should be.

There are different types of marketing approval that can be granted. These can be linked to further evidence generation to be able to move to a 'normal' approval. The regulator can also require post-marketing surveillance as part of on-going monitoring of product safety.

Again, it is probably inevitable that there is debate about what the requirements should be for further evidence generation. This stems from the costs being borne by companies, and the multiple stakeholders who have an interest in the information that then becomes available. Companies also operate in a competitive environment, even in rare diseases, and hence they will have a concern about who can access information and for what purpose.

Acceptance that there will be more limited evidence and greater uncertainty to consider in payer decisions with a continuum between treatments for very rare diseases and rare diseases….but debate about what is reasonable and no clear cut off point between ultra-orphan drugs and orphan drugs.

11 Making better decisions

There seems to be consensus amongst those we spoke to, and via our review of how decisions are made by agencies, that small sample sizes will feed through into significant and greater uncertainty in both clinical effectiveness and cost effectiveness compared to non-orphan products. This is also recognised in the literature (OHE, 2009.) However, it was also recognised that this would differ at either end of the rare disease spectrum: products to treat very rare diseases would, in general, suffer most from limited evidence and greater uncertainty, as the spectrum moves towards more common rare diseases, this would decrease.

A broader issue, and one not specific to orphan drugs, is that it is challenging for companies to provide a full cost effectiveness analysis close to launch. In part that reflects specific characteristics of the disease: survival outcome may well take years to evidence with confidence. Companies are expected by agencies to put as full a case together as possible, even if that means presenting results that have wide ranges in ICERs.

Those that we spoke to expressed concerns that the way in which HTA agencies approach orphan medicines could be a barrier to access. For some, the fear is that agencies may be seeking a level of certainty that is not possible given both the small sample sizes and the costs of generating that evidence base. For others it is the different approaches of the agencies that is a concern; SMC and AWMSG have orphan drug modifiers whereas NICE does not, while AGNSS has a wide framework to assess products to treat less than 500 patients across England. Other agencies, including SMC and AWMSG, apply modifiers to the same approach that they take to non-orphan drugs.

Decisions need to take account of a number of factors, some easier to measure than others… but debate in how well this is accommodated within existing approaches.

There seems to be consensus amongst many of those that we spoke to, and via our review of how decisions are made by agencies, that there are a number of relevant factors to consider. Although not necessarily described as such, the multi-criteria decision making approach is illustrated with the existing frameworks used by many as they assess medicines, both within the UK and further afield. There are some differences in the exact wording used, but all have additional factors or 'modifiers' that play a role in deliberation. Nearly all of these all build on an initial cost per QALY assessment.

Where rarity is highlighted, it is unclear just how important this is as part of the broader assessment of clinical benefits, costs, and uncertainty in deciding to pay for a drug, and whether that is restricted or not (for example, for certain types of patients rather than the whole patient population). There is also debate about whether, and how, rarity is valued by society.

For others, the concern is that agencies may not be able to fully capture the value of treatment (a wider concern expressed for common diseases too).

There are also concerns about the balance between efficiency and equity that underpin decision making. Some also felt that opportunity costs and the pursuit of utilitarian goals of the greatest good for the greatest number simply leaves those with rare diseases behind.

Inconsistencies in decision making processes and recommendations….which lead to gaps and costs.

Within the UK there are different approaches taken to payer decisions. This can cause some significant frustrations for patients in terms of different recommendations being made. Differences can be in the form of:

- a 'yes' from the regulator but a 'no' from the payer(s). In part, this might reflect a lack of awareness of the responsibilities of the regulator versus the payer(s). It may also reflect a frustration that although these agencies are considering different factors, they will often draw on some of the same evidence and yet draw different inferences (such as their respective views on the appropriateness of surrogate outcome markers);
- a 'yes' from one national HTA agency versus a 'no' from another (or a more restrictive recommendation);
- a 'yes' from one regional/local agency versus a 'no' from another.

Gaps can appear when no national agency undertakes an appraisal, leaving the decision to be made at a lower level. This is generally more opaque.

The costs of having multiple and differing decision-making approaches falls on different stakeholders. Many of those we spoke to were frustrated at having to duplicate

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their efforts and tailor to each agency's requirements, at both devolved national level and PCT level (or equivalent). That applies to companies and patients, and clinicians too. And of course, all agencies are ultimately funded by UK tax payers so there is a cost borne by society for running multiple agencies.

No system can anticipate every eventuality… role for exceptional cases.

Although many countries have a framework to appraise medicines, there is recognition that some cases may be 'exceptional'—a decision essentially made for an 'average' patient may not be appropriate for all. Exceptional funding is a feature in many countries and is part of the UK system too.

Not just the recommendations that matter… implementation is key.

Considerable resources and effort go into appraising medicines, but the value of any recommendation lies in implementation. Positive recommendations should ensure patients get access, negative recommendations should ensure that dis-investment follows to fund other more valuable activity. This is an issue for all medicines.

11.2 Improving current approaches

Our research, particularly from talking to those involved in decision making along the pathway to access, has confirmed how difficult it is to make judgements around orphan medicines. No-one felt that it was easy to balance:

- the benefits and risks that are 'reasonable' for society in the development of new orphan medicines;
- the benefits and uncertainty that are 'reasonable' for society to pay for in funding new orphan medicines.

And nearly all felt that there were some merits in how these decisions are currently made including:

- efforts to take a wider perspective (e.g. proposals for VBP could include the impact on carers or returning to work);
- patient involvement;
- expert clinician involvement.

However many felt that improvements can and should be made in the future.

While access to orphan drugs has been the primary focus of our research, many of the issues we have explored have wider relevance, such as how the NHS as a whole responds to the needs of patients with rare diseases.

We recommend that:

Patients should be involved in early decisions about R&D for orphan drugs: working with individual companies to identify targets and appropriate patient-focused outcome measures. This work should also involve regulators.

We have heard convincing concerns from patient representatives that their needs are not always clearly identified and transmitted back to those starting or refining the development of new drugs. This may not be an easy task, but we believe it would be worthwhile. That could mean:

- individual companies working with patient representatives to identify targets: for example, how they might value a treatment that is delivered differently or minimises side effects;
- individual companies working with patient representatives to identify patient-focused outcomes that can be measured as part of clinical trials and in other data collections (e.g. registries). These may be the same as those currently used in clinical decision making, but they may be different. These may or may not be product and disease specific. They could cover the importance of living independently, for example, which could apply more broadly to rare diseases and indeed common diseases too.

If companies work with patients to refine endpoints to be used in trials, then these will also need to be accepted by regulators, otherwise they will not add value to one of the key decisions that affect access to orphan drugs.

EMA and HTA agencies should continue to explore the concept of real world evidence generation via EUnetHTA Joint Action 1 and 2. This should include a pilot using an orphan drug.

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Although it will differ according to the specific disease and product, there is scope to explore how requirements can be designed to meet multiple needs: safety, effectiveness and cost effectiveness. There is already work underway and we recommend that EUnetHTA JA considers a pilot using an orphan product. This should also take into account the views of patients, clinicians and industry.

Member States (MS) should work together to explore the feasibility of sharing information arising from compassionate use monitoring, as part of individual MS strategies for rare disease.

This will ensure that decisions can draw on a range of sources of information, and in the context of rare diseases even a small addition to the sample size can make an improvement to the evidence base. Once again, this will differ according to the specific disease and product, but it could provide more insight than if countries work alone.

Agencies should apply multiple criteria in informing their recommendations and ensure appropriate patient involvement. There is scope to explore building more consistency across agencies in the UK.

Considerable effort already goes into the assessment of orphan drugs by NICE, SMC, AWMSG and AGNSS. Over time their approaches have been refined, including adding in further modifiers to decisions, and through AGNSS the development of a new framework to inform recommendations for ultra-orphan drugs. Such a wide assessment should form the basis of NICE's approach to orphan drugs. We also recommend that agencies explore ways to move towards consistency in how orphan drugs are assessed and appraised. Over time this could even move towards a single UK wide approach, so to free up resource enabling consideration of more orphan drugs and be more proportionate in terms of appraisal costs and budget impact. It would also support a more a streamlined process for often the same people (patients, expert clinicians, companies) to contribute to those decisions.

We believe that involvement with patients and expert clinicians is crucial in this process. Both will have specific insights and can contribute to a holistic view of the clinical benefits and risks, and the product's value for money. Although these are well-cited principles, and mechanisms currently exist, there is scope to review and build on existing approaches. There is scope to learn from the approach of AGNSS which also included significant patient involvement, including a novel approach of providing dedicated, tailored support for patient organisations to prepare their submission.

Full details of the approach to VBP are not yet known. It is too early to take a decision on whether VBP will be appropriate to consider orphan drugs.

With so little known about the practicalities of VBP, we do not recommend that orphan drugs are immediately part of this system. New orphan drugs could over time transition into VBP, depending upon the way in which VBP is designed and implemented in the future. That may include patient access schemes, which can either lead to an NHS discount and/or monitoring of health outcomes with a change to the real price based on those outcomes.

Orphan drugs should be explicitly included in ongoing work to support access.

There is not currently a straight-forward link between a positive recommendation and funding for products in England. This is not just an orphan drug issue, but a more general one. There are a number of disconnections which can result in a positive recommendation at the national level yet limited or variable patient access at the local level. However, there are opportunities for new approaches to improve implementation of NICE guidance under Innovation, Health and Wealth, or other changes in the NHS in England, such as the Mandate, and these should explicitly consider orphan drugs that have already been recommended for use by NICE.

We also recommend more research to be undertaken with the UK general population to explore the presence and scale of a societal premium to treat rare diseases. The research we found is not UK based or is early piloting and exploring techniques. This key part of the evidence base is missing; it is needed to support the emphasis placed on rarity in the future, whether that is within VBP or a separate process.

We have focused our research on the pathway to access to orphan drugs. We know that there are other wider issues that need addressing, including off-label prescribing and the broader innovative environment, as well as the broader health care system environment. The interaction between these and the pathway to access to orphan drugs is also likely to be a rich source for further research.

Glossary

Biomarker: an indicator of a biological state, such as the level of a protein in the blood.

Clinical commission groups (CCGs): groups of GP Practices that will be responsible for buying health and care services for patients, taking over the role from Primary Care Trusts. Taken from: *http://www.datadictionary.nhs.uk/data_dictionary/nhs_business_definitions/p/primary_care_trust_de.asp?shownav=1*

Commissioners: those agencies who manage a budget for a defined population in England.

Cost effectiveness assessment (CEA): compares the costs and health effects ofan intervention to assess the extent to which it can be regarded as providing value for money. This informs decision-makers who have to determine where to allocate limited healthcare resources. Taken from: *http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Cost-effect.pdf*

Compassionate use: permits use when patients have an unmet medical need and there is a promising medicine that has not yet been authorised (licensed) for their condition.

Committee for Medicinal Products for Human Use (CHMP): committee that decides on marketing authorisation for new medicines.

Committee for Orphan Medicinal Products (COMP): Committee that decides on orphan drug designation.

Conditional marketing authorisation: a type of marketing authorisation when a product can demonstrate positive benefit-risk balance, based on scientific data, pending confirmation.

Centralised procedure: rapid and EU wide authorisation. Taken from: *http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/03/WC500074885.pdf*

European Public Assessment Report (EPAR): a report which provides details of the scientific evidence used to inform the application for marketing authorisation.

Health Technology Assessment (HTA): a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Taken from: *EUnetHTA, HTA definition, http://www.eunethta.eu/Public/About_EUnetHTA/HTA/*

Marketing authorisation (MA): medicines which meet the standards of safety, quality and efficacy are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold. Taken from: *http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/index.htm*

Marketing authorisation under exceptional circumstances: a type of marketing authorisation granted when comprehensive data on a product cannot be provided.

Market exclusivity: a time period for the manufacturer to re-coup research and development costs.

Incremental cost effectiveness ratio (ICER): summary result of cost effectiveness analysis.

Orphan drug: In the European Union (EU), this is a drug to treat less than 5 in 10,000 people in the EU. Taken from: EMA, Orphan Designation, *http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac058002240ce*

Orphan medicinal product: an alternative name for an orphan drug, undated.

Payers: those agencies with a remit to consider budgets. Can also be termed commissioners in the context of the English NHS.

Pathogenesis of the disease: the mechanism by which the disease is caused.

Precision medicine: medicines increasing tailored to specific groups of patients.

Glossary

Prevalence: underlying number of people with the disease.

Rare disease: a disease that affects fewer than 5 in 10,000 people. Taken from: *http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf*

Rapid review: a streamlined approach to synthesising evidence. Taken from: *http://www.systematicreviewsjournal.com/content/1/1/10*

Real world effectiveness: how well a medicine performs outside of the artificial clinical trial environment, and the real value to the patient and their carers delivered by the medicine.

Regulators: those agencies with a remit to assess the safety, efficacy and quality of new medicines.

Risk Management Plan (RMP): a formal plan to manage risks of new medicines post authorisation.

Specialised services: services that help improve the lives of children and adults with rare diseases or disorders. Taken from: *http://www.specialisedservices.nhs.uk/*

Ultra-orphan drug: there is no formal definition but these are drugs to treat very rare diseases.

Value Based Pricing (VBP): proposals for changing the way that the UK prices and reimburses new medicines. Price will be linked to an assessment of the value of a new medicine to the NHS.

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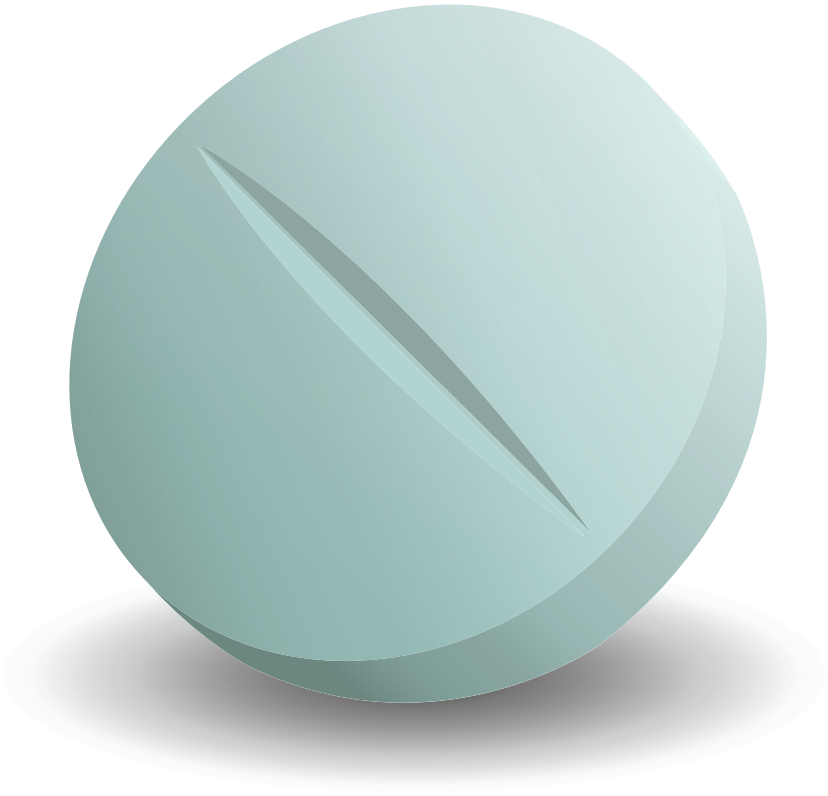

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