Appendix A

Approved products with orphan drug designation in the European Union*

Indication (disease)	Brand name	International Non-proprietary Name (INN)	Company	Date of approval
Acromegaly	Somavert	Pegvisomant	Pfizer	2002
Acute promyelocytic leukaemia	Trisenox	Arsenic trioxide	Cell Therapeutics	2002
Adrenal cortical carcinoma	Lysodren	Mitotane	Laboratoire HRA Pharma	2004
Adrenal insufficiency	Plenadren	hydrocortisone	DuoCort Pharma	2011
Advanced renal cell carcinoma	Nexavar	Sorafenib tosylate	Bayer	2006
Acute lymphoblastic leukemia	Evoltra	Clofarabine	Bioenvision	2006
Acute lymphoblastic leukemia	Atriance	Nelarabine	Glaxo	2007
Acute lymphoblastic leukemia and Chronic myelogenous (or myeloid) leukemia	Sprycel	Dasatinib	Bristol-Myers Squibb	2006
Acute myeloid leukemia	Ceplene	Histamine dihydrochloride	EpiCept	2008
Amyloidosis	Vyndaqel	Tafamidis	Pfizer	2011
Angioedema	Firazyr	Icatibant acetate	Jerini	2008
Anthracycline extravasation	Savene	Dexrazoxane	TopoTarget	2006
Barrett's oesophagus	Photobarr	Porfimer sodium	Axcan Pharma	2004
Cryopyrin-Associated Periodic Syndromes	Ilaris	Canakinumab	Novartis	2009
Cryopyrin-Associated Periodic Syndromes, including FCAS	Rilonacept Regeneron	Rilonacept	Regeneron	2009

*2020health is grateful for all of the insights from experts; the content however of this report is independent and may not reflect the views of experts and sponsors but represents only the views of the 2020health project team. The research was funded by an unrestricted educational grant from Pfizer, Genzyme and Shire.

Appendix A

Approved products with orphan drug designation in the European Union

and MWS				
Cataplexy in patients with narcolepsy	Xyrem	Sodium oxybate	UCB	2005
Chronic iron overload owing to blood transfusions	Exjade	Deferasirox	Novartis	2006
Chronic pain requiring intrathecal analgesia	Prialt	Ziconotide	Elan	2005
Chronic myelogenous (or myeloid) leukemia	Glivec	Imatinib mesylate	Novartis	2001
Chronic myelogenous (or myeloid) leukemia	Tasigna	Nilotinib	Novartis	2007
Conditioning treatment prior to conventional haematopoietic progenitor cell transplantation	Tepadina	Thiotepa	Adienne	2010
Fabry's disease	Fabrazyme	Agalsidase beta	Genzyme	2001
Fabry's disease	Replagal	Agalsidase alpha	Shire	2001
Familial adenomatous polyposis	Onsenal	Celecoxib	Pharmacia-Pfizer	2003
Gaucher's disease	Zavesca	Miglustat	Actelion	2002
Gastrointestinal Stromal Tumors and metastatic Renal cell carcinoma	Sutent	Sunitinib	Pfizer	2006
Glycogen storage disease type II (Pompe's disease)	Myozyme	Alglucosidase alpha	Genzyme	2006
Gram-negative bacterial lung infections in cystic fibrosis	Cayston	Aztreonam lysinate	Gilead	2009
Hairy-cell leukaemia	Litak	Cladribine	Lipomed	2004

Appendix A

Approved products with orphan drug designation in the European Union

Hereditary tyrosinaemia type 1	Orfadin	Nitisinone	Swedish Orphan	2005
Homocystinuria	Cystadane	Betaine anhydrous	Orphan Europe	2006
Haematopoietic progenitor cell transplantation	Busilvex	Busulfan	Pierre Fabre	2003
Hyperammonaemia	Carbaglu	Carglumic acid	Orphan Europe	2003
Hyperphenylalaninaemia	Kuvan	Sapropterin dihydrochloride	Merck	2008
Idiopathic Pulmonary Arterial Hypertension	Thelin	Sitaxentan sodium	Encysive	2006
Idiopathic Pulmonary Fibrosis	Esbriet	Pirfenidone	InterMune	2011
Intra-operative photodynamic diagnosis of residual glioma	Gliolan	5-aminolevulinic acid hydrochloride	Medac	2007
Lennox–Gastaut syndrome	Inovelon	Rufinamide	Eisai	2006
Mobilize progenitor cells prior to stem cell transplantation	Mozobil	Plerixafor	Genzyme	2009
Mucopolysaccharidosis	Aldurazyme	Laronidase	Genzyme	2003
Mucopolysaccharidosis type II (Hunter's syndrome)	Elaprase	Idursulfase	TKT	2006
Mucopolysaccharidosis VI	Naglazyme	Galsulfase	BioMarin	2006
Multiple myeloma	Revlimid	Lenalidomide	Celgene	2007
Multiple myeloma	Pharmion	Thalidomide	Celgene	2008

Appendix A

Approved products with orphan drug designation in the European Union

Osteosarcoma	Mepact	Mifamurtide	Immuno-Designed-Molecules	2008
Pulmonary Arterial Hypertension	Tracleer	Bosentan	Actelion	2002
Pulmonary Arterial Hypertension	Ventavis	Iloprost	Schering	2003
Pulmonary Arterial Hypertension	Revatio	Sildenafil citrate	Pfizer	2005
Pulmonary Arterial Hypertension and chronic thromboembolic pulmonary hypertension	Volibris	Ambrisentan	Glaxo	2008
Paroxysmal nocturnal haemoglobinuria	Soliris	Eculizumab	Alexion	2007
Patent ductus arteriosus	Pedea	Ibuprofen	Orphan	2004
Primary apnoea in premature newborns	Nymusa	Caffeine citrate	Chiesi Farmaceutici	2009
Primary IGFI deficiency due to molecular or genetic defects	Increlex	Mecasermin	Tercica	2007
Renal cell carcinoma	Torisel	Temsirolimus	Wyeth	2007
Renal cell carcinoma	Afinitor	Everolimus	Novartis	2009
Respiratory Tract Infections Cystic Fibrosis	Tobi podhaler	Tobramycin	Novartis	2011
Severe myoclonic epilepsy in infancy	Diacomit	Stiripentol	Biocodex	2006
Sickle cell syndrome	Siklos	Hydroxycarbamide	OTL Pharma	2007
Soft tissue sarcoma	Yondelis	Trabectedin	PharmaMar	2007
Subependymal giant cell astrocytoma	Votubia	everolimus	Novartis	2011

Appendix A

Approved products with orphan drug designation in the European Union

associated with tuberous sclerosis complex				
Thrombocythaemia	Xagrid	Anagrelide hydrochloride	Shire	2004
Treatment of Lambert–Eaton myasthenic syndrome	Firdapse	Amifampridine	EUSA PHARMA	2009
Treatment of chronic ITP	Revolade	Eltrombopag olamine	GlaxoSmithKline	2010
Treatment of CLL in patients who are refractory to fludarabine and alemtuzumab	Arzerra	Ofatumumab	Glaxo	2010
Treatment of immune thrombocytopenic purpura	Nplate	Romiplostim	Amgen	2008
Treatment of myelodysplastic syndromes, Chronic myelomonocytic leukaemia and Acute myeloid leukemia	Vidaza	Azacitidine	Celgene	2008
Type 1 Gaucher's disease	Vpriv	Velaglucerase alpha	Shire	2010
Wilson's disease	Wilzin	Zinc acetate dihydrate	Orphan Europe	2004

Source: 63 identified in COMP and EMASS, 2011; further 5 identified in Orphanet, 2012a

Note: International Non-proprietary Name (INN) is the generic name given to a drug by the World Health Organisation

Appendix B

National Institute for Health and Clinical Excellence (NICE) and orphan drugs

The National Institute for Health and Clinical Excellence (NICE) [1] was set up in 1999. NICE (2012h) provides "*independent, authoritative and evidence-based guidance on the most effective ways to prevent, diagnose and treat disease and ill health, reducing inequalities and variation*".

The remit of NICE is wide; ranging from the consideration of drugs, devices and public health interventions through different types of guidance. Technology appraisals (TA) are one part of NICE's work and provide guidance on the use of new technologies to the National Health Service (NHS) in England and Wales. The NHS in England is legally obliged to fund technologies that are positively appraised by NICE (NICE, 2012i).

Formally the decision to appraise a specific technology is made by Ministers at the Department of Health (DH). A number of criteria are used to inform the decision to appraise a technology or not, including (NICE, 2008):

- Is the technology likely to result in a significant health benefit, taken across the NHS as a whole, if given to all patients for whom it is indicated?
- Is the technology likely to result in a significant impact on other health-related Government policies (for example, reduction in health inequalities)?
- Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated?
- Is there significant inappropriate variation in the use of the technology across the country?
- Is the Institute likely to be able to add value by issuing national guidance? For example, in the absence of such guidance is there likely to be significant controversy over the interpretation or significance of the available evidence on clinical and cost effectiveness?

Around 40% of drugs new to the UK market are considered by NICE every year (Houses of Parliament Parliamentary Office of Science and Technology, 2010).

NICE sets out both the methods that are considered appropriate and the processes according to the type of guideline that is being produced in a number of documents (NICE, 2008; 2009c; 2009d). Key elements include clinical effectiveness and cost effectiveness but the appraisal can also consider issues of acceptability, appropriateness and preference of patients and clinicians, feasibility and impact, and equity and equality (NICE 2008). NICE has at its heart a consideration of opportunity costs, stating that

"Technologies can be considered to be cost effective if their health benefits are greater than the opportunity costs measured in terms of the health benefits associated with programmes that may be displaced to fund the new technology " (NICE, 2008).

The process for a NICE guideline differs according to the specific type of guidance (e.g. a Single Technology Appraisal (STA) or a Multiple Technology Appraisal (MTA)). Key features in the process include the following:

Scoping phase. This includes considerations about the relevant comparator(s) to the new medicine as well as features of the patient population etc. The scope is consulted upon and NICE proactively identifies groups who are likely to have an interest.

Assessment phase. This is via submissions from different interested parties. Manufacturers are asked to make a submission (but do not always do so, with 11 non-submissions from 256 appraisals, from the 1st March 2000 to 31st May 2012 (NICE, 2012j)). The manufacturer's submission is subject to review by an independent Evidence Review Group (ERG) or there is a separate submission from an independent Assessment Group. Others are invited to make

[1] Soon to be known as the National Institute for Care and Excellence reflecting changes from the Health and Social Care Act 2012 and a remit for social care

submissions including patient organisations and health care professionals. NICE sets out some expectations for the appropriate evidence base to be used by manufacturers in their submission, including the role of Randomised Controlled Trials (RCTs) and other sources (such as registers) for the clinical effectiveness evidence base. NICE also sets out some expectations for the appropriate cost effectiveness analysis, including the reference case. The reference case is a standard analysis that includes

Element of health technology assessment	Reference case
Defining the decision problem	The scope developed by the Institute
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice
Perspective on costs	NHS and Personal and Social Services (PSS)
Perspective on outcomes	All health effects on individuals
Type of economic evaluation	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review
Measure of health effects	Quality Adjusted Life Years (QALYs)
Source of data for measurement of HRQL	Reported directly by patients and/or carers
Source of preference data for valuation of changes in Health Related Quality of Life (HRQL)	Representative sample of the public
Discount rate	An annual rate of 3.5% on both costs and health effects
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit

Source: *NICE, 2008*

Appraisal phase. This is where the Appraisal Committee (AC) considers and deliberates based on the evidence. There are four ACs and each is made up of a number of representatives including from the NHS, patient and carer organisations, academia and pharmaceutical and medical devices industries (NICE, 2009e). The Committee will consider the submissions made, ask clarification questions as necessary and come to a view on the recommendation that they are minded to make. The Committee is expected to take into account:

- The broad balance of clinical benefits and costs.
- The degree of clinical need of patients with the condition or disease under consideration.
- Any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of the Institute by the Secretary of State and any guidance issued by the Secretary of State.
- The potential for long-term benefits to the NHS of innovation.

The AC is also able to draw upon supplementary guidance, such as guidance from the Citizens Council (NICE, 2012g) (a group of 30 people drawn from the general population who come together to consider cross cutting questions). Their recommendations and conclusions are incorporated into Social Value Judgements, which provides guidance to ACs in their deliberations.

The Citizens Council was asked to consider whether or not the NHS should be prepared to pay premium prices for drugs to treat patients with very rare diseases in 2004. Their deliberations revealed different opinions amongst the Council, with (NICE, 2004a):

- 16 members thinking that, with certain conditions, the NHS should consider paying premium prices;
- four members thinking that the NHS should pay whatever premium price is required; and
- 7 members thinking that the NHS should not consider paying premium prices, and should make decisions using the same approach as to any other treatment.

AC deliberations will be translated into a consultation document (an Appraisal Consultation Document (ACD)) which is made available for public comment. Not all the information that is included in submissions will necessarily be available for public comment, with some information held back as it is considered commercial in confidence or academic in confidence. The AC will consider the evidence including the estimated cost effectiveness of the technology. The AC does not use a hard and fast 'threshold' but are more likely to recommend use when the incremental cost effectiveness threshold (ICER) is below £20,000 per QALY. Between £20,000 to £30,000 per QALY the AC will consider the degree of certainty around the ICER, whether Health Related Quality of Life (HRQL) has been appropriately captured, and innovativeness of the technology which may not have been captured. Over £30,000 per QALY the AC needs to be able to identify a stronger case.

The AC will then discuss responses to the consultation. Pending that discussion they will come to a view on the recommendation they will make in final guidance (Final Appraisal Determination (FAD).

Final guidance will be made available following these deliberations and consultation, however there is scope for appeals should stakeholders (and not just manufacturers but others too have appealed in the past, with 70 past appeal hearings (NICE, 2012f)) which can lead to further rounds of deliberation and consultation.

NICE has considered orphan products, but not all of them. Our analysis of the NICE website suggested that NICE has considered 18 indications of the 68 orphan drugs with marketing authorisation up to the end of 2011.

NICEs approach does not specifically differ for orphan products, although they have debated the need to take a different approach. In 2006 NICE set out its

National Institute for Health and Clinical Excellence (NICE) and orphan drugs

response to a request from the Department of Health on appraising orphan drugs (NICE, undated). That work built on discussions and debate across a number of groups (including for example the Royal College of Physicians) undertaken during 2004. NICE noted that they had appraised orphan drugs using their current approach (as it stood then) and had not encountered particular difficulties. They noted that orphan drugs tended to have high incremental cost effectiveness ratios (ICERs). However, NICE suggested 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 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;
- potentially for life-long use

In these cases, NICE could draw on the ICERs from previously appraised ultra-orphan products and apply a different decision rule: 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. NICE did not set up a parallel process for consideration of ultra-orphan products .

Appendix C

Scottish Medicines Consortium (SMC) and Orphan Drugs

The Scottish Medicines Consortium(SMC) was set up in 2001. The SMC provides *"advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the clinical and cost-effectiveness of all newly licensed medicines, all new formulations of existing medicines and new indications for established products (licensed from January 2002)"* (SMC, 2012).

SMC appraises all new medicines, although in practice we did not find appraisals for all the products approved with orphan indications licensed by European Medicines Agency (EMA). SMC aims to provide guidance within 12 weeks of products becoming available (SMC, undated).

SMC sets out both the methods that are considered appropriate and the processes according to the type of guideline that is being produced in a number of documents. Key elements include clinical effectiveness and cost effectiveness. SMC also has a number of 'modifiers' which can allow flexibility in formulating a recommendation. These, in addition to the explicit guidance for orphan drugs (discussed below) includes (SMC, undated):

- Evidence of a substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of 3 months but the SMC assesses the particular clinical context in reaching its decision;
- Evidence of a substantial improvement in quality of life (with or without survival benefit);
- Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group;
- Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS;
- Possible bridging to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a defined proportion of patients;
- Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication. Some possible examples include caffeine injection for the treatment of apnoea of prematurity and betaine anhydrous for the adjunctive treatment of homocystinuria.

The process for developing a SMC recommendation includes:

Assessment phase, based on a submission from the manufacturer. Manufacturers must fill in New Product Assessment Form (NPAF). Submissions may also come from patients too. The manufacturer submission needs to show that the medicine will:

- provide additional health benefits that are valued by patients compared to current Scottish practice and that this is at a net cost to the NHS that offers acceptable value in relation to other uses of the same resources, or offer equivalent levels of health benefit to patients at an equivalent or lower net cost to the NHS.

The manufacturers submission is expected to follow SMC guidance and the methodology used by the manufacturers to include (Timony, 2012):

- The perspective adopted on costs should be that of the NHS in Scotland and social work.
- The evidence submitted must be assembled systematically and synthesised in a transparent and reproducible way.
- All data used to estimate clinical and cost-effectiveness must be presented clearly in tabular form and include details of data sources.
- Clinical and cost-effectiveness needs to be considered over an appropriate time horizon relevant to Scottish practice and patients and all

relevant treatment options for the specific patient groups should be compared.

- In general, cost-utility analysis is the preferred form of economic evaluation, with health effects expressed in terms of quality-adjusted life-years (QALYs).

- The SMC considers modelling a relevant framework within which available evidence can be synthesised and estimates of clinical and cost-effectiveness generated. The annual discount rate recommended for both costs and benefits is 3.5%.

- Uncertainty surrounding the estimates of cost-effectiveness needs to be included.

Some of this information will be available publicly, but not all reflecting commercial in confidence parts of the submission.

Appraisal phase. The SMC is made up of around 40 members who have a variety of backgrounds: doctors, primary care, secondary care, pharmacists, healthcare management, public partners, pharmaceutical industry and a health economist (SMC, 2012). SMC is helped to make decisions by a smaller committee, the New Drugs Committee (NDC) which provides a purely scientific review.
SMC deliberations will be translated into a Detailed Advice Document (DAD) which is made available after 4 weeks of the original SMC meeting. The manufacturer and any manufacturers of comparator products used in determining relative cost effectiveness are sent the DAD earlier and can raise any issues with SMC staff. Manufacturers can re-submit in the case of a 'not recommended' piece of advice.

SMC does have specific guidance relating to consideration of orphan drugs (from 2007). Although they still expect comprehensive and complete submissions from manufacturers (as they would for non-orphan products) the SMC states that *"orphan drugs may have a less well developed clinical trials programme and, therefore, that less information than usual may be available for some sections"* (SMC, 2012). Although the assessment process is the same for all products, in the case of orphan medicines the SMC may consider additional factors:

- whether the drug treats a life threatening disease;

- substantially increases life expectancy and/or quality of life;

- can reverse, rather than stabilise, the condition; or

- bridges a gap to a "definitive" therapy.

SMC notes that there may be a joint responsibility for the NHS and the manufacturer to monitor use, including through the use of registers.

Appendix D

The All Wales Medicines Strategy Group (AWMSG) and Orphan Drugs

The All Wales Medicines Strategy Group (AWMSG) was set up in 2002 (Welsh Health Circular, 2003). The AWMSG provides "timely, independent and authoritive advice on new medicines" (AWMSG, undated).
AWMSG appraises new medicines where no NICE guidance is expected for at least 12 months from the date of submission. From 2010, AWMSG had funding to consider all new medicines not on the NICE work programme (AWMSG, 2012b). NICE guidance supersedes AWMSG guidance where the two differ (AWMSG, 2012c). AMWSG aims to provide guidance within 6 to 9 months of licensing (2012b).

NHS Trusts and Local Health Boards are expected to follow guidance from AWMSG.

AWMSG has considered orphan products, but not all of them. Based on our searches of the AWMSG website, 45 orphan drugs have been considered.

The process for developing an AWMSG recommendation includes:

Assessment phase, based on a submission from the manufacturer. This includes a range of data including a pharmacoeconomic evaluation. This should state clearly the context of the evaluation, the comparator, and take the perspective of the NHS Wales and personal social services (AWMSG, 2012d).

Appraisal phase. The AWMSG is made up of around 30 members (AWMSG, 2012e) who have a variety of backgrounds: NHS clinicians, pharmacists, healthcare professionals, academics, health economists, industry representatives and patient advocates (AWMSG, undated). The Welsh Medicines Partnership collates and evaluates evidence, and then the New Medicines Group (NMG) assesses the evidence. The NMG makes an initial recommendation which is then considered by the AWMSG. The AWMSG recommendation then goes to the Minister. Companies are able to comment on the draft assessment report, and the preliminary appraisal recommendation (AWMSG, 2012e).

Final guidance (the Final Appraisal Recommendation (FAR) will be made available following these deliberations and opportunities for the manufacturer to comment.
AWMSG does have specific guidance relating to consideration of ultra-orphan drugs (from 2011). AWMSG defines ultra-orphan drugs as those that treat diseases with a prevalence of less than 1 in 50,000. AWMSG consider the same criteria as for non-orphan products, but recognise that the evidence will "necessarily be weaker". AWMSG/NMG also note that the ICERs may be higher than for non-ultra-orphan products and therefore will consider (2011b):

- 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. The AWMSG / NMG will consider whether the medicine:
    a. represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment);
    b. whether it can plausibly generate substantial health gains over existing treatments for the individual (e.g. >1 QALY).

In addition, all patients receiving approved ultra-orphan drugs should be entered into registries.

Appendix D

The All Wales Medicines Strategy Group (AWMSG) and Orphan Drugs

The Advisory Group for National Specialised Services (AGNSS) is part of NHS Specialised Services. NHS Specialised Services is a national organisation (in England) which commissions specialised services for those with rare diseases or disorders (NHS Specialised Services, undated a). These are generally services that affect less than 500 people across England (NHS Specialised Services, undated b).

AGNSS is a committee that advises Ministers on which services should be nationally commissioned and the centres that should provide them. AGNSS was also to consider a small number of new drugs and technologies. This would only be where NICE decided that the new drug is not suitable for a NICE appraisal because of the very small patient numbers (please see Appendix B: NICE and orphan drugs for a fuller explanation of NICE).

AGNSS would normally be expected to receive a referral from NICE and would also normally expect that the drug would have a EU designated orphan drug designation (NHS Specialised Services, undated c).

A framework was developed to support the development of AGNSS recommendations, including the following criteria (NHS Specialised Services, undated d):

1. The product, service or technology will usually consist of no more than 500 patients and/or four centres in England.

2. The product, service, or technology is clearly defined.

3. The clinical need for national commissioning of the product, service, or technology is significant and well defined.

4. There is a clear clinical pathway for the product, service, or technology, including criteria for referring patients and a co-ordination strategy for conditions that are served by more than one clinical specialty.

The target patient group or subset is distinct for clinical reasons.

There will be significant benefits from national commissioning and concentrated provision, which might include improved clinical quality, focused clinical expertise, more efficient use of NHS resources.

1. The product, service or technology will have a greater clinical benefit than alternative forms of care.

2. The product, service or technology can be accessed by all patients who are eligible for NHS treatment.

3. There is enough evidence to determine that a full review of the product, service, or technology will be useful.

Within a full application to AGNSS, there would be a detailed assessment based on 12 core criteria within 4 groups. These include (AGNSS, undated):

1. Does it work?

i. Severity and ability of patients to benefit

ii. Clinical safety and risk

iii. Clinical effectiveness and potential for improving health

2. Does it add value to society?

iv. Stimulating research and innovation

v. Needs of patients and society

vi. Is it a reasonable cost to the public?

3. Average cost per patient

vii. Overall cost impact and affordability including opportunity cost

viii. Value for money compared to alternatives

4. Is it the best way of delivering the service?

ix. Best clinical practice in delivering the service

x. Economic efficiency of provision

xi. Continuity of provision

xii. Accessibility and balanced geographic distribution

This framework was piloted from October 2010. No information is available publicly on the pilot and no formal decisions have been taken by Ministers (at the time of writing) resulting from the application of this framework to an orphan drug.

AGNSS' work was under a moratorium during the summer of 2012 (SHCA, 2012). In July it was announced that the work of AGNSS would go to NICE from April 2013 (DH, 2012c). From the 1st April 2013 AGNSS will formally cease to provide advice to Ministers.

Appendix F

Advisory Group for National Specialised Services (AGNSS) and Orphan Drugs

In Australia companies must submit an application for reimbursement, known as Pharmaceutical Benefit Scheme (PBS) listing. Submissions are considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

Orphan drugs are separately identified in guidance for company submissions. In this context, an orphan drug is identified as affecting 2,000 people in Australia (Australian Government, Department of Health and Ageing, undated).

Guidance states that:*"PBAC is aware of, and sympathetic to, the difficulties faced by sponsors of orphan drugs. Furthermore, the committee does not set a minimum standard for the type and level of evidence or other information that can be included in a submission to PBAC. However, it would be unlawful for PBAC not to consider comparative costs and effectiveness"* (Australian Government, Department of Health and Ageing, undated).

Guidance also makes reference to the 'rule of rescue'. In this context, the rule of rescue applies when four factors are present:

1. *"No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.*
2. *The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.*
3. *The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.*
4. *The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC)"* (Australian Government, Department of Health and Ageing, undated).

The guidance makes it clear that the rule of rescue is supplementary, and does not replace the evidence based consideration of comparative cost effectiveness. The guidance also acknowledges the challenges involved in applying the rule of rescue. This includes the limits from factor 1, that means it cannot be used for a second drug including when inclusion is on the basis of cost minimisation analysis (i.e. same effectiveness but lower cost) (Australian Government, Department of Health and Ageing, undated).

The potential for overall inefficiencies unless PBAC compensates when considering drugs that fall outside of the rule of rescue.

Appendix G

Orphan drugs and provincial funding approaches in Canada

Canada has a provincial health care system, with a mix of both public and privately funded health care.

Decisions on pricing and reimbursement are influenced both by the national agency, the Canadian Agency for Drugs and Technologies in Healthcare (CADTH), but affordability and budget constraints are managed by provinces themselves.

CADTH has been identified as the main access hurdle in Canada (Kumar and Bachman, undated). Cost effectiveness ratios for many orphan drugs are higher than the threshold used to inform CADTH recommendations, unless products are curative. Although recommendations from CADTH are not binding of provinces, who hold budget responsibility for health care, in practice they are considered very influential. For some provinces though, there is scope to fund some orphan drugs via what have been called 'specialised access mechanisms' (Kumar and Bachman, undated).

These arrangements are not necessarily universal for all orphan drugs, and more than one approach can be taken within a province. The two provinces with specific policies for orphan drugs are set out below (Kumar and Bachman, undated).

Ontario

Special Drugs Program. Examples of medicines paid for from this program include: erythropoietin for end stage renal disease, HGH for children with growth failure, clozapine for schizophrenia and alglucerase for Gaucher's Disease

Trillium Drug Program. This is not specifically for orphan medicines, but contributes to the cost of medicines for those who have a high prescription drug cost relative to their household income (Ontario Trilium Drug Programme, 2008). Because some orphan medicines are high cost, this can include orphan medicines (although we did not identify specific products)

Exceptional Access Program (EAP). Covers non-listed products on a case by case basis

Alberta

Rare Diseases Drug Program. Rare disease is defined in this context as a genetic disorder affects patients which occur in <50,000 Canadians or <50 Albertans. Decisions are made via an expert committee, including on decisions on treatment guidelines, critieria for reimbursement, and monitor the response to therapy. Patients will still need to make a contribution to the costs of their medicines (Alberta Health and Wellness, 2008). A number of diseases were eligible for coverage, including Gaucher's disease, Fabry Disease, MPS-I (Hurler/Hurler Scheie), Hunter disease and Pompe disease (Alberta Health and Wellness, 2008). Funding is being provided for 'ethical and compassionate reasons', funding products that cost between $250,000 to $1million per patient per year (Alberta Health and Wellness, 2008). Clinicians must apply for funding for individual patients. The application goes through a checking process to ensure that the patient is eligible (for example, having been a resident for over five years), and then on to the review panel made up of clinical experts. Funding is for up to 12 months, and if treatment is required, another application is required. Funding is only given when there is prior approval (Alberta Health and Wellness, 2008).

The approach in Alberta essentially provides a ring fenced fund for orphan drugs. It has been suggested that this can reduce the hurdle for access, and could allow for a higher reimbursement price (Kumar and Bachman, undated).

Appendix H

Orphan drugs and Haute Autorité de Santé (HAS) and the Transparency Committee in France

In France there is a 2 step process for pricing and reimbursement of medicines (ISPOR, 2009).

In step 1 there is a technical assessment from the Haute Autorite de Sante (HAS, and essentially the HTA element). HAS also hosts the Commission d'Evaluation des Médicaments who assess:

- the Medical Benefit (SMR): it appraises whether the drug should be reimbursed and what could be the reimbursement rate;
- the Improvement of Medical Benefit assessment (ASMR): the grading provides a basis for price fixing in comparison with alternatives;
- the target population eligible for treatment in the reimbursement scheme.

In step 2 reimbursement status can be granted by Commission de Transparence (Transparency Commission). They consider the opinion of the Commission d'Evaluation des Médicaments. The rate of reimbursement is fixed by the Union Nationale des Caisses d'Assurance Maladie (UNCAM).

Subsequently, a reimbursement price negotiated with Comité Economique du Médicament (CEM), and the price fixed by the Comité Economique des Produits de Santé (CEPS) after negotiation with the company.

Orphan drugs have been identified as an area of challenge within the French pricing and reimbursement system. The CEPS, a committee concerned with pricing, is *"questioning the value of continuing to provide support and special benefits for medicines with a high turnover when their profitability on the market is at least as firmly guaranteed as that of most non-orphan medicines"* (Meyer, undated).

Appendix I

Orphan drugs and Pharmaceutical Management Agency (PHARMAC) in New Zealand

The Pharmaceutical Management Agency (PHARMAC) is a key agency in influencing products which will be reimbursed in New Zealand.

Their approach is focused on cost effectiveness, using the cost per Quality Adjusted Life Year (QALY).

PHARMAC have a policy to provide funding under exceptional circumstances (NZORD, 2011). Although there are concerns that PHARMAC's policy does not adequately deal with specialised medicines for rare diseases, they do include consideration of seriousness and urgency. These were principles advocated by the New Zealand Organisation for Rare Disorders (NZORD). The policy does not explicitly include orphan drugs, but it is of interest as it may enable consideration of some treatments for rare diseases. The latest policy was introduced with accompanying media materials which suggest that 'patients no longer need to have a rare condition to be considered for funding'. NZORD say that rarity should not be an obligatory criteria but highlight how a range of factors should be considered which could still permit access to some treatments for rare diseases (NZORD, 2011).

It is probably too early to determine any impact of this latest policy because it was effective from the 1st March 2012 (PHARMAC, 2011). However, there is anticipated to be further funding allocated to meeting exceptional circumstance requests for funding (from around $4million to $6.5million) (NZORD, 2011).