Access to Rare Disease treatment

A Discussion paper of experience in six countries

Tony Hockley
Department of Social Policy
London School of Economics & Political Science

The author is grateful to Pfizer Ltd for sponsorship of this discussion paper, which was produced in collaboration with Public Policy Projects. This paper comprises the LSE contribution to the project.

January 2018

1. Introduction

Advances in rare disease treatment benefit everyone. They have always represented the first step towards better treatment of common diseases, but the science of rare disease today is leading the way to more personalised, more effective, and less wasteful care(Blue Cross, 2017). Such is the pace of progress, however, that managing the introduction of these new treatments into health systems has become an important element of health policy alongside increasing awareness of the high rate of healthcare utilisation amongst patients with rare diseases(WA, 2015).

This paper looks at some of the salient features of health policies that are now affecting patient access to medicines for rare diseases, known formally as Orphan Medicinal Products (OMPs) and less accurately as "Orphan Drugs". It does so across a small selection of countries chosen on the basis of their broad comparability to England in terms of national income and health spending. Even once an OMP is licensed successfully the achievement of patient access to that therapy can face a variety of other one-off or sustained hurdles, across the spectrum from initial diagnosis to receipt of the prescribed treatment. Despite these hurdles serious rare diseases tend to benefit from significant public support for their adoption within health systems, and for those countries with a domestic pharmaceutical industry the advantages of a vibrant rare disease R&D sector are much sought after.

In 1983 US President Reagan legislated to create a regulatory system to support the development of "orphan drugs" for rare diseases, known as the Orphan Drug Act(Rao, 2013, p. 12). The Act introduced tax credits for research into rare diseases, supported and streamlined the assessment process, and 7 years market exclusivity. Japan and Australia followed suit in 1993 and 1997 respectively, although the US scheme was the most generous in terms of financial support through research grants and tax credits. Australia was also less generous on market exclusivity, which was kept similar to the general treatment of pharmaceuticals(Orphanet, 2017b). Countries with a domestic pharmaceutical R&D industry are understandably more generous in terms of R&D incentives, whereas other countries appear to focus on assistance with local regulatory hurdles. Whereas just 10 drugs or biologics were registered by the FDA in the decade prior to the Orphan Drugs Act, more than 600 have been licensed since then.(FDA, 2017a) In 2012 the US took further steps to encourage drug development in paediatric rare diseases, by legislating for a system offering "priority review vouchers" to companies that bring forward a paediatric rare disease drug for assessment. The voucher would entitle the sponsor to obtain prioritisation for one of their subsequent products(FDA, 2017b).

By 1995 the European Union was being pressed by the French health minister, Simone Weil, to take similar steps, whilst the French held the Presidency of the European Council of Ministers(Hansard, 1995). European legislation was eventually agreed and came into force in 2000(Orphanet, 2010). The countries of Europe recognised that they could no longer afford to fall behind as an attractive base for the leading edge of pharmaceutical research and development, nor ignore the moral case for the state to address the market failure that prevented firms from making the necessary investments because of the small number of people affected by each disease.

The European Commission explains the special treatment of orphan drugs saying that:

> *"Society cannot accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people"(European Commission, 2005).*

Having pressed the European Union to legislate on rare diseases **France** was also the first of the European countries to develop its own national Rare Disease Plan, the first four-year edition of which it launched in 2004 to improve diagnosis, research, treatment and care provision(Douste-Blazy *et al.*). The plan underwent considerable scrutiny, in order to inform subsequent, more detailed plans(Ayme and Rodwell, 2013, p. 64). The third plan is to be released soon(MSS, 2017c).

Between 2000 and 2016 the European legislation attracted some 2,714 applications from sponsor firms seeking an orphan designation, leading to 1805 designations. The annual application rate has grown steadily since 2001, reaching 329 in 2016 although the number of products receiving a marketing authorisation has been more stable(CEC, 2014) peaking at 21 in 2015, but falling back to 14 in 2016(CEC, 2005). There are significant differences between the US and EU in both the proportion of designations that lead to a licensed orphan medicine and the average delay between designation and authorisation. In the US 14% of designated orphan drugs have been approved, compared to 8% in the EU. The mean delay in the US was cut from around three years in 2004 to less than six months in 2015, In the EU it has *risen* from a similar length of time in 2004 to almost four years in 2015. Most orphan drugs licensed within the EU have first been authorised in the US(Korchagina *et al.*, 2015).

To qualify for European designation as an Orphan Medicinal Product (OMP) the disease to be treated must be either life-threatening or chronically debilitating, and prevalent in less than five in 10,000 people. Furthermore, the product itself must offer significant benefit in the absence of a satisfactory alternative.

The primary incentive is the provision of 10 years of market exclusivity, during which time a "similar" product will not be licensed for the same indication. Although this does not guarantee a monopoly, as alternative products for the same indication can still be licensed, it has proven successful as an incentive system. The European legislation includes a provision to review and reduce the term of market exclusivity should the product produce excess profits(CEC, 2008).

Incentivising research and development of orphan drugs does not, of course, mean that these medicines are put into use in national health systems. By their nature orphan drugs will involve innovative technology and be supported by data only from small clinical trials. They can also be expected to be relatively expensive when compared to medicines for large populations, where the R&D costs can be spread over large numbers of patients. These factors can raise additional barriers to patient access to orphan drugs, even after a swift passage through the licensing system. In 2015 the European Commission published a review of European Union country initiatives to support the availability of orphan drugs, as well as measures to support research and development(CEC, 2015). A comprehensive review of 35 national systems for access to orphan drugs published in 2015 noted that: "Differences in pricing and reimbursement policies and budgetary considerations across countries may result in inequities in access to orphan drugs"(Gammie *et al.*, 2015).

In writing this discussion paper we have looked at a four major European Union countries. In addition we review experience in Australia, which was one of the first countries to follow the US in legislating to encourage orphan drug development, and in Canada, which is often used as a non-European comparator in health policy analysis.

In total, therefore, we have selected a sample of six major developed country health systems to look at. Two countries outside of the European region are included, namely **Australia** and **Canada**. **Australia** was one of the first countries to follow the US lead in creating a specific regulatory system for orphan drugs, and therefore has significant experience in this area of policy. **Canada** is often used as a comparator to European health systems given the extent of state involvement in funding and the share of GDP committed to health. The four European countries comprise two that spend slightly more of their GDP on health than the UK and two that spend slightly less. Additionally, Australia and Canada both benefit from co-operation agreements with the European Medicines Agency(EMA).

The 2016 populations of the European countries in the sample range from around 46 million in **Spain** to 83 Million in **Germany**, putting the **UK** roughly in the middle of this range at 66 million. **Australia** and **Canada** are somewhat smaller in population terms at 24 million and 36 million(World Bank, 2017). All are of sufficient scale that there should be few anomalies in the prevalence of rare diseases, and therefore the significance of orphan drug treatments and the capacity for relevant clinical knowledge. It is estimated that one in every 15 people could have a rare disease(WHO, 2013), meaning that even in the smallest country (Australia) studied we might expect a rare disease population of 1.6 million or more.

Whilst there are significant complexities in comparisons of health spending, particularly differences in measurement, it is useful to have some understanding of the general culture of health spending prior to making any comparison of health policies. Of the selected countries **Germany** has the highest per capita total health spending, at around £4270, but most are within the range of £3,200 and £3,700, including the UK. Only **Spain** and **Italy** spend significantly less, at around £2,500 and £2,600 respectively.

Health System Spending (GBP)				
	Total/%GDP (2016)	Pharmaceutical % of health spend (latest year)	State/compulsory per cap/current prices/PPP (2016)	Voluntary/Out of Pocket per cap/current prices/PPP (2016)
Australia	9.6	16	2454	1168
Canada	10.6	17	2570	1085
France	11	15	2789	749
Germany	11.3	14	3611	658
Italy	8.9	18	1957	652
Spain	9	18	1764	735
UK	9.7	12	2554	671
(CIHI, 2016; OECD, 2016; OECD, 2017) Note: USD amounts converted at $1.3/£1(BOE)				

Governments worldwide have recognised the economic and social value of supporting research in rare disease. In August 2017, for example, the **Australian** government announced an Aus$13million investment: *"to stimulate clinical trial and registry activity with priority to be given to under-researched health priorities, such as rare cancers and rare diseases"(DHAus, 2017b)*. Aside from the direct benefits to rare disease patients, the Government noted more generally that: *"Precision medicine holds the potential to transform medicine – It changes the paradigm to a treatment that is tailored to the individual and the exact nature of their disease"(DHAus, 2017b).*

The French Minister of Health reaffirmed in November 2017, during the fifth rare diseases' conference, that solidarity in health is a national priority and hence announced many measures to continue improving rare diseases diagnosis, treatment and care(FMR, 2017).

2. Regulation

The **European Union** and **Australia** operate specific market authorisation systems for orphan drugs, which facilitate their licensing. The Australian legislation of 1997 was partly driven by a concern that treatments were needed for trachoma and leprosy in the aboriginal population. It uses a disease prevalence of 1.2/10,000 people as the limit for orphan designation and offers five years of market exclusivity as well as fee waivers. The Australian

regulator, the Therapeutic Goods Administration (TGA), works closely with the US Food & Drug Administration (FDA) in the operation of the Australian Orphan Drugs Program, although it may supplement the selection of drugs assessed with some items specific to the Australian situation(Orphanet, 2017a). **Canada** lacks such a system, so that orphan drugs must follow the standard pharmaceutical licensing route(Gammie *et al.*, 2015).

It is, as yet, unknown what the UK arrangement with the centralised European licensing process will be following the intended UK withdrawal from the European Union in March 2019. This could range from a bespoke UK licensing process, co-operating with the US and EU systems, to a continuation of current participation. UK health and business ministers cited rare diseases as an area of close co-operation that should continue after 2019. They argued that: *"Drug development is a global business – and we will look to continue to work closely with the European Medicines Agency, and our international partners"(Hunt and Clark, 2017)*. The EMA already has agreements in place with regulators outside both the current 28 countries of the European Union and non-EU European Economic Area (EEA countries. The agreements can enable:

- The exchange of confidential data on orphan designation applications and post-authorisation pharmacovigilance
- Systems for mutual recognition on good manufacturing practice (GMP), including partnerships on inspections
- Secondment of officials

(Balzli and Landgraf, 2016)

Such agreements are already in place with a number of countries including Australia, **Canada**, Switzerland and, most recently, with the USA[1](EMA, 2017). More widely the initiation of the International Council on Harmonisation (ICH) by the EU, US and Japan in 1990 has supported significant progress towards international regulatory harmonisation. Switzerland now has some 16 bilateral agreements, covering all continents including multilateral co-operation in the ACSS Consortium[2](Balzli and Landgraf, 2016). There is, of course, the possibility that the UK MHRA will conclude MRAs with both the EMA and FDA, which could provide for faster access to rare disease treatments and an increase in the number of treatments if it can choose to accept decisions on a case-by-case basis(Hatswell, 2017).

Accelerated Access

The post-Brexit approach outlined above would, in effect, be similar to an adaptation of the UK Early Access to Medicines Scheme (EAMS), launched in 2014 and enabling access to medicines ahead of its EMA marketing authorisation. This voluntary scheme created a clear mechanism for the UK regulator (MHRA) to take risk-benefit judgements where there is a demand for early access to treatments for serious conditions whose needs are currently

[1] At the start of the mutual recognition agreement in (October 2017) the US had only confirmed the GMP inspection capability of 8 EU Member States, and will assess countries individually

[2] Australia, Canada, Singapore, Switzerland

unmet. Patients and clinicians can draw on this judgement in their treatment decisions. An early review of the scheme noted that, by itself, the scheme does little to support products to launch and become established(PWC, 2016).

A study published in 2009 credited the Netherlands and Italy, for providing a range of access schemes in rare disease and ensuring the collection of real-world data from early usage(Garau and Mestre-Ferrandiz, 2009). France provides "temporary authorisations (ATU)" as a compassionate use programme, allowing patients to be treated with an orphan drug prior to the marketing authorisation being granted. Most orphan drugs are, therefore, made available early due to this provision(CEC, 2015, p. 12). A 2003 ministerial decree in Italy makes a similar provision for situations where no alternative treatment is available, subject to approval by ethics committees, and free provision by the manufacturer(AIFA, 2016). Germany also allows compassionate use ahead of marketing authorisation, but again only if the product is made available free of charge(CEC, 2015, p. 13).

In order to support compassionate use ahead of market authorisation Italy has established a fund drawn from companies applying for a marketing authorisation. They each commit the equivalent of 5% of their expenditure on meetings and conferences to this fund, which amounted to €17 million in 2013(CEC, 2015, p. 14).

OMP Reimbursement Assessment & Pricing

The variety of purchasing systems that exists across the countries considered means that there are usually additional assessments and authorisations required after an orphan drug is licenced to enter a market.

A recent analysis of the Spanish non-oncology orphan drugs market revealed that only 18 out of 58 drugs (31%) licensed by the EMA in 2012-16 had received a pricing and reimbursement decision. Out of the 58 some 17 had not sought a "national code" in **Spain**, and 23 were still in the assessment process - half of which had been denied approval on current evidence(Iniesta *et al.*, 2017). Devolution of health decision-making in Spain means that there are significant geographic inequities in access to treatment for rare disease patients, whether between Spanish regions or between hospitals within a region. One survey showed that almost half of rare disease patients had been forced to travel outside of their region for treatment in the preceding two years, and 17% of patients lacked care because they could not travel(Feder, 2017). The best treatment is focused on the most developed areas of Spain; Madrid, Catalonia, and Andalucia, leading to calls for greater national action to address these inequalities(Diariofarma, 2016; Diariofarma, 2017). In June 2017 a total of 73 organisations gave their support to a consensus white paper on rare disease. The paper calls for measures to address the regional differences in access to diagnosis and treatment, better regional funding, and faster pricing and reimbursement decision making(Gaceta Medica, 2017).

It is unsurprising, given the financial challenges being faced by health systems, that managed entry agreements are increasingly popular as a means of accelerating access to orphan drugs whilst limiting the financial risks to the health system(Morel *et al.*, 2013). The Belgian Presidency of the EU Council in 2010 also initiated a European voluntary project to co-ordinate access, known as MOCA: The pilot project would enable participant countries to share information on unmet need, and work towards a system to modulate the costs of providing fair access across countries(MoCa, 2016).

The pricing and reimbursement system of a country is probably the single most important factor in determining access to orphan drugs and in explaining international variations in access(Gammie *et al.*, 2015). The question of whether to include factors other than therapeutic value in these decisions will have a significant impact on the result. Many countries do accept that the evidence base for orphan drugs will be limited, and take account of other factors, including unmet need, human value and social solidarity(Gammie *et al.*, 2015).

Under a framework agreement between the pricing committee and the pharmaceutical industry **France** operates a system whereby an orphan drug costing more than €50,000/patient/year is reimbursed provided the firm restricts sales to a specified limit and makes the drug available to all eligible patients(CEC, 2015).

In **Germany** all authorised orphan drugs are fully reimbursed by the statutory social health insurer (GKV). Orphan drugs that accrue less than €50 million are exempt from the standard cost/benefit assessment process. The costs assessment of new drugs has a 12-month time limit after the issue of a marketing authorisation, during which time the drug is reimbursed at the manufacturer's price.

In **Spain** the pricing and reimbursement systems represents a major barrier to access(Alvarez del Vayo and Athie-Chauvet, 2017), because the country offers no special assessment criteria for orphan drugs(ISC, 2016). A 2016 report for the Spanish health technology assessment agency, AETS, concluded that the current system was inadequate for the firms producing orphan drugs and for patients: incentivising drug development but restricting access(ISC, 2016).

In order to accelerate access to orphan drugs **Italy** allows the submission of a pricing and reimbursement application on the day that the EMA publishes its Opinion on the product, rather than wait for the formal Commission Decision. The subsequent consideration is limited to a 100-day time limit. Regardless of the pricing and reimbursement negotiations, the formal launch of an orphan drug cannot be delayed in Italy by more 60 days of the Commission Decision, although it would only be available without reimbursement until pricing and reimbursement are agreed(CEC, 2015, p. 14).

Italy offers some protection for holders of orphan drug marketing authorisations. For most pharmaceutical companies the 2014 *Legge di Stabilità* economic legislation requires a

clawback from them when the overall spending ceiling is breached. Firms offering approved orphan drugs (on the AIFA list) are excluded from having to make these revenue repayments(CEC, 2015, p. 14).

Australia provides a Life Savings Drugs Program (LFDP) to enable access to expensive drugs that have been rejected by the Pharmaceutical Benefits Advisory Committee (PBAC). Drugs are included in the program on the advice of the Chief Medical Officer (CMO), and the prescribing physician must reapply annually to obtain approval for the eligibility of each treated patient(DHAus, 2017a).

The 2016 Spanish AETS report made a comparison of several countries' systems for funding access to orphan drugs, producing the table below.

	Spain	France	Italy	Germany	Sweden	Belgium	Netherlands	UK	Australia	Canada	USA
Shared Risk Agreements	X	X	X	X	X			X	X		X
Price-Volume Agreements		X									
Temporary Use Authorisations		X									
Patient Access Schemes			X					X	X		
Specific Funds			X				X	X	X	X	X
Patient Cost Limit						X					
Source: ISC (2016)											

Whether or not rare diseases receive special treatment within co-payment or private market systems can have a major impact on access to care due to the high costs usually involved. This means that for orphan drugs there can be little practical difference between the **UK** "all or nothing" reimbursement system and systems requiring co-payment unless there is an exemption for orphan drugs. As mentioned above Australia operates a Life-Savings Drugs Program for drugs that have been rejected by the HTA agency. Italy maintains a substantial list of rare diseases and disease groups[3] that warrant free service, with exemption from the usual co-payments(Rodwell and Ayme, 2014).

If only partial reimbursement is offered then co-payments can become a significant barrier to access, although most that subject patients to co-payments do offer special systems to protect against the financial impact once a specified level is reached, which is the case in both **Canada** and **Germany** (Gammie *et al.*, 2015).

3. Diagnosis

[3] Livelli Essenziali di Assistenza (LEA)

The presence of a clear diagnostic system, including routine screening, could be expected to make a substantial difference to access, given the impact of the visibility and public recognition of a rare condition.

Australian states have long operated a Newborn Bloodspot Screening Program, which currently aims to achieve early diagnosis and treatment of 25 rare diseases. Whilst the Program is implemented by the individual Australian state health departments, screening rates appear to achieve almost complete coverage of Australian newborn children(DHWA, 2015, p. 16; AG, 2017). A survey of European health systems in 2011 highlighted large disparities between countries, and in some cases within countries. At that time **Italy** was reported to be screening for just 2 conditions, **France** for 5, the **UK** for 7, **Germany** for 15, and **Spain** for 27. The same study looked at what was done with the screened samples in terms of how much the regulatory system supports screening as a tool for subsequent clinical practice. This found that **Spain,** with the highest number of conditions screened, had the least developed regulatory system, whereas **France** and the UK had the most developed(CEC, 2011).

By way of current **UK** comparison the NHS newborn programme now screens for 14 conditions recommended by the UK National Screening Committee(PHE, 2013; PHE, 2017), the same number as is now the case in Germany(Dharssi *et al.*, 2017, p. 11). **Canada** has a list of 22 conditions in a national list, although some provinces screen for more than 40 conditions(Andreatta, 2013).

Canada has an established network of diagnostic centres(Dharssi *et al.*, 2017, p. 10). **France** operates a system of 131 'centres of reference' for rare disease and 502 'centres of competence'. The purpose of these centres is, among others, to facilitate diagnosis of rare diseases and improve care delivery(MSSDF, 2016). These centres are currently being asked to renew their accreditation for the period from 2017 to 2022 period(MSS, 2017a). This followed from a government decision to make renewed efforts to facilitate diagnosis and improve patients' clinical pathways(Legifrance, 2017) and to more generally strive for excellence in service delivery(MSS, 2017c). Additionally, a French national "National Bank" for rare diseases (*Banque Nationale de Donnees Maladies Rares*) is being developed with direct funding from the Ministry of Health. This is gathering all anonymised patients' data, with the aim to document healthcare delivery for all patients with rare disease treated in the national specialized centres and analyse its improvement. This is linked to a wider French ambition in its "Plan Genomique 2025" to make the country a leader in genomic and precision medicine(MSS, 2017b). In stark contrast to this ambitious plan, **Italy** simply maintains a national list of centres for rare disease, from information supplied by the regions. This lack of co-ordination and homogeneity across the country means that many patients must transfer around the country for diagnosis and treatment(Eurordis, 2010).

In a survey of 800 rare disease patients in **Australia** almost one third reported having to wait five years or more for a diagnosis, with most seeing three or more doctors en route to a diagnosis, and half having had a prior incorrect diagnosis(DHAus, 2017a).

Within Europe it has been **France** and **Germany** which led with the development and implementation of national rare disease plans(Dharssi *et al.*, 2017, p. 3); this has been an important step towards consistency in diagnosis.

The Leibniz University of Hannover, **Germany** has established a portal for rare diseases, with €750,000 of financial support from the German Federal Ministry of Health. In addition to providing information for patients, it also offers guidance to clinicians on diagnosis and treatment(NAMSE, 2017).

4. Delivery of Care

In **France** the second national rare diseases 2011-2016 plan(MSS, 2011) aimed, among other things, to foster the production of national diagnosis and treatment protocols (*Protocoles Nationaux de Diagnostics et de Soins*) in order to reduce inequalities in delivery, and to promote the reimbursement of innovative drugs. In the plan's evaluation, released in 2016, it was mentioned that the plan had somewhat failed against this objective as only a few protocols had been produced in the following years(HCSP, 2016). Nevertheless, the French national "rare diseases platform", which was created in 2001 has developed into a significant organisation with a wide range of public and private supporters and participants, including clinicians and patient groups. This acts as a valuable gateway for patients, providing a unified two-way communication channel, and is used by the Ministry of Health to consult with all rare disease stakeholders(PMR, 2017).

Patient groups are well established in **France, Germany, Italy** and the **UK**, playing an active role in rare disease policy(Dharssi *et al.*, 2017, p. 13)y, thus providing a degree of "voice" for rare diseases within a health system(Dharssi *et al.*, 2017),. These often bring together many small groups to create a presence that would otherwise be difficult to achieve. The Italian group UNIAMO, for example, comprises more than 100 patient organisations in Italy, covering more than 600 rare diseases(Rodwell and Ayme, 2014).

Since 2008 Italian patients have benefitted from a national telephone and email helpline based at the national centre for rare diseases at the ISS and funded by the Ministry of Health, although it not only supports patients and their families, but also care providers and other health organisations(Rodwell and Ayme, 2014).

The survey of **Australian** rare disease patients found that only 20% knew of a patient registry for their condition, although almost nine out of ten patients said that they would be willing to join a registry if one existed(Molster *et al.*, 2016, p. 7).

In 2001 **Italy** established regional registries and a national registry at the Isituto Superiore Sanità (ISS) following a ministerial decree that this should happen. In 2008 in **Italy** the National Centre for Rare Diseases, known as CNMR, was also established at the ISS (Rodwell and Ayme, 2014) to develop, promote and disseminate scientific research and information in rare

disease. This initiative was intended to help overcome the regional inequalities inherent within the Italian he(Rodwell and Ayme, 2014)alth system. The National Centre would work not only on epidemiological surveillance but also on regional and national planning of measures to assist in meeting rare disease needs. National data collection improved from 62% territorial coverage in 2009, to 97% in 2012 due to these reforms.

Conclusions

Whilst no country offers an exemplar in rare disease it is clear that those which have developed and operated a **national plan** for rare disease tend to show the most consistency of policies across the whole access pathway from diagnosis to treatment, so that there are fewer gaps within the overall strategy.

The picture is never as clear as it may appear. Our sample revealed, for example, dramatic disparities in the number of conditions screened for in newborn children. This ranged from single figures in Italy to as many as 40 in some Canadian provinces. Too often, it seems, the range of conditions screened bore no relationship with the capacity to provide access to treatment. Spain for example, has the highest level of screening in the European countries within the sample, but some of the lowest rates of reimbursement approval of OMPs.

Most countries have attempted to find ways to meet the demand for compassionate access to OMPs before they are licensed but only when there is high unmet need . Often this is only possible if the manufacturer makes the product available free of charge, although some have used a special fund to support early access. This might come from public funds, as in Australia, or through some form of pharmaceutical levy, as in Italy.

It is a testament to the rising influence of rare disease patient groups that there are now numerous initiatives and policies to improve the speed at which new products become available. The French operate an interesting system, that enables products costing more than €50,000pa to launch with reimbursement, but with the requirement that the total costs stay below a fixed threshold and that all patients are given access. Other countries simply set a time-limit on the pricing and reimbursement assessment. This is, for example, the case in Italy, where a 100-day limit applies, from the date of the Opinion from the EMA, rather than from the subsequent formal Decision from the European Commission.

What is clear from this short paper is that the pressure for improved access is very real, and it is international. Perceptions of social solidarity are particularly strong when it comes to meeting the needs of people with rare disease. Similarly, several countries have identified the potential for industrial advantage in this important and growing sector. Whilst France has long pushed the rest of Europe to do more for rare diseases, in the name of social solidarity, its

successive national plans have also been very clearly motivated by the potential for competitive advantage.

Finally, those countries doing most have taken action at the national level. Rare disease needs cannot be met in a disaggregated way, reliant on autonomous local services. Indeed, the initiative is now moving towards global co-operation, typified by the EMA agreements with Australia and Canada, and more recently with the American FDA. Global co-operation can be expected to facilitate an even faster rate of licensing, and countries will need to work even harder to ensure a timely transition from discovery to licensing to patient access.

Recommendations for Further Research

Analysis of the impact of newborn bloodspot screening on rare disease outcomes. The diversity of screening protocols may offer useful evidence.

A direct comparison of rare disease plans and their impact on access to OMPs and clinical outcomes

The relationship between early access programmes on subsequent pricing and reimbursement processes.

References

AG (2017) *Standing Committee on Screening*. Available at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/newborn-bloodspot-screening (Accessed: 11th November 2017).
AIFA (2016) *National Report on Medicines use in Italy. Year 2015*. Rome. [Online]. Available at: http://www.aifa.gov.it/sites/default/files/OsMed_2015_Eng.pdf (Accessed: 15th November 2017).
Alvarez del Vayo, M. and Athie-Chauvet, P. (2017) 'Medicamentos huérfanos: la odisea de tratarse cuando tienes una enfermedad rara', *El Mundo*. Available at: http://www.elmundo.es/ciencia-y-salud/salud/2017/10/29/59f1971b268e3e7d3b8b4677.html (Accessed: 14th November 2017).
Andreatta, D. (2013) 'Canada has no national standard for newborn screening. Here's why it should', *Globe & Mail*, 25th August 2013. [Online] Available at: https://beta.theglobeandmail.com/life/health-and-fitness/health/canada-has-no-national-standard-for-newborn-screening-heres-why-it-

should/article13940675/?ref=http://www.theglobeandmail.com& (Accessed: 13th November).
Ayme, S. and Rodwell, C. e. (2013) *2013 Report on the State of the Art of Rare Disease Activities in Europe*. [Online]. Available at: http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesV.pdf (Accessed: 14th November 2017).
Balzli, P. and Landgraf, C. (2016) 'Swissmedic emphasises international co-operation', *pharmazeutische Medizin*, 18(2). Available at: https://www.swissmedic.ch/ueber/01398/01401/index.html?lang=en (Accessed: 13th November 2017).
Blue Cross (2017) *Five Benefits of Rare Disease Research*. Available at: https://bcbsnd.areavoices.com/2017/02/28/five-benefits-rare-disease-research/ (Accessed: 7th November).
BOE (2017) *Statistical Interactive Database: Daily Spot Exchange Rates against Sterling*. Available at: http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp?Travel=NIxSTx&into=GBP (Accessed: 11th November).
CEC (2005) *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005.* European Commission. Available at: https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/inventory_2006_08_en.pdf (Downloaded: 7th November 2017).
Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products.
CEC (2011) *Short Executive Summary of the Report on the practices of newborn screening for rare disorders implemented in Member States of the European Union, Candidate, Potential Candidate and EFTA Countries*. Available at: http://ec.europa.eu/chafea/documents/news/Summary_20120110.pdf (Accessed: 13th November).
CEC (2014) *Implementation Report on the Commission Communication on Rare Diseases; Europe's challenges, and Council Recommendation of 8 June 2009 on an action in the field of rare diseases*. Brussels.
CEC (2015) *Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products:State of Play 2015* (SWD(2015) 13 FINAL). [Online]. Available at: https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf (Accessed: 7th November 2017).
CIHI (2016) *Prescribed drug spending in Canada 2016*. Available at: https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC3333(=en (Accessed: 10th November 2017).
Dharssi, S., Wong-Rieger, D., Harold, M. and Terry, S. (2017) 'Review of 11 national policies for rare diseases in the context of key patient needs', *Orphanet J Rare Dis*, 12(1), p. 63.
DHAus (2017a) *Other supply arrangements outside the Pharmaceutical Benefits Scheme (PBS)*. Available at: http://www.health.gov.au/lsdp (Accessed: 9th November 2017).

DHAus (2017b) *Rare cancers and rare diseases - Research Grants*. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/mrff-rare-cancers-rare-diseases-grants-2017 (Accessed: 9th November 2017).
DHWA (2015) *WA Rare Diseases Strategic Framework 2015=18*.State of Western Australia. [Online]. Available at: http://ww2.health.wa.gov.au/~/media/Files/Corporate/Reports and publications/PDF/Rare-diseases-strategic-framework.pdf (Accessed: 11th November 2017).
Diariofarma (2016) 'El COF de Sevilla denuncia trabas para acceder a medicamentos huérfanos', *Diariofarma*. Available at: https://www.diariofarma.com/2016/10/31/cof-sevilla-denuncia-trabas-acceder-medicamentos-huerfanos (Accessed: 14th November 2017).
Diariofarma (2017) 'El PSOE pide 15 millones en los PGE para los nuevos fármacos huérfanos', *Diariofarma*. Available at: https://www.diariofarma.com/2017/05/28/psoe-pide-15-millones-los-pge-los-nuevos-farmacos-huerfanos (Accessed: 14th November 2017).
Douste-Blazy, Monchamp, M.-A. and d'Aubert, F. *French National Plan for Rare Diseases 2005-2008*. Available at: http://www.orpha.net/actor/EuropaNews/2006/doc/French_National_Plan.pdf (Accessed: 13th November).
EMA (2017) *Mutual Recognition Agreements*. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001843.jsp&mid=WC0b01ac058005f8ac - chapter5 (Accessed: 13th November 2017).
European Commission (2005) *Inventory of Community and Member States' incentive measures
to aid the research, marketing, development and availability of
orphan medicinal products. Revision 2005.* European Commission. Available at: https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/inventory_2006_08_en.pdf (Downloaded: 7th November 2017).
Eurordis (2010). Eurordis.
FDA (2017a) *Developing products for rare diseases & conditions*. Available at: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm (Accessed: 12 January).
FDA (2017b) *Rare paediatric disease priority review voucher program*. Available at: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm (Accessed: 13th November).
Feder (2017) *Las Enfermedades Raras en cifras*. Available at: https://www.enfermedades-raras.org/index.php/enfermedades-raras/enfermedades-raras-en-cifras (Accessed: 14th November).
FMR (2017) *Maladies rare: Discours Ministre*. Available at: http://fondation-maladiesrares.org/wp-content/uploads/2017/11/Maladies-rare-Discours-ministre.pdf (Accessed: 7 December).
Gaceta Medica (2017) 'Nuevos apoyos al documento de consenso en enfermedades raras que respalda la AGP', *Gaceta Medica*. Available at: http://www.gacetamedica.com/politica/nuevos-apoyos-al-documento-de-consenso-en-enfermedades-raras-que-respalda-la-agp-ME969709 (Accessed: 14th November 2017).

Gammie, T., Lu, C. Y. and Babar, Z. U. (2015) 'Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries', *PLoS One*, 10(10), p. e0140002.
Garau, M. and Mestre-Ferrandiz, J. (2009) *Access mechanisms for orphan drugs: A comparative study of selected European countries*. London. [Online]. Available at: https://www.ohe.org/publications/access-mechanisms-orphan-drugs-comparative-study-selected-european-countries (Accessed: 15th November 2017).
Hansard (1995) *House of Commons: Written Answers* (187-8W). London. [Online]. Available at: http://hansard.millbanksystems.com/written_answers/1995/jun/07/eu-health-council - S6CV0261P0_19950607_CWA_73 (Accessed: 7th November 2017).
Hatswell, A. J. (2017) 'How do we avoid disaster when exiting the European Medicines Agency? Making the most of Brexit in pharmaceutical regulation', *Ecancermedicalscience*, 11, p. ed67.
HCSP (2016) *Evaluation du plan national maladies rares 2011-16*. Available at: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwjyrOyH2enXAhUB_aQKHZKGDz4QFgg3MAE&url=http%3A%2F%2Fwww.hcsp.fr%2FExplore.cgi%2FTelecharger%3FNomFichier%3Dhcspr20160310_evalplanationalmaladiesrares2.pdf&usg=AOvVaw3hJAsfvMi15JdH9Toe2zMl (Accessed: 7 December).
Hunt, J. and Clark, G. (2017) 'The UK wants to continue to work with the EU on medicines', *Financial Times* (5th July 2017). [Online] Available at: https://www.ft.com/content/a94326ac-5dbd-11e7-9bc8-8055f264aa8b (Accessed: 13th November 2017).
Iniesta, M., Zetchi, N., Lopez, N., Cuesta, M. and Rosa, M. (2017) *Situation actual sobre la accesibilidad a los medicamentos huérfanos en España*. Available at: http://www.aelmhu.es/docs/PosterACCESIBILIDADALOSMMHH11-08-2017.pdf (Accessed: 14th November 2017).
ISC (2016) *Criterios de financiación y reembolso de los medicamentos huérfanos*. Available at: http://gesdoc.isciii.es/gesdoccontroller?action=download&id=17/06/2016-16c31d38eb (Accessed: 14th November).
Korchagina, D., Tomita, N., Falissard, B., Toumi, M. and Tavella, F. (2015) *Orphan designations and approvals in the EU, USA and Japan* (Accessed: 13th November).
Legifrance (2017) *Instruction interministerielle No DGOS/DGS/DGRI/2017/204*. Available at: http://circulaires.legifrance.gouv.fr/index.php?action=afficherCirculaire&hit=1&r=42401 (Accessed: 7 December).
MoCa (2016) *MEDEV: MoCa Pilot Project - Stage 2: Revised Terms of Reference*. Available at: https://www.eurordis.org/sites/default/files/files/MOCA Revised Terms of Reference endorsed Jan-2016.pdf (Accessed: 9th November).
Molster, C., Urwin, D., Di Pietro, L., Fookes, M., Petrie, D., van der Laan, S. and Dawkins, H. (2016) 'Survey of healthcare experiences of Australian adults living with rare diseases', *Orphanet J Rare Dis*, 11, p. 30.
Morel, T., Arickx, F., Befrits, G., Siviero, P., van der Meijden, C., Xoxi, E. and Simoens, S. (2013) 'Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries', *Orphanet J Rare Dis*, 8, p. 198.

MSS (2011) *Plan Maladies Rare 2011-14*. Available at: http://solidarites-sante.gouv.fr/IMG/pdf/plan_national_maladies_rares_2011-2014.pdf (Accessed: 7 December).
MSS (2017a) *Appel a projets labellisation CRMR*. Available at: http://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/appel-a-projets-labellisation-crmr-319118 (Accessed: 7 December).
MSS (2017b) *Banque Nationale de Données Maladies Rares (BNDMR)*. Available at: http://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/focus (Accessed: 7 December).
MSS (2017c) *Maladies Rares*. Available at: http://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/ (Accessed: 7 December).
MSSDF (2016) *Instruction No. DGOS/PF4/2016/11*. Available at: http://circulaires.legifrance.gouv.fr/pdf/2016/01/cir_40460.pdf (Accessed: 7 December).
NAMSE (2017) *Zwischenbericht zur Umsetzung des Nationalen Aktionsplans fuer Menschen mit seltenen Erkrankungen*. Available at: http://www.namse.de/images/stories/Dokumente/namse_monitoringbericht_mai_2017.pdf (Accessed: 14th November 2017).
OECD (2016) *Health at a Glance: Asia-Pacific 2016*. Available at: http://dx.doi.org/10.1787/health_glance_ap-2016-39-en (Accessed: 10th November 2017).
OECD (2017) *Health Expenditure and Financing*. Available at: http://stats.oecd.org/viewhtml.aspx?datasetcode=SHA⟨=en (Accessed: 10th November 2017).
Orphanet (2010) *About Orphan Drugs*. Available at: http://www.orphanet.org.uk/national/GB-EN/index/about-orphan-drugs/ (Accessed: 7th November).
Orphanet (2017a) *About Orphan Drugs: Orphan Drugs in Australia*. Available at: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_AUS (Accessed: 13th November 2017).
Orphanet (2017b) *Comparison of the various policies on orphan drugs worldwide*. Available at: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_COMPARISON (Accessed: 13th November 2017).
PHE (2013) *Newborn blood spot screening: programme overview*. Available at: https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview (Accessed: 11th November).
PHE (2017) *Current UK NSC recommendations*. Available at: https://legacyscreening.phe.org.uk/screening-recommendations.php (Accessed: 11th November).
PMR (2017) *La Plateforme Maladies Rares: Un centre de ressources unique*. Available at: http://www.plateforme-maladiesrares.org/presentation/la-plateforme-maladies-rares.html (Accessed: 7 December).
PWC (2016) *The Early Access to Medicines Scheme (AMS): An independent review*. Available at:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/509612/eams-review.pdf (Accessed: 13th November).
Rao, G. R. (2013) 'FDA commemorates 30th anniversary of the Orphan Drug Act', *FDA Voice*. Available at: http://blogs.fda.gov/fdavoice/index.php/2013/01/fda-commemorates-30th-anniversary-of- the-orphan-drug-act/ .
Rodwell, C. and Ayme, S. (2014) *2014 Report on the state of the art of rare disease activities in Europe*. [Online]. Available at: http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesIT.pdf (Accessed: 15th November 2017).
WA (2015) *Study points to scale of rare disease impact*. Available at: http://ww2.health.wa.gov.au/News/Study-points-to-scale-of-rare-disease-impact (Accessed: 7th November).
WHO (2013) *Rare Diseases*. Available at: http://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf (Accessed: 11th November 2017).
World Bank (2017) *Data*. Available at: https://data.worldbank.org/indicator/SP.POP.TOTL (Accessed: 11th November 2017).