Orphan and Rare Disease Products—The Payer Perspective

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Abstract: The paper is to look at the affordability of orphan medications across the globe and whether payer attitudes to high-price medications are changing in the face of rising healthcare expenditure and tighter budgets. We conducted an online semi-quantitative survey of 10 European markets, the United States and Japan (Q1-Q2 2014) to understand how payers’ views and attitudes are changing in response to new treatments coming to market for rare and ultra-rare conditions. The payers selected for the survey hold or have held senior positions within their respective market institutions. The United States and Japan were included in the study to provide international context to the European results. Responses were anonymised in accordance with good market research principles. The research shows that 75% of respondents surveyed believe that the current approach to orphan drug pricing is unsustainable in the future and 92% predict a tougher approach from payers going forward. 75% of payers do not believe that patent expiry alone will free up the necessary space for innovative orphan and ultra-orphan products. 83% of the payers surveyed believed that less than half of all orphan and ultra-orphan drugs coming to market are supported by an adequate evidence base for reimbursement. The environment for orphan medicines across the globe is changing; and as the financial performance of countries begins to diverge, so do attitudes towards the funding of orphan medicines. The increasing number of rare diseases, and treatments available, is forcing payers to view orphan drugs in a new light and they are becoming increasingly sceptical about the prices charged in relation to the clinical benefit offered. As rare disease spending becomes a higher proportion of pharmaceutical spending, payers will need to take action to curb this trend.

Key words: Cost-containment, orphan, payer, pharmaceutical, rare diseases.

Nomenclature
EMA: European Medicines Agency
HTA: Health Technology Assessment
NICE: National Institute for Health and Clinical Excellence

1. Introduction

Healthcare markets are under increasing pressure and as budgets are becoming squeezed, most countries are facing a formidable challenge to manage the rapid increasing cost of healthcare [1]. Against this backdrop, new and innovative treatments to tackle rare diseases are coming to market with a significant cost attached to them. This article looks at the challenges faced by payers across the globe in dealing with orphan drugs, the sustainability of the current pricing structure and what pharmaceutical companies can do to improve their communication with payers.

In this study, we set out to find out the response from payers across the globe to developments in the orphan and ultra-orphan disease space. The research revealed that as the financial performance of countries begins to diverge, so do attitudes towards the funding of orphan medicines. The increasing number of rare diseases, and treatments available, is forcing payers to view orphan drugs in a new light and they are becoming increasingly sceptical about the prices charged in relation to the clinical benefit offered. In Section 2, we discuss the materials and methodology employed in the study, which includes details of the survey and the geographical scope. In Section 3, we describe the headline findings in the context of key developments in the rare disease space (please note that the full study results are available in Appendix). In Section 4, we discuss the wider context of the research before finalising our conclusion in Section 5.
2. Materials and Methods

We conducted a 10 question online semi-quantitative survey of 10 European markets, the United States and Japan between February and July 2014. The online survey was hosted by SurveyMonkey® and participants were paid an honorarium to complete the questionnaire which took approximately 30 min to complete. The survey questions were multiple choices, with the ability to add additional information in free text where possible. The 10 European markets selected (in alphabetical order) were Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden and the United Kingdom. The United States and Japan were also included to give the European results an international context. Respondents who were selected to participate in the survey currently hold or have held senior positions within their respective market institutions and have an expertise in the orphan drug space. Responses were anonymised in accordance with good market research principles.

3. Results

3.1 Payer Concerns with Orphan Drugs

The treatment of rare diseases is an interesting phenomenon in that although each condition may only affect a small number of patients, when combined, they amount to a significant patient population. According to EURORDIS [2], a non-governmental alliance of patient organisations, there are 6,000 rare diseases which potentially affect 30 million European patients. Payers are becoming concerned about the number of new medicines coming to market to tackle rare diseases and more importantly, the high cost that is associated with treatment. In our survey, cost and the price of medicines was the most frequently mentioned concern about orphan drugs coming to market [3].

Friction between pharmaceutical companies and payers is beginning to emerge and in the UK, the cost-effectiveness body NICE has openly criticised the price of Alexion’s eculizumab for the treatment of aHUS (atypical Haemolytic Uraemic Syndrome) [4]. This trend is not just limited to orphan drugs; and the negative response in the US market to aflibercept, a drug for colorectal cancer, is further evidence of manufacturer prices being brought under closer scrutiny by payers [5]. The orphan drug legalisation has incentivised a generation of manufacturers to develop treatments for small numbers of patients, which although in line with the objectives of the orphan drug legislation, is now creating a problem for healthcare systems in that the prices charged for innovative treatments are perceived by payers across the globe to be unsustainable (Fig. 1).

If payers are beginning to question the value of orphan drugs, the key issue is whether they will begin to stop patients with rare diseases accessing the latest treatments. Our survey revealed that 92% of respondents thought that payers are likely to become tougher towards orphan drugs in the future [3]. The UK respondent suggested that one approach payers might take is to split rare diseases between orphan and ultra-orphan conditions; in order to enable higher prices for the rarest conditions, payers might take a tougher approach to those with larger patient populations with the potential for greater budget impact. This view is given even greater weight by the notion that healthcare budgets cannot expand to make room for new and innovative treatments for rare diseases. Manufacturers of rare disease treatments point to recent pharmaceutical blockbusters coming off-patent and claim that there is “space for funding innovation”. Respondents to our survey largely disagree with this viewpoint and 75% of respondents think that patent expiry alone is not enough to compensate for the funding of new and current orphan drugs (Fig. 2).

3.2 Evidence Requirements

The regulatory framework for orphan drugs acknowledges the challenges of conducting clinical
trials in rare diseases, particularly when it comes to small numbers of patients. However, if the regulatory framework allows drugs for rare diseases to be licensed, payers need to assess them. Respondents were clearly sceptical of the evidence being presented; 83% of the payers surveyed believed that less than half of all orphan and ultra-orphan drugs coming to market are supported by an adequate evidence base for deciding on reimbursement. For example, eculizumab was approved for usage in aHUS based upon three studies involving 67 patients [6]. Likewise, BioMarin’s new treatment for mucopolysaccharidosis type IVA (MPS IVA, also known as Morquio A syndrome), elosulfase alfa, was approved on the basis of a trial involving 176 patients [7]. On the one hand, both conditions have small patient numbers, estimates vary between 1 in 200,000 live births and 1 in 450,000 live births [8] for MPS IVA and 1-9 per 1,000,000 [9] for aHUS which

Fig. 1  Do you feel the current prices charged for orphan drugs are sustainable in the future [3]?
Source: RJW & Partners (2014) [3]. “The business model of orphan drugs is unsustainable; as the number of orphan drugs proliferates, the overall cost is going to be a significant share of healthcare expenditure for a small proportion of patients—this is ethically questionable.” Spanish Respondent, Payer Insight Survey, 2014.

Fig. 2  A number of high profile drugs are going off-patent in the next couple of years making considerable savings to the healthcare system—in your view, does this allow for the funding of new and current orphan drugs [3]?
demonstrates the difficulty in recruiting patients for large scale clinical trials. On the other hand, following approval, payers have to assess the clinical value of these treatments, which is difficult to establish given the limited data available. Elosulfase alfa was approved on the basis of the 6MWT (6-minute walk test). Before treatment, patients could walk on average slightly over 200 m in 6 min. After 6 months, patients treated with the recommended dose of elosulfase alfa could walk an extra 37 m on average in 6 min, compared with an increase of 14 m in patients receiving placebo [7].

Here lies the inherent problem for payers; in the USA, elosulfase alfa treatment costs $380,000 per patient per year but the supporting clinical evidence in the form of the 6MWT makes it difficult for payers to assess elosulfase alfa’s value for the healthcare service. Elosulfase alfa is clearly a treatment which has great potential and the study results suggest that the medicine could have a profound effect on the quality of life of patients by improving how well they breathe or climb stairs, and in children, how well they grow [7]. However, the 6MWT, which is the clinical endpoint that drives the regulatory approval of Enzyme Replacement Therapies such as elosulfase alfa, is an endpoint deemed suitable for regulatory purposes but perceived by payers as much less so for the evaluation of the clinical value a treatment offers. Consequently, payers have difficulties justifying the money spent on treatments like elosulfase alfa, even though they are positive towards the therapy and its potential benefits.

Pharmaceutical companies acknowledge the lack of evidence at evaluation and the difficulties payers have to assess the true value of treatments and increasingly use supportive anecdotal evidence such as patient case studies to show the potential real world impact of their treatments. Our survey suggests that payers do not see this approach as very valuable, with 50% of respondents claiming that the evidence is not very useful and 25% claiming that it has no impact at all in decision-making (Fig. 3).

3.3 Communicating with Payers

It is clear from the survey that payers thought that the way pharmaceutical companies engage with payers could be improved. Payers want greater transparency and it is clear that the UK HTA body NICE has found the lack of information available regarding the overall cost of eculizumab frustrating [4]: “Alexion insisted that its information about the overall cost of eculizumab...
be kept confidential and so NICE is unable to share these details of the Alexion submission with stakeholders. We're disappointed about this decision, for which we have not had an adequate explanation.” —Sir Andrew Dillon, NICE Chief Executive, March 2014. Demonstrating the value of orphan disease medication to payers will only become more necessary as time increases. The US respondent from the survey suggested that sticking purely to the minimum requirement for regulatory approval was going to cause further friction in the future as payers become more stringent with orphan disease treatments and ask pharmaceutical companies to further demonstrate the true value of their product [3].

4. Discussion

There lies an inherent problem with orphan drugs in that on the one hand there is a regulatory framework which is incentivising manufacturers to develop drugs for rare conditions by allowing companies to gain marketing approval with only a limited data set and on the other hand the payer institutions are struggling to evaluate them in terms of value to the healthcare system because of the scarcity of clinical data. As orphan drugs continue to grab the headlines for being expensive drugs, there is going to be an ever increasing focus from cost sensitive payers to ask companies to justify the high cost of their medications (Table 1).

The system to incentivise manufacturers to develop treatments for rare diseases clearly works as intended and with well over 50 treatments coming to market since 2002 [11], we should celebrate that patients with rare and debilitating diseases are accessing treatments developed exclusively for them. The science behind the treatments is impressive; and the companies who manufacture drugs for these conditions would point to the cutting edge technology and the research and development costs to justify their pricing structure. However, with an increasing number of orphan drugs and the absence of hard data to effectively assess the clinical benefits of these new treatments, payers are beginning to ask manufacturers to justify high prices for orphan treatments.

As with high-priced non-orphan drugs and other medical interventions, it appears that the debate with orphan drugs is steering towards the question how to best spend the financial resources which are by definition limited. For example, by controlling the money spent on orphan drugs for a small number of people, more resources could be put towards genetic testing which has the potential to influence a larger number of lives across the population.

The key issue is financial sustainability; and the survey results demonstrate that payers are sceptical that the prices currently charged for orphan drugs can go on indefinitely. The problem for pharmaceutical companies developing drugs for orphan diseases is that the debate on high prices is not limited to the domain of orphan drugs but also takes place with respect to broader disease areas such as cancer and multiple sclerosis. The prices of products like sofosbuvir, ivacaftor, Trastuzumab emtansine and Sipuleucel-T to name a few, have been criticised as being too high. Because of the position they sit in, it is only natural that payers feel pharmaceutical prices are high, but if the perception is that pharmaceutical companies are being too aggressive with prices across the board, this is likely to spark policy responses from payers. As the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Condition</th>
<th>Annual cost</th>
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<tr>
<td>Eculizumab</td>
<td>Alexion</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
<td>$440,000</td>
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<tr>
<td>C1 esterase inhibitor (human)</td>
<td>Viropharma</td>
<td>Hereditary angioedema</td>
<td>$417,000</td>
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<tr>
<td>Elosulfase alfa</td>
<td>BioMarin</td>
<td>Morquio A (MPS IVA)</td>
<td>$380,000</td>
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<tr>
<td>Idursulfase</td>
<td>Shire</td>
<td>Hunter syndrome</td>
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<td>Galsulfase</td>
<td>BioMarin</td>
<td>Maroteaux-Lamy syndrome (MPS VI)</td>
<td>$375,000</td>
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Source: (San Francisco Business Times, 2014) [10].
number of treatments for orphan diseases increases, these products may become increasingly attractive for payers to target for cost-containment as it is niche area with high expenditure.

Obvious ways for payers to start are policies that focus on the requirement of collecting data post-launch and to make any continued funding conditional upon favourable outcomes of these data. A number of countries like France and Italy are already moving in that direction. Another way of dealing with high costs of orphan treatments is to allow very high prices only for ultra-orphan drugs with a very small number of patients, and push back on prices of orphan drugs which have a higher number of patients and in which, at least in theory, it should be possible via larger-scale clinical research to give a better insight into the clinical benefits. Although some payers, such as NICE in the case of eculizumab, are trying another route by getting insight in the development and production costs of orphan drugs, for reasons of commercial confidentiality, we expect companies not to voluntarily disclose this sensitive information.

In order not to run into price and funding issues with payers, companies will have to become better at communicating the value of their new products. Even though this may be difficult due to small patient populations, they will also need to strengthen the evidence base of their products at time of submission for funding. This means going beyond what is required from a regulatory perspective. An important challenge will be to generate data that show payers the relevance of a new treatment for the quality of life—in a very practical sense—of patients.

5. Conclusions

The environment for orphan medicines across the globe is changing; and as the financial performance of countries is under threat, attitudes towards the funding of orphan medicines seem to converge. The survey has demonstrated that the increasing number of rare diseases is forcing payers to view orphan drugs in a new light and they are becoming increasingly sceptical about the prices charged in relation to the clinical benefit offered. There is space for innovation; and patent expiry is freeing up funds, but rare diseases are competing with other therapy areas for limited budget.

The more orphan drugs that come to market with high prices will dictate what healthcare systems can bear. Patient advocacy and political will add another dimension to the rare disease debate.

References


Appendix: Full Survey Results.

We conducted a 10 question online semi-quantitative survey of 10 European markets, the United States and Japan between February and July 2014. The online survey was hosted by SurveyMonkey® and participants were paid an honorarium to complete the questionnaire which took approximately 30 minutes to complete. The survey questions were multiple choice with the ability to add qualitative answers where possible. The 10 European markets selected (in alphabetical order) were Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden and the United Kingdom. The United States and Japan were also included to give the European results an international context. Respondents who were selected to participate in the survey currently hold or have held senior positions within their respective market institutions and have an expertise in the orphan drug space. Responses were anonymised in accordance with good market research principles.

Fig. A1  As a (ex-) payer, what are your three main concerns about orphan drugs? (Q1)

Fig. A2  Do you feel the current prices charged for orphan drugs are sustainable in the future? (Q2)
Fig. A3  Do you feel that payers are becoming tougher towards orphan drugs? If so, what are likely to be the main hurdles to access in the foreseeable future? (Q3)

Fig. A4  In your view, what proportion of orphan drugs are supported by an adequate evidence base for reimbursement? (Q4)

Fig. A5  How useful do you find anecdotal evidence such as patient case-studies? Does it have any impact on decision-making (Q5)?
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Fig. A6  Could we ask you to rank the following disease areas in terms of priority to fund? (Q6)

Fig. A7  Do you envisage financial agreements such as Patient Access Schemes to become more prevalent in orphan diseases? If so, why? (Q7)

Fig. A8  A number of high profile drugs are going off-patent in the next couple of years (e.g., Lantus) making considerable savings to the healthcare system—in your view, does this allow for the funding of new and current orphan drugs? (Q8)
Fig. A9  Which is more important to you—(a) the cost per patient? Or (b) the overall budget impact? (Q9)

Fig. A10: How can the pharmaceutical industry improve the way they communicate with payers? (Q10)