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EDITORIAL

Orphan drugs policies: a suitable case for treatment

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Abstract
Context Current orphan drug policies are unsatisfactory when viewed from almost all perspectives. Patients find that, although therapies are available for many rare conditions, access to care is sometimes restricted. Pharmaceutical manufacturers have responded to the incentives for research embodied in orphan drug legislation, only to find that funds are not made available to pay for therapies once developed. Those funding health care find that most orphan drugs do not justify funding based on standard value for money criteria, yet that they face political problems if they fail to provide funding for therapy.
Methods A literature review was conducted in order to determine the precise nature of the problems and to suggest potential solutions.
Results Current orphan drug policies are not fit for the purpose and initiatives need to be taken in the areas of (1) clarifying society's views about the priority to be given to orphan drugs, (2) revising the arrangements for pricing and reimbursement of orphan drugs, (3) defining the priorities for research into rare diseases and (4) developing 'joined up' policies to deal with these issues.
Conclusions Without changes in the current policies, pharmaceutical companies will eventually cease responding to the incentives to develop orphan drugs, because they will increasingly be uncertain whether the drugs, if developed, will be reimbursed.

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Introduction

Drugs are granted an orphan designation if they are for the treatment of rare diseases that are life-threatening or seriously debilitating. The definition of 'rare' varies from jurisdiction to jurisdiction, being a disease or condition affecting fewer than 200,000 patients in the US (6.4 per 10,000 inhabitants) or a disease with a prevalence of 5 per 10,000 or lower in the European Union. Incentives have been given to pharmaceutical companies to develop orphan drugs to meet what is perceived to be an unmet need. These include 'pull' incentives such as guaranteed market exclusivity (up to 7 years in the US and up to 10 years in the EU) and 'push' incentives such as tax credits for clinical research in the US, or reduction of licensing fees, scientific advice and protocol assistance in both the US and EU [1].

However, with the growth in the use of health technology assessment (HTA) to control the adoption and diffusion of health technologies [2], current orphan drug policies are increasingly being viewed as unsatisfactory from almost all perspectives. The payers for health care find that, because of their high prices, most orphan drugs do not justify funding based on cost-effectiveness, but payers often face political problems if they fail to give approval for funding. Manufacturers, having responded to the incentives for research embodied in orphan drug legislation, find that reimbursement is sometimes not approved for the therapies once developed. Consequently, patients find that, even if therapy is available for their rare condition, access to care is sometimes restricted.

The issues surrounding orphan drugs also divide the academic community. Some researchers argue that the

notion of 'social benefit' embodied in current reimbursement processes is too narrow [3]. Others argue, on a utilitarian basis, that the opportunity cost of treating rare diseases is too high [4], or point to the 'excessive' profits made by manufacturers and 'orphan drug creep', whereby some drugs with an orphan designation are also indicated for treatment of diseases with a much larger patient population [5].

This article argues that current orphan drug policies are not fit for the purpose and discusses the issues that need to be clarified in any revision of policy. The objective is not to provide complete solutions to all the policy problems, but rather to set out a roadmap whereby they can be resolved.

Clarifying society's values

A starting point for designing any health policy is to clarify society's views and objectives in relation to the issues concerned. Although there is scant evidence on what the general public in different countries expect from their health care system, the utilitarian perspective of maximising the total benefits to the population as a whole is a reasonable starting point, particularly in jurisdictions where public financing of health care predominates. This notion also underpins most of the assessments of value for money conducted in those jurisdictions where these are explicitly required. Namely, the implicit or explicit objective is to maximise the total health gain from the use of health care resources, although the methods for measuring health gain vary from jurisdiction to jurisdiction. However, since orphan drugs are never as cost-effective as drugs for more prevalent diseases, departures from a strict utilitarian perspective would have to be justified if they were to be funded. That is, society would have to be willing to give up some of the health gain to the population as a whole.

Several surveys relating to the funding of orphan drugs have been conducted in order to explore the stated preferences of members of the community. Discussions within the National Institute for Health and Care Excellence (NICE) Citizen's Council in the UK concluded that members would be prepared to give priority to the treatment of "ultra-orphan" diseases (which NICE defines as diseases with a prevalence of less than 1,000 patients in the UK or less than 1 in 50,000 people), but did not place a value on rarity per se [6]. This finding was echoed in a large survey of public preferences for medicines prioritisation criteria among 4,118 adults in the UK [7]. Respondents did not support the special funding status for treatments of rare diseases, although they did express a preference for treating disease where there are no alternative treatments available, and for treating more severe diseases, even when the costs were higher, although not when the effectiveness was less.

The largest and most recent survey focussing on orphan diseases was conducted using a random sample of 1,547 Norwegian citizens. Despite strong general support for statements expressing a desire for equal treatment rights for patients with rare diseases, there was little evidence that a societal preference for rarity exists if treatment of patients with rare disease is at the expense of treatment of those with common conditions [8]. This survey took into account several methodological issues, such as the method used to solicit responses and the framing of the problem, but several uncertainties remained. Although the authors concluded that their findings 'support the view that treatments for rare disease should not be exempt from standard considerations of cost-effectiveness', they also noted that there may be 'other unexplored reasons to favour special funding status for orphan drugs, majority opinion is not necessarily a good measure of what is ethical'.

One of the findings of the Norwegian survey was the apparent confounding effect that respondents had a general concern about fairness in the allocation of health care resources, yet did not have a preference for prioritising rare diseases over common ones. Also, in the survey by Linley and Hughes [7], it was found that, under cost trade-off conditions, there was a shift in preference towards the populations that were more costly to treat. This was counter to expectations and the authors argued that 'the most plausible interpretation is that respondents are expressing a general preference for fairness in access to treatment based on need, irrespective of ability to benefit or cost'.

One explanation of these apparently conflicting findings in surveys is that there are two notions of equity: horizontal equity (equal treatment of equals) and vertical equity (unequal treatment of unequals) [9]. In their comment on the paper by Desser et al., McCabe et al. [10] argue that it is time to revisit policies for orphan drugs 'for equity's sake', arguing that 'the implication from the study is that funding policies that take resources from the national health care budget to fund these treatments are not what the public wants'. The notion being applied here is that of horizontal equity. The notion of vertical equity would regard those suffering from rare diseases as a minority, defined by their genetic make-up, that *are* entitled to special treatment. The problem is that it is not clear which of those two notions of equity would take precedence in a given policymaking context. Therefore it is important that survey respondents understand the consequences of their responses. For example, given the relatively high cost of the treatments, it is not possible to allow equal access to the sufferers from rare diseases without supporting the principle of vertical equity.

In surveying the general public about such a complex issue, it is likely that the way in which the question is

framed can have a major impact on the response. Therefore, we would recommend that prior discussion take place on the nature of the question(s) to be asked, as often happens before major referendums. Surveys should employ methods, such as conjoint analysis [11], that explicitly explore the trade-offs between the various attributes of therapies including their differential cost. Also, it might be worthwhile exploring use of the person trade-off method, first proposed by Nord [12]. Under this approach, the relative values individuals place on health gains for different kinds of people are determined by asking respondents to vary the number of people in one group whilst holding constant the number in the other group so as to find a point of indifference.

In addition, rather than just asking respondents about their views on rarity, it might be better to ask direct questions about special funding for patients suffering from rare diseases, whether it should exist at all and, if so, to what extent. Also, some insights into the community's views might be gained from examining revealed preferences in situations where society is already paying a premium to allow small population groups to gain access to health care, such as individuals living in sparsely populated areas who may need more expensive helicopter transport, or their own local services, despite the fact that they may be infrequently used. It is not at all certain that these premiums for access to care are of the order of those society is being asked to pay for orphan drugs, but it could be a starting point for the discussions about providing preferential funding.

Revision of pricing and reimbursement policies for orphan drugs

Although the priority should be to clarify society's preferences regarding the treatment of rare diseases, attention also needs to be given to current pricing and reimbursement procedures. One of the strands in the current literature about the funding of orphan drugs is the suggestion that current prices may be 'excessive'. Côté and Keating [5] point to the fact that the companies developing orphan drugs are often very profitable and that orphan drugs are viewed as a good business opportunity. Whilst it is important that orphan drugs are as profitable as non-orphans if society wants them, they should not be disproportionately more profitable. It has been estimated that the average cost of bringing a pharmaceutical product to market is approximately $1.3 billion USD, mostly distributed between different stages of clinical development [13]. It is possible that the cost of bringing an orphan drug to market is somewhat less, mainly because the expensive phase III clinical programme, where data on efficacy and safety are provided to the regulator, is more limited [14]. In 2007 Genzyme estimated the cost of developing their Pompe disease drug Myozyme to be around $500 million USD [15]. On the other hand some of the drugs with orphan designation, such as those for rare cancers, do have extensive phase III clinical studies [12].

The growing trend among payers towards paying for the value added by a drug, for example through 'value-based pricing' [16], as opposed to the cost of bringing the drug to market, circumvents the need to know the costs of clinical development. However, to the extent that orphan drugs are regarded as being 'special', it may not make sense to use cost-effectiveness alone as a basis for pricing. Other approaches such as multi-criteria decision-making (MCDA) have been proposed [17]. MCDA enables decision-makers to explicitly trade off various factors against each other, such as the seriousness of the condition and the lack of suitable treatment alternatives, alongside cost-effectiveness. It is particularly useful when conflicting priorities do not share a common unit of valuation and the EMAs have explored its use for regulatory decision-making [18] when different features of benefit and risk have to be prioritised. However, use of MCDA or other approaches to consider these additional factors may still not justify the high prices of most orphan drugs.

Therefore, it might be necessary to revert to one of the approaches that has fallen out of favour for conventional pharmaceuticals, such as 'cost plus' or 'rate of return' [19]. Although more research and discussion are required, a reasonable starting position would be that, with equivalent investment risks, society would not sanction higher rates of return from the development and production of orphan drugs than those from conventional medicines. Thus, if the prices for the majority of pharmaceutical products were being determined by value for money criteria, equivalent rates of return on orphan drugs might be a reasonable basis for establishing prices. Given what we currently know about the relative costs of research and the much smaller market for orphan drugs, this could provide some justification for higher prices. However, some of the problems with a rate-of-return approach to price regulation would need to be tackled, such as the difficulties in allocating shares of global R&D joint costs to particular products including accounting for the costs of those drugs that 'fail' during the clinical development process. The inability to solve these problems was one reason for this approach to fall out of favour in the past.

Another issue is that drugs with an orphan designation in one indication are often licensed for one or more other indications. If the justification for a higher price is dependent to a large extent on the notion that there are fewer patients available in order to recoup the investment in research, this is clearly undermined if some

drugs with orphan designation have substantial sales in total. Additional indications do, of course, require additional clinical studies; however, in some cases the additional indications are not for small (orphan) populations. Côté and Keating [5] argue that companies may exploit payer willingness to accept higher prices for orphan drugs by launching first in an orphan indication in order to obtain a high price and hoping that this price will be maintained as another, larger, indication is added.

Whether this strategy is consciously employed by companies or not, it is clear that the view taken on the price of a given drug should reflect all its licensed indications. Nevertheless, how one would tackle this issue is unclear. In some of the value-based pricing schemes under discussion, prices would be determined by the value added by the drug in each of its indications [16]. Then, if a single overall price is required, this could be a weighted average of the sales in each indication. Orphan designation, and any consequent price premium, should be used to incentivise the development of drugs for patients with rare conditions. It should not be the prime basis for establishing the price for drugs that are widely used when all their licensed indications are considered.

Kanavos and Nicod [20] suggest that the legislative framework could be refined to define when an orphan treatment is 'sufficiently profitable'. Thus, consideration could be given to developing rules for revoking orphan status in situations where the total patient population becomes substantial, although it would be important to retain incentives for companies to develop additional orphan indications, including for drugs that are already marketed or are expected to be marketed for a more common (non-orphan) condition. Marketing drugs for an additional orphan condition should not necessarily affect the drug's orphan status. Revocation of orphan status would not take away any other forms of exclusivity or intellectual property (IP) protection, but would make competitive entry easier. It could also result in payers revising prices where these were linked to orphan status per se rather than to the characteristics of the disease, or the health gain achieved by use of the treatment.

It is likely that the current trend towards the use of technology assessment and economic evaluation will continue, whereby the reimbursement of any medical technology will depend on an evidence-based assessment of its clinical and cost-effectiveness. Setting aside the potential caveats on price, and the impact this will have on cost-effectiveness, there is no reason to suppose that orphan drugs should escape scrutiny by payers of evidence on effectiveness.

In this context the approach to assessment suggested the Province of Ontario is helpful [21]. Based on the principles of accountability for reasonableness [22], they propose a seven-step approach based on the notion that the level of evidence we could reasonably expect from a new drug depends partly on the potential size of the patient population, which has a major influence on the ability to conduct randomised controlled trials. This does not mean that we should definitely accept lower levels of evidence for orphan drugs. For example, the question of whether clinical trials should be of sufficient duration to measure final, as opposed to intermediate, endpoints is an issue that needs to be considered in relation to the epidemiology of the disease and the likely reliability of intermediate, or surrogate, outcomes, irrespective of whether the disease is rare or not. Therefore, in situations where the phase III clinical programme is limited, it will usually be important to consider post-launch data collection, for example by insisting that all patients receiving the therapy are entered into a registry. If there is uncertainty about longer term benefits, then consideration should be given to coverage with evidence development or pay-for-performance schemes—as in the case of non-orphan drugs.

Another current debate concerns whether there should be a separate process for orphan drug reimbursement, with a ring-fenced budget [23]. Various reviews of mechanisms for the pricing and reimbursement of orphan drugs demonstrate that a variety of approaches exist in different jurisdictions [24]. In the UK, orphan drugs that qualify as highly specialised treatments (HSTs), having previously been considered in a separate process, are now to be assessed by the NICE. To quality for HST status the prevalence has usually to be <500 patients in England [25]. These treatments were previously assessed by the Advisory Group for National Specialist Services (AGNSS). NICE is to modify the approach it applies to conventional therapies to cover these products recognising that "Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions" (NICE, paragraph 36) [26].

It is clear therefore that the establishment of special arrangements only makes sense if, based on our understanding of societal preferences, orphan drugs (or a subcategory of "ultra orphans" or "highly specialised treatments") are considered to be 'special'. Whilst assessing all medicines within the same process would facilitate consistency in decision-making and minimise the potential for special pleading, evidence suggests that attempts to subject orphan drugs to the standard processes of HTA and value-for-money assessment are politically sensitive [27]. If it is known in advance that most of these drugs will not be cost-effective based on standard criteria, why undertake the assessments in the first place, unless

there is the possibility that better value for money could be obtained if the drugs were better targeted? It might be better to acknowledge at the outset that high-priced orphan drugs will not be reimbursed, thereby avoiding wasting resources on their assessment.

Better definition of research priorities

For several years, manufacturers have been given incentives to undertake research into orphan diseases. These vary by jurisdiction, but include subsidies and promises of extended market exclusivity. Currently, manufacturers are free to respond to these policy incentives as they see fit. Orphan designation is not only based on the prevalence of the disease but also its severity, but there are concerns that too much emphasis has been placed on rarity per se, as opposed to the individual (patient) and social burden that the various diseases impose, or the availability of suitable treatment alternatives. This issue has become especially relevant given advances in 'personalised medicine' where a subset of the patient population can be defined by the existence of a biomarker [28]. For many of these patients, an acceptable treatment already exists, but their response to treatment can be improved by targeting the therapy. This has raised fears that manufacturers will 'salami slice' treatment indications in order to qualify for orphan status. Therefore, a tightening of the designation of 'orphan' is warranted, as in an ideal world it would require not only that the drug is for a rare and serious disease, but also that the disease had been deemed high priority for research because there is currently no acceptable therapy.

In addition, new mechanisms for funding research could be considered, such as targeted funding for research in diseases where a prior assessment has been made that there is a substantial unmet need. A number of mechanisms have been suggested for doing this, including the creation of prizes equal to the social value of innovation through a system of patent buyouts. The manufacturer would then, having received a return on R&D in the form of a prize, set prices equal to manufacturing costs [29]. However, it would be essential to ensure the prize was credible, as has been achieved with the Advanced Market Commitment offered by the Global Alliance for Vaccines and Immunisation (GAVI) for pneumococcal vaccine [30].

Also, product development partnerships (PDPs), such as the Medicines for Malaria Venture (MMV), the international AIDS Vaccine Initiative (IAVI) and the Institute for One World Health (IOWH) [31], have been used in the search for drugs for global health challenges and could provide a model for tackling orphan drugs if prices were not high enough to provide a return. Leading donors for PDPs include the Bill and Melinda Gates Foundation (BMGF), USAID, the United Kingdom Department for International Development and the Dutch Ministry of Foreign Affairs [32]. For example, MMV uses "push" funding from the BMGF and other donors to fund clinical development of malaria drugs by companies in exchange for contractual guarantees that drugs will be made available to key populations at affordable prices [33]. We should note however that if the fundamental issue is that payers do not think orphan drugs are worth the money and society supports that view, then the social value of innovation offered in any "prize" is unlikely to stimulate R&D and using "push" funding to finance R&D is unlikely to be justified. However, if the challenge is to get around payer concerns in order to better reflect the views of society, these approaches offer promise, and the PDP model in particular has a proven track record in global health [30].

Developing joined-up policies for orphan drugs

Probably, the biggest concern about current policies for orphan drugs is that the policies for stimulating research and providing reimbursement are at odds with one another, leading to inefficiencies if scarce resources are devoted to the research and development of drugs that are not going to be used. The logic we have set out above implies that we first need to establish whether society is willing to make any sacrifices in other areas of health care to provide funding for orphan drugs. If the answer is no, then we need go no further.

However, if the answer is yes, clearly we need better coordination between the policies guiding the research into orphan drugs and the policies guiding reimbursement. One option would be for policy makers to be more explicit about their priorities. A recent report by Orphanet [34] lists several hundred rare diseases and most of the policy discussion within the European Union considers actions that should be considered to further the development and availability of drugs for rare diseases *as a group*, not the priorities among rare diseases [35]. In the USA, however, the Institute of Medicine [36], in discussing options for accelerating research and development in rare diseases, argued that mechanisms for weighing priorities for research would be a key component of the overall strategy. If the priorities were made more explicit, the indication to manufacturers would be that those drugs deemed higher priority would be more likely to be reimbursed, if developed. The other dimension of 'joining up' policies, given the small number of potential patients per country, would be increased collaboration by governments at an international level, since pharmaceutical companies' research decisions are made on the global basis.

Conclusions

This article sets out a number of options for redesigning current orphan drug policies. Whilst the list given here is not exhaustive, we believe this topic requires attention. Otherwise, policies for orphan drugs will continue to be unsatisfactory when considered from all viewpoints. Without changes in the current policies, pharmaceutical companies will eventually cease responding to the incentives to develop orphan drugs, because they will increasingly be uncertain whether the drugs, if developed, will be reimbursed.

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