

Minireview

Developing and paying for medicines for orphan indications in oncology: utilitarian regulation vs equitable care?

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Despite 'orphan drug' legislation, bringing new medicines for rare diseases to market and securing funding for their provision is sometimes both costly and problematic, even in the case of medicines for very rare 'ultra orphan' oncological indications. In this paper difficulties surrounding the introduction of a new treatment for osteosarcoma exemplify the challenges that innovators can face. The implications of current policy debate on 'value-based' medicines pricing in Europe, North America and elsewhere are also explored in the context of sustaining research into and facilitating cancer patient access to medicines for low-prevalence indications. Tensions exist between utilitarian strategies aimed at optimising the welfare of the majority in the society and minority-interest-focused approaches to equitable care provision. Current regulatory and pricing strategies should be revisited with the objective of facilitating fair and timely drug supply to patients without sacrificing safety or overall affordability. Failures effectively to tackle the problems considered here could undermine public interests in developing better therapies for cancer patients.

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The Thalidomide tragedy led, in 1962, to amendments to the United States Food and Drugs Act and subsequently to new UK and EU legislation on the licensing of medicines. Measures introduced from that time onwards have required companies to demonstrate with increasing rigour to external regulators the safety and efficacy of their products before marketing.

Such reforms, together with developments in areas such as research methodology, have been associated with substantial increases in the costs of introducing new medicines. Despite the productivity and profitability of the research-based pharmaceutical industry in the period 1950–2000, its continuing economic viability – and arguably that of partner organisations in the public sector – is today relatively uncertain.

Many authorities now believe that there is a need to review and where possible simplify and better coordinate all forms of drug regulation, including for example clinical trial requirements (Academy of Medical Sciences, 2011). There is also a need to ensure that price controls and pharmaceutical payer policies are fully consistent with goals such as those of orphan drug law.

Given the challenges inherent in bringing any new medicine to market – which when research failures are accounted for, is estimated to cost over \$1000 million per successfully marketed product (Kaitin and DiMasi, 2011) – it is understandable that in the past private (and public and voluntary) sector enterprises often focused their attention on developing and supplying treatments for diseases that affect relatively large numbers of

relatively affluent people. This left people with rare diseases, or conditions confined to poor communities, under-served.

However, the advocacy from the 1970s onwards of patients' organisations such as the United States National Organisation for Rare Disorders (NORD) (2010) helped to give developing effective treatments for 'orphan' diseases increased priority. NORD's lobbying, alongside that of other agencies, was to a considerable degree responsible for the successful passage through Congress of the 1983 Orphan Drug Act (ODA).

Further, there are today fewer opportunities for developing new treatments for common conditions, because of past successes. Pharmaceutical companies have consequently had little choice but to become more involved in 'orphan research'. The full financial impacts of this may yet to have been realised.

Against this background this paper reviews issues relevant to ongoing research into medicines for rare and very rare oncological indications. The introduction of Mifamurtide (MTP), a treatment for young people with osteosarcoma, exemplifies the difficulties that could be encountered.

Concerns regarding the proposed introduction of 'value-based pricing' (VBP) for new medicines are also discussed from the perspective of those seeking to improve treatment for rare disorders, and for specific aspects of common cancers. As molecular profiling of the latter identifies increasing numbers of sub-types, orphan drug legislation will become increasingly relevant to anti-cancer medicines development.

DEFINING ORPHAN INDICATIONS

The US Orphan Drug Act (ODA) applies to conditions affecting fewer than 200 000 Americans. This currently translates to approximately 7 per 10 000 individuals. It offers manufacturers

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7 years of marketing exclusivity, exceptions from certain FDA fees and additional regulatory advice and tax benefits.

There are in total over 5000 rare diseases, about 80% are genetically based (EURODIS, 2010). They at present collectively affect some 25 million North Americans and in the order of 30 million European Union citizens (Committee for Orphan Medicinal Products, 2011).

The ODA was followed by similar provisions in Singapore (1991), Japan (1993), Taiwan and Australia (1998). The EU eventually followed suit in 2000, with a Directive that justified a special status for orphan drugs on the basis of equity. It stated that 'patients suffering from rare conditions should be entitled to the same quality of treatment as other patients'. In the EU, orphan conditions are considered to have a prevalence of less than 5 cases per 10 000 of population. The European provisions offer up to 10 years of market exclusivity, together with other forms of support.

The ODA has been called 'the most successful legislative action in recent US history' (Haffner, 2006). The available evaluations indicate that it has successfully encouraged pharmaceutical innovation and offers a robust model of how public policy can stimulate research and development when candidate technologies are otherwise likely to generate inadequate private returns.

The European legislation has also been of value. It may sometimes have caused treatments that were in practice already in use for 'off-label' indications to be offered in better formulated and evidenced, but also more expensive, presentations. However, innovative products and applications have unquestionably resulted. Examples of therapeutic developments that have received orphan drug designation range from Riluzole for motor neurone disease (ALS) to Temozolomide for malignant gliomas.

In the period between the adoption of the EU legislation in 2000 and the end of 2010, a total of 63 designated orphan medicines received marketing authorisation. Some 40% were for oncology indications (Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat, 2011). However, in the individual EU Member States the availability of these treatments varies from over 90% being reimbursed to under 30% (Le Cam, 2011).

BRINGING DRUGS FOR ORPHAN INDICATIONS TO MARKET

Osteosarcoma is the most common primary malignant tumour occurring in bone. Yet, it has an incidence of only 2.5–4 cases per million total population (Mirabello *et al*, 2009). It therefore falls under the NICE definition of a very rare 'ultra orphan' disease, as it affects less than 1000 people in the United Kingdom. There are less than 1000 new cases diagnosed each year in the US and about 1500 in the EU (Figure 1).

Even with surgery and multiple chemotherapy, the prognosis for patients with osteosarcoma is relatively disappointing. In the region of 60–70% of patients are cured of localised osteosarcoma. However, those diagnosed with metastatic disease have seen little recent progress. The long-term event-free survival rate is less than 30% (Kager *et al*, 2010).

Mifamurtide is a relatively new medicine for people with osteosarcoma. It was granted orphan drug designation by the FDA in 2001 and by the European Medicines Agency (EMA) in 2004. Its to date partial introduction exemplifies the barriers that the makers of orphan cancer medications may have to overcome during the drug development and supply process.

Once a potentially useful new treatment has been identified, clinical trials must be undertaken. Trial design for drugs for orphan diseases is often (primarily because of their infrequency) hindered by a lack of data on disease progression, poor diagnostics and inadequately defined clinical endpoints. In addition, the rarity of conditions such as osteosarcoma makes recruiting sufficiently large numbers of patients inherently difficult and expensive.

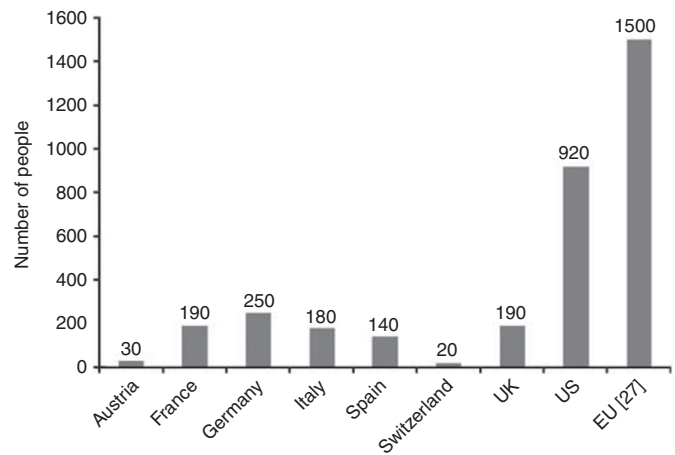


Figure 1 Estimated osteosarcoma incidence in selected countries. On the basis of a mean incidence three case per million using the World Bank and EUROSTAT population figures for 2010.

In the case of MTP, the evidence needed to support a successful European marketing application was derived from a trial called the Intergroup Study 0133. This was the largest ever randomised trial in osteosarcoma. It recruited in total nearly 800 US patients aged less than 31 years and took 5 years (1993–97) to gain sufficient numbers (Meyers, personal communication). It involved a substantial investment by the US National Cancer Institute.

In outline, all patients in the study received 'backbone' treatment using Cisplatin, Doxorubicin and Methotrexate. The addition of MTP resulted in a statistically significant improvement in survival. In absolute terms, the latter increased from 70 to 78% at 6 years (Meyers *et al*, 2008; Meyers, 2011). The great majority of these individuals live on without disease re-occurrence (Kager *et al*, 2010).

However, Intergroup 0133's findings were originally presented to the FDA with 3-year follow-up data (Meyers *et al*, 2005). Because of concerns about the statistical approach and findings offered at that time MTP was denied FDA approval in 2007. (Licensing refusal is a not uncommon outcome in the orphan drugs context. Joppi *et al* (2009) found the success rate for applications to be 63%, compared with over 70% for drugs for non-orphan indications.) The Administration requested an additional clinical trial. Yet, organising this would be both expensive and difficult given that in 2005 another major osteosarcoma trial – the EUROpean-American Osteosarcoma Study (EURAMOS) – had begun recruitment.

Further evidence of the effectiveness of MTP, based on Intergroup Study 0133 with 6-year follow-up data and a more robust statistical analysis, was submitted to the EU's EMA in 2009. As a result MTP now has a marketing authorisation in all 27 Member States, together with Iceland, Liechtenstein and Norway. However it remains unlicensed in the United States.

Even in Europe, osteosarcoma patient access to MTP is variable. Although it is now reimbursed by health-care funders in countries such as Germany, Spain, Italy and Austria, this is not the case in, for instance, France. In the UK NICE has, following a revision in its assessment model, recently approved MTP as cost-effective for NHS use for osteosarcoma. But this was nearly 30 months after it was accepted as effective and safe by the EMA (National Institute for Health Clinical Excellence, 2011).

The MTP example thus shows that even when an orphan drug is licensed it may still in practice be unavailable to those patients unable to pay, or able to obtain it via trial participation. From patients', clinicians' and pharmaceutical investors' perspectives there is a need for more consistent policies towards and decisions

on rare condition treatments across the world's major markets, and for better coordination of regulatory and payer policies.

Given current trends towards more 'personalised' treatments, there is from a cancer care viewpoint a danger that failures to resolve tensions between equity-based orphan drug legislation on the one hand and more restrictive 'NICE type' utilitarian approaches to drug pricing and reimbursement on the other will, in addition to causing individual injustices, over time inhibit therapeutic improvement. This could prove contrary to not only patient wishes but also to long-term social and economic public interests.

FAIR DRUG ACCESS AND SUSTAINABLE INNOVATION

Costing medicines development is controversial. This is in part because of issues such as the extent to which expenditures on failed research should be attributed to successfully marketed treatments. Regarding 'orphan drugs', there is a lack of definitive empirical research. However, it is realistic to conclude that although (depending on the accounting conventions used, and phase 3 costs incurred) such medicines may for individual indications normally be less costly to develop than treatments for prevalent conditions, their unit costs will be significantly higher.

This means that drugs for rare indications will typically be much more expensive per course provided and unit of welfare gained than similarly effective medicines for common complaints. If in cases such as that of MTP the fact that conducting adequately powered trials can be unusually costly is also taken into account this asymmetry will be further amplified.

Such observations provide powerful reason for where possible minimising the cost of pre-market trial requirements in the orphan and ultra-orphan drug licensing contexts, and for questioning approaches such as that to date taken by the FDA in the context of MTP. In this particular instance it could have been feared that the viability of the EURAMOS trial of established therapies would be impaired if more osteosarcoma patients were able to access MTP (Bielack, 2010). But this would be a perverse reason for delaying marketing approval for MTP, given the robust evidence of young adult survival advantage available.

Such concerns support the further acceptance of the 'coverage with evidence development' model now gaining traction in the United States (Cohen, personal communication). 'Orphan drugs' can only become successful medicines if they are provided to patients who benefit from them. Failures to agree adequate and timely reimbursement provisions undermine the well-being of individuals who have uncommon treatment needs and risk research and development investments. At the same time they do not always save the overall community money. This is partly because (as indicated earlier) the costs of 'marketing failures' must ultimately be loaded onto successful products, if private sector-funded research and development is to generate levels of profitability sufficient to incentivise ongoing investment. Some medicines designated as orphan products, perhaps most notably Glivec/Gleevec, have proved highly profitable. However, organisations such as Eurordis have warned against unwarranted extrapolations based on such exceptional instances (Le Cam, 2011).

It can in addition be argued that innovation in areas such as oncology is best seen as a single extended process, rather than a series of separate, fragmented steps. At some stages the rate and scale of progress may be disappointing. But when most, if not all, cancers can be prevented, cured or successfully contained, the long-term benefits to humanity will in all probability far outweigh the aggregated development costs of the individual technologies involved.

To put the current financial burdens imposed by orphan medicines into context, they have been estimated to represent in the order of 1–2% of national medicine budgets (or 0.01–0.03% of GDP) in

European countries (Orofino *et al*, 2010). With regard to oncology, the United States – the world's largest user of anti-cancer drugs – spent about 0.2% of its national wealth on anti-cancer medicines in 2010 (Catchpole and Taylor, 2011). This represents a significant but not unaffordable sum. The proportion of GDP spent on anti-cancer treatments in other OECD nations is typically lower.

Some commentators have warned that new 'cancer medicine' costs could in future impose unsustainable burdens on health services. But when factors such as the impacts of established oncology (and other) treatment patent expiries and increased payer reluctance to accept high-unit cost medicine prices (even in environments such as the US – see Hyde and Dobrovolsky, 2010) are factored in, such concerns appear at best exaggerated. It is more probable that the financial sustainability of private sector medicines research in fields such as oncology will become increasingly fragile, unless measures are taken to offset this hazard.

In fact, although treatments for uncommon indications are expensive at the individual episode of care level, their rarity limits their total cost even where high-unit prices are permitted. Current European, US and international policy debate on VBP for medicines should take this and other caveats into account.

Relevant proposals involve relating the maximum 'affordable' prices of pharmaceutical innovations to the cost of the additional quality-adjusted life years (QALYs) they provide. The theoretical strengths and weaknesses of this approach cannot be detailed here. However, with regard to medicines for rarer indications, it is worth emphasising that the crude application of utilitarian approaches that favour funding research and treatments for common disorders could become a major barrier to further progress in cancer treatment.

Enhanced understandings of disease mechanisms may in future allow more anti-cancer drugs to be developed as treatments for several orphan indications in ways which may in overall terms prove highly profitable, despite the imposition of relatively low 'cost per QALY' affordability thresholds. Yet, there will be many instances when this is not the case.

Some influential participants in the current policy debate recommend that 'cost per QALY'-based approaches to medicine pricing should make no special allowances for factors such as indication rarity (McCabe *et al*, 2005). However, Drummond *et al* (2007) have aptly asked 'why have incentives to develop (orphan) drugs if they will later be judged by criteria on which they are doomed to fail?'

CONCLUSION

During the last half-century governments and agencies across the world have increased their requirements for assuring the safety and efficacy of medicines. They have also put in place arrangements for encouraging the development of drugs for rarer oncological and other conditions. These have in many respects been successful. But in some instances, obtaining a marketing authorisation is needlessly challenging and costly. Enabling valuable medicines to be accepted for normally reimbursed use can be even more difficult.

There is a danger that political and regulatory approaches to assuring safety and 'cost effective' medicine prices will offset the intended impact of 'orphan drug' policies. Such mismatches could, if unresolved, seriously undermine both privately and publicly funded medical and pharmaceutical research in oncology.

Protecting patients and communities from unacceptable drug side-effects – such as the teratogenic consequences of inappropriate Thalidomide use – is a vital priority. However, if public and patient interests are to be served efficiently, unnecessary regulatory costs and restrictions should be avoided. Safety at any cost is not a desirable policy objective.

Similarly, legislators and decision makers concerned to ensure social justice and value for money in health care should also seek to ensure that when treatments for rare conditions are licensed they are, notwithstanding the conflicts of interest surrounding medicines pricing, rapidly accepted for reimbursement. Pharmaceutical payers' policies should be aligned with those of other agencies seeking to defend legitimate public interests in, and beyond, the health sector.

There is hence a powerful case for concluding that even if there is less than complete knowledge of an orphan drug's profile at the time of a marketing application, the most equitable future approach will typically be to grant a conditional license and to monitor the medicine's value in normally funded use. To permit this disputes

about the initial prices of new treatments should be resolved in ways which neither needlessly delay patient access to them nor undermine the confidence of research investors. In the final analysis 'excess' profits can be repaid. Lost lives cannot.

Conflict of interest

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