Orphan drug legislation: lessons for neglected tropical diseases

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SUMMARY

In the last 20 years, orphan drug legislation (ODL) has been adopted in several countries around the world (USA, Japan, Australia, and the European Union) and has successfully promoted R&D investments to develop new pharmaceutical products for the treatment of rare diseases. Without these incentives, many life-saving new drugs would have not been developed and produced.

For economic reasons, the development of medicines for the treatment of diseases prevalent in the developing world (or tropical diseases) is lagging behind. Among several factors, the low average per-capita income makes pharmaceutical markets in developing countries appear relatively unprofitable and therefore unattractive for R&D-oriented companies.

The case of ODL may offer some useful insights and perspectives for the fight against neglected tropical diseases. First, the measures used in ODL may also be effective in boosting R&D for neglected tropical diseases, if appropriately adapted to this market. Second, small-sized companies, which have played a successful role in the development of orphan drugs for rare diseases, may also represent a good business strategy for the case of tropical diseases. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Despite the fact that medicines are special goods aimed at saving lives and curing diseases, the pharmaceutical industry operates like any other private industry. It is compelled by market forces to make investments that seek to maximize future returns. In other words, pharmaceutical firms in a market-driven system respond mainly to economic and profit drivers rather than social or human imperatives. As a consequence, companies may decide not to develop or produce medicines that seem effective in treating life-threatening diseases but do not meet financial profitability criteria.

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There are two categories of medicines generally neglected by pharmaceutical companies: (i) drugs for rare diseases, and (ii) medicines for tropical diseases. Various authors (Reich, 2000; Kremer, 2002; Kremer and Glennerster, 2004) and organizations (such as MSF and WHO) have argued that, because of the vital importance of pharmaceuticals, there is a need to introduce coherent public interventions and effective economic incentives to boost research and development (R&D) investments and the subsequent production of these medicines.

In recent years, different programs have been introduced to alter these market mechanisms and make investments in these areas more appealing to pharmaceutical companies through a series of economic incentives. Among these efforts, orphan drug legislation (ODL) has been adopted in several countries, such as the US, Japan, Australia, and the European Union, and has successfully supported the generation of new drugs for rare diseases. In contrast, the number of orphan products developed for neglected tropical diseases is still limited. This situation has led some authors (Pécoul *et al*., 1999; Trouiller *et al*., 1999, 2002) to consider ODL as an inappropriate strategy for addressing the lack of pharmaceuticals for tropical diseases.

The present paper examines the possible reasons for the lack of adequate R&D investment in tropical diseases and proposes changes to orphan drug laws to make them more responsive to this issue. In the next section, the paper discusses some general principles of pharmaceutical R&D decision-making. Section ''Orphan Drug Laws'' introduces the main elements of ODL in different countries, with attention to strengths and weaknesses. In section ''Orphan Drug Designation: What Has Been Achieved So Far?,'' the impact of ODLs on the development of new drugs for rare diseases is analyzed and compared to the limited achievements in tropical diseases. In section ''Potential Improvements to Orphan Drug Laws,'' we discuss possible changes to this legislative framework to make it more appropriate for the tropical diseases market. Finally, we describe business models emerging in the orphan drugs market that could be applied to the case of neglected tropical diseases.

R&D DECISIONS IN THE PHARMACEUTICAL INDUSTRY

The development of a new drug is a lengthy, costly, and risky process. A company's decision to invest in R&D for a certain therapeutic area does not depend solely on cash availability at that time, but rather on the difference between expected revenues and costs over a future period of time (generally 5–7 years from market launch). If the expected capitalized value of the R&D expenditure is less than the expected discounted stream of profits, the company will consider R&D spending for that disease a good investment. Since manufacturing variable costs are generally low for most pharmaceutical products, the key determinant of research investments is the present value of the expected revenue generated by a product (Grabowski and Vernon, 2000).

In simplified terms, the expected revenue is estimated as the product of the medicine's unit price times the volume of drug sold in the market. The market unit price depends on (among other things): (i) the average income of the population affected by the targeted disease, and (ii) the quantity of drug that the pharmaceutical

company expects to sell in the market. The volume sold depends on (among other things): (i) the prevalence of the targeted disease, and (ii) the efficiency of the logistics and distribution system for the final drug.

These calculations for the two types of drugs considered here—those for rare diseases (such as Gaucher's Disease, Huntington's Disease, and several cancer sub-types), and those for tropical diseases in poor countries (such as malaria, trypanosomiasis, schistosomiasis, tuberculosis)—yield expected revenues insufficient to justify an investment. For rare diseases, this is due to the low prevalence of the targeted disease. For tropical diseases, the condition, though common, is found mostly in poor countries, where the majority of the population is unable to pay the high prices of new medicines.

The matrix in Figure 1 combines the two dimensions mentioned above: (i) disease prevalence and (ii) average national income. The case of rare diseases is captured by the bottom right-hand box: high average income of the patients but low prevalence of the targeted disease. The problem of drugs for tropical diseases is shown by the top left-hand box: high prevalence of the targeted disease but low average income of the people affected by the disease.

Other issues have also negatively affected expected profits and discouraged pharmaceutical companies from investing in medicines aimed at poor countries. A weak infrastructure for distributing and selling medicines in these countries, for instance, reduces the ability of effectively meeting the existing demand. Furthermore, the lack of an effective system of intellectual property protection in many poor nations and the possibility that cheap copies of the drug can be produced and sold in an unregulated manner have created heated debates about how to balance fair competition with access to drugs. The signing of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) in 1994 partially helped to calm these controversies. Still, several international organizations and NGOs have warned that patent protection and TRIPs might not lead to increased
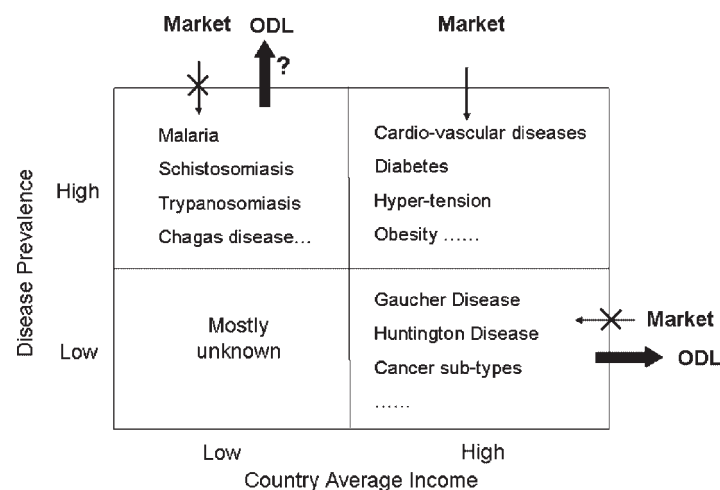

Figure 1. Market-responsiveness matrix for the pharmaceutical industry

production of drugs targeted at the needs of poor countries and could worsen the already limited access to essential drugs (WHO, 2006).

Because of the strong disincentives for pharmaceutical companies to invest in new products for tropical diseases, a host of other organizations have acted. International organizations such as WHO, and NGOs such as MSF and the Bill & Melinda Gates Foundation, and partnerships of various stakeholders, have all taken roles in advocating for expanded access of poor countries to existing drugs, in supporting the discovery of new medicines for tropical diseases, and in facilitating through public–private partnerships the relationships between developing countries and pharmaceutical companies. A successful example, in this respect, is the long-standing Mectizan Donation Program in which ivermectin, a drug against river blindness, is donated by a pharmaceutical company (Merck & Co., Inc.) and distributed in developing countries thanks to the support and network of WHO, the World Bank, and UNICEF (Peters and Phillips, 2004).

Experience shows that the market works best in promoting R&D investments for diseases that are prevalent in the developed world. This is confirmed by data on the ten most widely sold pharmaceuticals worldwide and their corresponding therapeutic areas: cardiovascular diseases, chronic hypertension, obesity, depression, and diabetes (Kumar and Zaugg, 2003). For both rare and tropical diseases, potential drugs can be called ''orphans of profitability.'' As a consequence, in a system driven solely by market rules, rare and tropical diseases are likely to be assessed by most R&D-oriented pharmaceutical companies as inappropriate targets for investment.

The orphan drug designation is a public policy measure intended to stimulate private R&D investments in neglected diseases. In this sense, the orphan drug designation is a tool used by public institutions to correct market rules that do not promote particular goods that societies (mainly industrialzed and rich) consider of social value. Orphan drug laws achieve this goal within a market logic by changing the structure of incentives to make profitable something that was considered unprofitable. We next examine how this approach has worked in several different market settings.

ORPHAN DRUG LAWS

In 1984 the United States promulgated the first law specifically designed to encourage R&D investments in areas normally neglected by pharmaceutical companies. Subsequently, several other countries have adopted similar laws: Japan in 1993, Australia in 1998, and the European Union in 2000. Despite some differences, these laws have a number of common core elements (Table 1).

The designation of ''orphan drug'' status is based on two criteria:

(1) *Epidemiological criterion*: The product is aimed at curing/treating a disease with a low prevalence or a ''rare'' disease. Some laws include additional requirements (i.e., there is no alternative treatment available, that the disease is life-threatening or chronically debilitating, or that the drug has high added-value in terms of efficacy and safety).

Table 1. Comparison of orphan drug programs

	USA	European Union	Japan	Australia
1. Scope	Drugs	Drugs	Drugs and medical devices	Drugs
2. Designation criteria				
Disease prevalence	Less than 200 000 (75 per 100 000)	Less than 50 per 100 000	Less than 50 000 (40 per 100 000)	Less than 2000 (11 per 100 000)
Nature of disease	Rare only	Life threatening, chronically debilitating; no alternative treatment	Rare and serious; no other treatment; high efficacy and safety	Rare only
Financial return on product	Yes	Yes (returns over 7 years)	No	Yes
3. Incentives				
Protocol assistance	Yes	Yes	On request	On request
Fast-track procedure	Yes	Not known	High priority	Priority
Tax credits	Up to 50% of clinical research costs	Member State specific	Six per cent of clinical and non-clinical costs	No
Exemption from registration fee	Yes	Reduced fees	No	Yes
Research grants	Clinical studies (pharma and academia eligible)	Member State specific	Clinical and non-clinical studies (pharma only)	No
Market exclusivity	7 years	10 years	For orphan drugs re-assessment of marketing approval after 10 years instead of 4 years	No
4. No. of orphan drugs approved/ designated (2003)	238/1200	7/126	94/172	33/63

(2) *Economic criterion*: For that product, irrespective of disease prevalence, there is no reasonable expectation that R&D and production costs will be fully recovered by sale revenues in the country where orphan status is granted.

The Japanese legislation is an exception in that it does not include the economic criterion. Moreover, while the scope of the legislation is in most cases limited to drugs, biologicals, and vaccines, in Japan the law includes medical devices.

Orphan drug laws combine a set of incentives that are designed to allow pharmaceutical companies to reduce their overall R&D costs and at the same time to recoup the costs thanks to a monopolistic market position and, consequently, the possibility of setting high unit prices.

The literature on research incentives distinguishes between push and pull approaches. Push mechanisms are incentives that operate upstream during the research-and-development process and involve costs to the public sector, such as tax credits and research grants, without a guarantee that a viable drug will be delivered. For example, a number of push programs, involving multiple stakeholders, currently support research on diseases of great impact in poor countries and provide support for the development of new drugs or vaccines (e.g., the International AIDS Vaccine Initiative, the Medicines for Malaria Venture, and the Malaria Vaccine Initiative). Pull mechanisms, on the other hand, operate downstream, reward a research output, and offer public incentives for development of a product (Reich, 2000). One example is advance purchase commitments by governments and philanthropic foundations where they agree to buy vaccines for AIDS, malaria, or TB once they are developed (Berndt and Hurvitz, 2005a). In comparison to drugs, vaccines are particularly suitable for this kind of incentive as they are generally quite inexpensive, simple to administer, and can be easily integrated in successful immunization programs able to reach a very broad population.

The most common push mechanisms included in the existing orphan drug programs are:

- Protocol assistance for clinical trials (automatic or on request).
- Fast-track procedures (or high priority).
- Tax credits (mainly for clinical research expenses).
- Exemption from registration fees.
- Research grants.

In this respect the US Orphan Drug Act offers particularly favorable conditions with tax credits that can reach up to 50% of clinical costs. The Australian legislation does not provide either research grants or tax credits, while the European Union leaves to individual Member States the decision of supporting the development phases for specific orphan drugs. Hence, the lack of harmonization within the European Union and the necessity to apply for support in individual Member States complicates the process in Europe.

The long market exclusivity offered through the orphan drug designation (Table 1) is considered a very powerful pull mechanism and a strong incentive for R&D investment. This tool prohibits the regulatory agency from accepting marketing authorization for any similar medicinal product in the same therapeutic area

for 7–10 years (varies by country). Breach of market exclusivity can be permitted if the new product is clinically superior or, in the case of the European legislation, can be reduced to 6 years if, after 5 years of exclusivity, the product "is sufficiently profitable" (Sheridan, 2004). The EU Commission is in the process of defining the criteria by which sufficient profitability will be determined (Alcimed, 2005).

The period of exclusivity under the US law begins when the drug receives final approval from the FDA, and the product can be granted market exclusivity even when a patent for that same product is not or cannot be awarded (Goldman *et al.*, 1992). For example, many biotechnology products are not eligible for patent protection because they were synthesized and their structure were published before their medical use became known.

ORPHAN DRUG DESIGNATION: WHAT HAS BEEN ACHIEVED SO FAR?

There is general consensus that at least some of the orphan drugs now on the market would not have been produced without the incentives provided by ODL (Goldman *et al.*, 1992; Arno *et al.* 1995; Rhode, 2000; Haffner, 2006). In the US, in the 24 years following the passage of the Orphan Drug Act (ODA), 282 drugs and biological products, providing treatment for more than 14 million patients in the United States, have come to market with orphan drug status. In the 8–10 years before 1982, by contrast, only 10 treatments for rare diseases were approved by the FDA and brought to the market (Haffner, 2006). Of the approved orphan drugs, 56% are for chronic diseases, and the two major therapeutic categories are rare forms of cancer, such as ovarian cancer and hairy-cell leukemia, and metabolic disorders often associated with single-gene mutations—such as Gaucher's Disease, Fabry's Disease, Tyrosinemia Type 1, and Mucopolysaccaridosis Type 1 (Haffner *et al.*, 2002). Since the introduction of OD legislation in 2000, the European Union has registered around 250 orphan medicinal products mainly for the treatment of rare forms of cancer, although only 18 products were subsequently approved (Joppi *et al.*, 2006).

Roughly 20% of orphan designations awarded by the FDA are for novel biotechnology products and include the latest biological therapies such as monoclonal antibodies, cell-based therapies, and tissue-engineered products. The US law, therefore, appears to have supported the forefront of research and development based on the application of new techniques in molecular and cell biology and on cutting-edge scientific knowledge of disease. In fact, the majority of orphan grant funding (approximately US $13.5 million per year) has been awarded to investigators in academic centers and start-up firms (Haffner *et al.*, 2002). The companies with the highest number of products with orphan designation are medium-sized biotech and pharmaceutical firms (i.e., Genzyme Corporation, Orphan Medical, Serono, and Pharmacia), and companies such as Amgen and Genentech that started as small biotechs and have developed into large businesses that maintain a science-based R&D approach.

In general, the orphan drug market has offered levels of profitability that are not comparable with the pharmaceutical industry's traditional blockbuster drugs (with sales over US $1 billion). If we limit ourselves to the case of rare genetically

transmitted diseases, annual sales of most products range between US $50 million (e.g., Aldurazyme, for the treatment of mucopolysaccharidosis type 1) and US $300 million (e.g., Fabrazyme for Fabry's Disease; Pulmozyme for cystic fibrosis). As a result, it can take several years before the producing company reaches the break-even point (Cerezyme, for Gaucher's Disease, with sales over US $850 million in 2005 is an exception) (Datamonitor, 2006). A study conducted in 1992 shows that three-quarters of licensed orphan drugs generated less than US $10 million in their first year on the market (Shulman *et al.*, 1992).

Successful orphan drugs have generated profits mainly due to the monopoly status guaranteed by the orphan designation and their consequent high prices (e.g., Gleevec, Cerezyme). In addition, in some instances, this effect has been augmented by subsequent extensions of the drug's application to other indications and the broadening of its market. A good example is represented by erythropoietin (EPO) that was approved as an orphan drug for a very limited target population (end-stage renal disease) and is now used to alleviate chemotherapy-induced anemia in a very broad group of patients, becoming in the US the single biggest expenditure for the public program Medicare (Cotter *et al.*, 2006).

In conclusion, the orphan drug designation has been successful in promoting R&D investments in the development of drugs for previously neglected rare diseases. Some of these products have been profitable and have supported the growth of the biotechnology sector. However, it is important to remember that the success of companies such as Amgen and Genentech and of their products depended not only on the incentives created by orphan drug designation but also on the deals and long-term relationships that these companies negotiated with big pharmaceutical companies that have greatly supported the R&D and marketing activities of these firms.

Finally, it should be noted that interest groups have played a key role in the development of orphan drugs for rare diseases. Patient advocacy organizations have often lobbied aggressively to promote legislation encouraging the development of these drugs and subsequently have pushed third-party payers (insurance companies in the case of the US and governments in the case of the state-funded systems) to provide full reimbursement of the products, despite their high unit prices. The manufacturers of orphan drugs have well understood the importance of these support groups and have collaborated with them in lobbying initiatives. It is worth mentioning, for example, the case of Gaucher's disease and Cerezyme, the drug developed by the biotech company Genzyme. In this case, patient groups have played a key role both in promoting R&D efforts and in arguing for full reimbursement for the drug therapy. Genzyme, in addition, started a partnership with the humanitarian organization Project HOPE with the aim of guaranteeing the reimbursement of Cerezyme around the world (Goldman *et al.*, 1992; Datamonitor, 2006; http://www.gaucherdisease.org).

The application of orphan drug designation to products for tropical diseases, however, is still uncommon, as shown by over 20 years of experience with the US. So far, only two tropical diseases (malaria and human African trypanosomiasis) have been defined as rare within the category of diseases of low prevalence imported to the US (sickness recorded within American territory and linked to a patient traveling in a known endemic and/or epidemic zone). Between 1983 and 1997, 15 of the 837

"orphan" products designated under the ODA had indications for tropical diseases (Trouiller *et al.*, 1999).

Only three drugs (eflornithine, halofantrine, and mefloquine) received orphan status as new products while the other 12 drugs were second-line or older products with new formulations. The two antimalarials (halofantrine and mefloquine) had already been developed by the Walter Reed Army Institute of Research as part of the US military infectious disease research program, and orphan status permitted expansion of clinical development. The production of eflornithine—an essential treatment for trypanosomiasis—had been discontinued by the manufacturer due to low profitability (Trouiller *et al.*, 1999).

In several cases, pharmaceutical companies have created partnerships with international agencies, such as WHO, and other organizations for the distribution of these drugs in developing countries either as donations or at special prices. For instance, in 2001 GSK reduced the price of halofantrine for the treatment of malaria from US $6.88 to $1 for developing countries (GSK, 2001). Similarly, pentamidine isethionate, an orphan drug for the treatment of human African trypanosomiasis, is available through WHO at US $3 per vial thanks to a special agreement between the international agency and the drug's producer, Aventis (Gastellu Etchegorry *et al.*, 2001).

In conclusion, despite the fact that in a few cases the US orphan drug designation turned out to be effective in sustaining the clinical development of drugs for tropical diseases, such cases are very limited and concentrate on diseases (such as malaria) prevalent among US travelers and military. Even in these few cases, there still remain serious problems of access in developing countries because of high prices and difficulties in distribution. Therefore, other mechanisms, such as preferential pricing, partnerships with international organizations, and drug donations, have been necessary to expand the availability of these medicines.

Achievements for neglected tropical diseases have been minimal under orphan drug laws compared to what has occurred for rare diseases. What accounts for this stark difference? Could ODLs be applied to promote the development of treatments for neglected tropical diseases? And which lessons can be drawn from the experiences with rare diseases and applied to neglected tropical diseases?

POTENTIAL IMPROVEMENTS TO ORPHAN DRUG LAWS

Let's first examine legislative intent. In the minds of most legislators, orphan drug laws were likely designed primarily to promote research in and production of drugs for rare diseases affecting their domestic markets, not to address the complicated issue of the lack of medicines in the developing world.

As mentioned above, in the US, two tropical diseases (malaria and human African trypanosomiasis) were explicitly defined as "rare" under the ODA based on the few cases recorded on the American territory and linked to individuals returning from endemic areas. In all other countries, tropical diseases are not specifically mentioned in orphan disease legislation. At the same time, diseases such as river blindness are listed as rare by the Office of Rare Diseases (ORD) of the US National Institutes of

Health (NIH) and by Orphanet, a consortium of European partners. These inclusions are based on the few cases of these communicable diseases that occur every year in industrialized countries when their citizens return from abroad. So, in principle, several tropical diseases would satisfy the requirements for orphan designation under the epidemiologic criterion.

However, in order to make ODLs a more appropriate tool to deal with the issue of tropical diseases, the status of ''orphan'' could be explicitly assigned to those drugs aimed at the cure and treatment of diseases defined as endemic to developing countries. In this case the type of disease targeted by the drug can be considered a sufficient condition to demonstrate un-profitability. This would represent a strong statement from industrialized countries that tropical diseases are a global concern and a shared responsibility for which richer societies are willing to find solutions and contribute economically.

Both push and pull mechanisms included in ODLs could be enhanced for tropical diseases. Push incentives in the form of research grants and protocol assistance can work effectively, as clinical trials are often difficult to organize and manage in poor countries and require large financial investments. However, as ODL is country-specific legislation, it might prove difficult to gain the necessary political support and financial resources in any individual country to fund R&D expenditures for tropical diseases. Therefore, the intervention of international organizations, such as UNDP, the World Bank, and WHO, or other philanthropic organizations is essential in creating a pool of resources to sustain R&D for tropical diseases. For instance, the Drugs for Neglected Diseases Initiative (DNDi), promoted by Médicins Sans Frontières (MSF), is aimed at creating a global public fund for R&D projects in the area of tropical diseases. DNDi taps into four major sources of funding: (i) public donors such as national or regional governments, the EU, international organizations, the World Bank, and UN agencies (WHO, UNDP); (ii) private funders such as specialized private foundations and large individual donors; (iii) DNDi founders; and (iv) the general public. DNDi grants could be linked to support in the application process for orphan drug designation with the US and European regulatory agencies. Or, vice versa, applicants for orphan drug designation in tropical diseases could automatically apply for additional grants from international entities, such as DNDi.

As for pull mechanisms, some questions have been raised regarding market exclusivity for drugs aimed at tropical diseases (Trouiller *et al.*, 1999). In addition, market exclusivity, like patents, might be a deterrent to developing new drugs or formulations in the same therapeutic area, an unfortunate consequence given the urgent public health concerns surrounding these diseases. Finally, market exclusivity assumes monopolistic prices unaffordable in developing countries. The recent legal dispute between Novartis and the Indian Government over the denial of patent protection to Gleevec, an anti-cancer drug, shows how intellectual property issues, market exclusivity, and the high prices that companies seek can become sources of acute tension between multinational pharmaceutical companies and developing countries (MSF, 2006).

Instead of acting on the market exclusivity instrument, therefore, the orphan drug designation could be enhanced by other pull mechanisms such as advance purchase

commitments. Under this scenario an agreement is negotiated with international organizations and/or national governments in the developed world to assure the purchase and distribution of a product at a predefined price acceptable to all parties. The first of these agreements has been promoted by the governments of Italy, the U.K., Canada, Russia, and Norway together with the Bill and Melinda Gates Foundation in support to the development of a pneumococcal vaccine. This approach has mainly been suggested for new vaccines, such as malaria, TB, HIV, and pneumonia/meningitis (Kremer and Glennerster, 2004; Berndt and Hurvitz, 2005a) but has seen less support of its application for development of medicines.

This solution, in fact, poses certain difficulties. For instance, the characteristics of the output to be purchased would need to be precisely defined and the price that would allow the producers to recoup the sunk R&D costs would need to be estimated. In general, there is extensive scientific knowledge about tropical diseases, the biological mechanisms of their development, and potential means of treatment (Kremer and Glennerster, 2004; Moorthy *et al.*, 2004). Consequently, it should be feasible to specify ex-ante the features of drugs/vaccines eligible for advance purchase commitment programs. Economists have offered estimates regarding the revenues necessary to cover R&D costs. For example, Robbins-Roth (2000) reports that $500 million in peak annual sales may be sufficient to attract R&D investments in pharmaceutical development, while Kremer and Glennerster (2004) argue that advance purchase programs, specifically targeted to vaccines, need to generate $2.3 billion in annual sales (Kremer and Glennerster, 2004: p. 90), considering the lower marketing costs and limited amount of private sales (sales to travelers and tourists and private sales in developing countries). Whether these estimates also apply to the advance purchase of drugs is still to be determined.

A second pull-incentive possibility is to establish different price tiers within an endemic developing country linked to orphan drug designation. In this approach, there would be high prices for those market segments able to self-pay for the drugs, and preferential prices for the rest of the population in developing countries (Abbott, 2002). This scenario may be hard to implement, as wealthy patient populations are difficult to identify in poor countries. It also raises equity issues by making the ''rich and sick'' different from the ''poor and sick.'' Furthermore, it could be difficult for pharmaceutical companies to politically sustain a differentiated pricing policy, and the policy could encourage parallel imports (where products sold at lower prices in one country are imported by consumers or distributors in high-price countries).

Finally, some authors (Kremer and Glennerster, 2004; Ridley *et al.*, 2006) have proposed combining orphan drug designation with such mechanisms as transferable patent exclusivity and transferable priority review. In the former case, the development of a drug for a tropical disease is rewarded with additional time on patent for a different product; in the latter, with the possibility to shift for another drug from a standard to a priority or fast review process. In both instances, the acquired right can be sold to another company. There are some drawbacks to these solutions. Having a patent extended could appeal to firms with blockbuster products but would result in a delay in the introduction of generic forms of the drug. Patients and governments would bear the costs of more expensive drugs for a longer time.

Shifting from a standard to a priority review also raises some issues. First, the review of other drugs would be held up. For this reason, Ridley and colleagues suggested a user fee of US$1 million for the company granted the orphan drug designation. Second, it is debated whether fast review affects the safety and efficacy of the approved drugs. Some studies (Olson, 2004) indicate that medicines with fast reviews lead to more adverse drug reactions, others (Berndt *et al.*, 2005b) show that shortening review times does not increase drug withdrawal rates.

BUSINESS MODELS IN THE ORPHAN DRUG MARKET FOR RARE DISEASES

Several analyses (Haffner, 1996; Haffner, 2006) show that the vast majority (more than 70%) of orphan drug producers are small companies, with R&D activity focused on biotechnology. Several factors have promoted this trend. First of all, research grants, fiscal subsidies, technical assistance, and the fast-track approval process included in the orphan drug laws have reduced the financial risks of R&D investments and facilitated the entry of small companies into the market (Borgman, 1992). Second, small biotech companies seem more willing than big pharmaceutical firms to take on risky and innovative projects as such companies are usually financed by a restricted group of risk-taking investors and venture capitalists. (The pattern of small companies taking on more risks is indirectly confirmed by DiMasi's 1995 study that showed small firms having the lowest success rate in the R&D process).

The most successful orphan drug producers (such as Amgen, Genentech, and Genzyme) have become financially viable and have earned profits even with relatively small markets, by exploiting the incentives of the ODL. All three companies were born from initiatives of university scientists with expertise in newly developed techniques or niche therapeutic areas and good entrepreneurial skills. The companies then pursued different strategies, largely specializing in three distinct areas (recombinant DNA technologies, monoclonal antibodies, and enzyme-replacement therapies, respectively), which allowed them to avoid direct competition. In addition, according to Pisano (2006), one of the critical aspects of Genentech's success, despite its small markets, has been the capacity to create long-term business relationships with big pharmaceutical companies, first Eli Lilly and more recently Roche. These arrangements supported Genentech's R&D activities and allowed it to re-fill its drug pipeline, while allowing the biotech company more time to learn from failures, accumulate capabilities, and exchange expertise, aspects of great value in such a risky business.

In recent years, a handful of new orphan drug designations suggest a new trend in using these laws for neglected tropical diseases. They also show how business models and arrangements from the area of rare diseases might be applied to tropical diseases.

In 2005, the Institute of OneWorld Health, a nonprofit pharmaceutical company mainly supported by the Bill & Melinda Gates Foundation, received orphan drug designation (both in the US and Europe) for paromomycin, an antibiotic able to treat visceral leishmaniasis or kala-azar (Hale *et al.*, 2005). Paromomycin had been

previously approved in the US under the ODA, was off-patent, and WHO had obtained the rights for the injectable form from Pharmacia/Pfizer. During clinical trials, WHO stopped the development of the antibiotic due to the lack of funding. OneWorld Health took the drug through late-stage trials in India, submitted an application to the Indian regulatory agency, and now owns, together with WHO, the license to the drug. In the meantime, OneWorld Health also applied for orphan drug designation for paromomycin in the US and in the European Union. Protocol assistance and incentives for clinical trials offered under the orphan drug laws were clearly beneficial to OneWorld Health. In addition, positive responses from FDA and EMEA, known for their rigorous standards, may have provided some symbolic value and accelerated drug approval in countries, like India, where the need was highest. Prior to the licensing of paromomycin, OneWorld Health had already obtained licenses for other drugs for tropical diseases from pharmaceutical companies and academia. For example, in 2004 OneWorld Health was granted exclusive license by Celera Genomics for a compound to treat Chagas disease, a parasitic disease transmitted by insect vectors, which is prevalent in Latin American and can lead to heart failure (Moukheiber, 2003). OneWorld Health represents an exception more than the rule thanks to a unique business model that combines some characteristics of a convential for-profit pharmaceutical company with innovative ways of creating not-for-profit partnerships, leveraging existing products and promoting social entrepreneurship (Hale *et al.*, 2005).

The 2005 orphan designation in Europe of a tuberculosis vaccine developed by Oxford University (Lang *et al.*, 2005) represents a second interesting case. The vaccine prevents tuberculosis in people already vaccinated by traditional BCG (Bacillus Calmette-Guerin). In Europe this is the first time orphan drug status has been granted for a product developed by a university and to an organization that clearly stated its intention of making the product available in developing countries. Once again, besides the financial incentives and the access to expert advice on drug development, approval by the EMEA has been viewed as a sign of confidence for the product and type of research.

A less clear-cut case involves the vaccine for Japanese encephalitis developed by a small Austrian biotech company, Intercell. The company aims at developing vaccines where there is "substantial unaddressed medical need." Japanese encephalitis is the leading cause of viral encephalitis in Asia, with 30 000–50 000 cases reported each year, especially in China, Japan, and Korea, and its incidence has increased due to the intensification of irrigated rice production. It is so far unclear what kind of policy Intercell will pursue to guarantee access to this product in these countries.

These three cases show that for tropical as for rare diseases, small companies and universities, rather than big pharmaceutical companies, are the more common drivers in the development of new products. All three firms have taken advantage of the incentives of orphan drug laws in the US and Europe. Similarly, as with successful biotech companies involved in rare diseases, these organizations have sought benefits (as in the case of OneWorld Health) or could potentially benefit by establishing very early on long-term partnerships with venture philanthropists, national governments, and international organizations (Kettler and Marjanovic, 2004).

CONCLUSIONS

So far, orphan drug designation has been used in only a few cases for the development of products aimed at neglected tropical diseases. The experiences suggest that this approach could represent a good starting point, especially if some provisions and incentives were adapted to the features of tropical diseases. It may also be necessary to link orphan drug designation with other types of programs and incentives, such as, for instance, international research funds and advance purchase commitments. In all cases, international organizations with broader mandates need to be involved and international pharmaceutical policies need to be developed for all neglected diseases in order to assist policymakers, funding agencies, and the research community in setting priorities.

The success of orphan drug designation for neglected rare diseases shows that, first, drug companies using orphan drug programs can still generate profits and recoup their R&D investments even with relatively small markets in the developed world. Second, the orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills.

In the current academic and policy debate, the development of new drugs for tropical diseases in poor countries has often been considered the responsibility of major multinational pharmaceutical companies. Instead, other actors—especially small companies with new and creative business models, universities, and not-for-profit organizations—appear to be leading the way in developing drugs for neglected tropical diseases. The orphan drug designation, even if not sufficient on its own, should be considered as a useful tool to support and reward these efforts.

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