

INTERNATIONAL PUBLIC
GOODS AND TRANSFER OF
TECHNOLOGY UNDER A
GLOBALIZED INTELLECTUAL
PROPERTY REGIME

Edited by

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In this collection, distinguished economists, political scientists, and legal experts discuss the implications of the ever more globalized protection of intellectual property rights for the ability of countries to provide their citizens with such important public goods as basic research, education, public health, and sound environmental policies. Such items increasingly depend on the exercise of private rights over technical inputs and information goods, which could usher in a brave new world of accelerating technological innovation. However, higher and more harmonized levels of international intellectual property rights could also throw up high roadblocks in the path of follow-on innovation, competition, and the attainment of other social objectives. It is at best unclear who represents the public interest in negotiating forums dominated by powerful knowledge cartels. This is the first book to assess the public processes and inputs that an emerging transnational system of innovation will need to promote technical progress, economic growth, and welfare for all participants.

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Increasing R&D incentives for neglected diseases: Lessons from the Orphan Drug Act

HENRY GRABOWSKI*

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1. Introduction

A number of studies point to the fact that new medicines have been a key factor underlying the substantial gains in longevity and quality of life realized by individuals over the last half century.¹ A recent survey by David Cutler and Mark McClellan analyzed the degree of medical progress in a number of major

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¹ See, e.g., David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFF. 11 (2001); Frank R. Lichtenberg, *Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS*, 20 HEALTH AFF. 241 (2001); MEASURING THE PRICES OF MEDICAL TREATMENTS (Jack E. Triplett ed., Brookings Institution Press 1999).

diseases.² They found pharmaceutical innovations have provided significant net benefits to patients across a wide spectrum of conditions, such as heart disease, cancer, and depression. These are diseases that are common to both developed and developing countries (i.e. “global diseases”). However, a review of the existing literature indicates relatively fewer R&D investment programs and medical advances devoted to diseases that are specific to and concentrated in developing countries.³ This would include infectious and tropical diseases, such as malaria, tuberculosis and leprosy, which afflict millions of individuals.

The basic challenge to stimulating more research and development on new medicines for these neglected diseases is how to overcome the barriers posed by the low income and ability to pay for health care that exists in developing countries.⁴ Insufficient revenues on the demand side of the market are combined with high fixed costs of R&D on the supply side. From a policy perspective, one needs to design government interventions that will alter the economic incentives that prevail in this situation.

The U.S. Orphan Drug Act of 1983 provides an instructive model in this case.⁵ Under this Act, the U.S. Congress created a set of incentives designed to encourage R&D investment on rare illnesses. This Act covers illnesses or conditions in the United States with a prevalence of less than 200,000 patients. Firms that develop drugs for rare conditions are eligible for a 50 percent tax credit on their clinical development expenses. Other incentives include development grants, counseling and guidance from the Food and Drug Administration (FDA), and a guaranteed seven-year market exclusivity period. This Act has led to an impressive increase in the number of new drugs for rare illnesses over the past two decades, with significant therapeutic benefits for patients.

The success of the U.S. Orphan Drug Act provides some insightful lessons for the R&D investment problem in the case of diseases endemic to developing countries. These diseases have been variously categorized as “diseases of poverty” or “neglected diseases.”⁶ In this chapter we shall use the term neglected diseases. From an economic perspective, diseases such as malaria or tuberculosis are also orphan diseases, even though they afflict millions of individuals. As in the case of orphan drugs for rare illnesses, the expected returns from

² Cutler & McClellan, above n. 1.

³ Bernard Pecol et al., *Access to Essential Drugs in Poor Countries: A Lost Battle?*, 281 J. AM. MED. ASS’N 361; WHO, *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options* (Geneva, 1996).

⁴ World Health Organization, *Report of the Commission on Macroeconomics and Health* (Geneva, 2002).

⁵ Orphan Drug Act, Pub. L. No. 97–414, 96 Stat. 2049 (1983), *codified at* 21 U.S.C., §§ 360aa–360dd (2000).

⁶ See WHO, above n. 4; Jean O. Lanjouw, *A Patent Policy Proposal for Global Diseases*, Brookings Policy Brief (June 2001); Michael Kremer, *Pharmaceuticals and the Developing World*, 16 J. ECON. PERSP. 67 (2002).

investing in treatments for these diseases are too small to cover the high fixed cost of pharmaceutical R&D. One strategy for policymakers is to enhance the U.S. Orphan Drug Act and its international counterparts to change this situation.

In this chapter, I investigate the feasibility of developing an orphan drug-type program oriented to the neglected diseases of developing countries. In the next section, I review recent economic studies of the pharmaceutical R&D process and analyze the factors that contribute to the large costs of developing new medicines. Then I turn to an analysis of the Orphan Drug Act and how it altered the incentives for R&D investment in the case of drugs for rare diseases. The third section focuses on how various push and pull strategies could be employed to increase the R&D investment in neglected diseases. The final section provides a summary and conclusions.

2. Economics of the pharmaceutical R&D process

Competition in the research-based segment of the pharmaceutical industry is centered on the discovery and development of medicines that satisfy an unmet medical need or improve upon existing therapies. Pharmaceutical research and development is a complex, costly, risky, and time-consuming process. Over the past decade, several economic studies have been undertaken of the pharmaceutical R&D process.⁷ These studies consider the probability of success, the cost and time to develop a new medicine, and the economic returns to drug R&D. They highlight the large technical and commercial risks associated with the pharmaceutical R&D process and the tremendous variability in the economic returns of new drug introduction.

2a. Costs and risks

The most obvious risk in drug development is that, despite a long and costly development process, most new drug candidates will not reach the market. Failure can result from toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, economic and competitive factors, and various other problems. Typically, a fraction of one percent of the compounds that are synthesized and examined in pre-clinical studies make it into human testing.⁸ Of these, only about twenty percent of the compounds entering clinical trials survive the development and FDA approval

⁷ Joe DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003); F.M. Scherer, *The Link Between Gross Profitability and Pharmaceutical R&D Spendings*, 20 HEALTH AFF. 216 (2001); Henry Grabowski et al., *Returns on Research and Development for 1990s New Drug Introductions*, 20 PHARMACOECON. 11 (2002).

⁸ Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2003*, at 3 (PhRMA 2003).

process.⁹ The prospect of a long and uncertain development period for a new drug is another source of risk in the drug development process. Recent new drug approvals have averaged nine years from the beginning of clinical trials to final FDA approval. The discovery and pre-clinical periods can add another three to five years to this process.¹⁰

In a recent study, several co-authors and I examined the representative costs for new drugs whose mean introduction date was in the late 1990s.¹¹ Our average cost estimate incorporates the expenditures for drug candidates that fail in the R&D process, since these costs must be recouped from the revenues of successful drug candidates. We found that it required over \$400 million in out of pocket expenditures (in 2000 dollars) to discover and develop the average U.S. new drug introduction.¹² If one also takes account of capital costs utilizing a risk-adjusted cost of capital appropriate for the pharmaceutical industry, capitalized R&D costs per new drug introduction are double the out of pocket costs.

R&D costs were shown to have increased at an annual rate of 7.4 percent above general inflation when compared to the costs for new drug introductions of the 1980s.¹³ A major factor accounting for this growth in costs is the size and number of clinical trials, which increased significantly in the 1990s compared to earlier periods. Other important factors include the growing complexity of trials (i.e., more procedures per patient), an increased focus on chronic diseases, and greater costs to recruit and maintain patients for these trials.¹⁴

2b. R&D returns

In another study, two colleagues and I examined the distribution of returns for 1990–94 new drug introductions.¹⁵ A key finding was that the sales and returns of new drugs exhibit tremendous variability. In particular, we found that a small number of drugs provide a disproportionate share of overall revenues. The search for these exceptional compounds, which generally involve significant therapeutic advances over established therapies, is a key driver of R&D competition in pharmaceuticals.

The worldwide life cycle of sales profiles for the top few deciles and the mean and median drugs are presented in Figure 1.¹⁶ This distribution of returns in pharmaceuticals is highly skewed. We found that only three of ten new drugs cover the R&D costs incurred by the mean new drug (including the costs of failed compounds and discovery costs necessary to generate new product leads). Hence, the R&D process is like a lottery in which most drug

⁹ Joe DiMasi et al., above n. 7, at 165. ¹⁰ *Id.* ¹¹ *Id.*

¹² *See id.* at 161–67. There is considerable variability around this estimated value depending on whether the new compound is for an acute or chronic illness, the particular class of diseases it addresses, its degree of innovativeness, and several other relevant factors.

¹³ *Id.* ¹⁴ *Id.* ¹⁵ Grabowski et al., above n. 7. ¹⁶ *Id.*

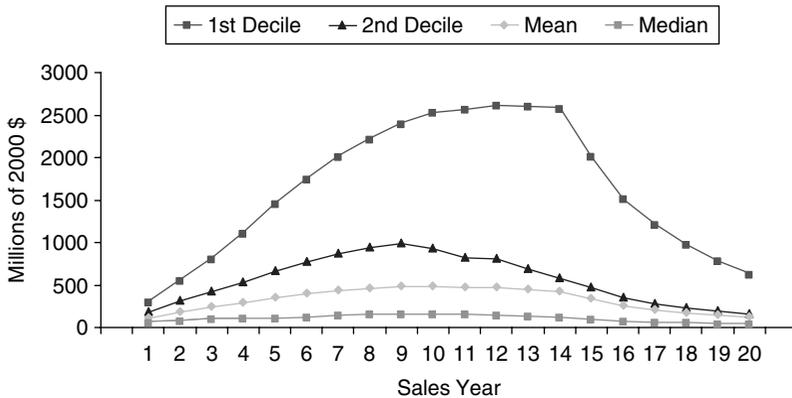


Figure 1. Worldwide Sales Profiles of 1990-94 New Chemical Entities

candidates taken into testing fail, a small number are marketed commercially and achieve modest financial returns, and a few drugs succeed in generating very large returns to the innovating firm.¹⁷

The highly skewed outcomes observed in Figure 1 reflect both the dynamic nature of the R&D process and the large scientific, regulatory and commercial risks that surround the process. Long time lags, the need to obtain regulatory approval from the FDA, and new drug introductions of competitors compound the various scientific and technical risks. These factors help explain the great variability in market sales and profitability that has been observed in every time cohort that we have examined since the 1970s.¹⁸ Even the largest pharmaceutical firms, with extensive pipelines of new drug candidates, exhibit great variability in the number of approvals and sales from their R&D investment in a given period.¹⁹

Vernon and I have performed two studies on the factors that influence the size of a company's total R&D expenditures.²⁰ The two primary factors that we found to be economically significant determinants of R&D expenditures in these studies were a firm's expected returns and its internally generated funds. We found that roughly 25 percent of each million-dollar change in cash flow

¹⁷ F.M. Scherer has shown that many industrial R&D activities are characterized by skewed outcome distributions. This is especially the case for venture capital investments. See F.M. SCHERER, *NEW PERSPECTIVES ON ECONOMIC GROWTH AND TECHNOLOGICAL INNOVATION* 71-80 (Brookings Institution Press 1999).

¹⁸ Grabowski et al., above n. 7, at 23-28.

¹⁹ See Henry Grabowski & John Vernon, *The Distribution of Sales Revenues from Pharmaceutical Innovation*, 18 *PHARMACOECON.* 21 (2000).

²⁰ Henry Grabowski & John Vernon, *The Determinants of R&D Expenditures in the Pharmaceutical Industry*, in *DRUGS AND HEALTH* (R. Helms ed., AEI 1981); Henry Grabowski & John Vernon, *The Determinants of Pharmaceutical Research and Development Expenditures*, 10 *J. EVOLUTIONARY ECON.* 201 (2000).

was directed toward increased R&D expenditures.²¹ The cash flows from successful new products are therefore important in funding R&D for future new product innovations.

2c. *The critical significance of patents in pharmaceuticals*

Patents have been found to be critically important to pharmaceutical firms in appropriating the benefits from drug innovation.²² The reason for this follows directly from the characteristics of the pharmaceutical innovation process. As discussed above, it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new medicine. Absent patent protection, or some equivalent market barrier, imitators could free-ride on the innovator's FDA approval and duplicate the compound for a small fraction of the originator's costs. In essence, imitation costs in pharmaceuticals are extremely low relative to the innovator's costs of discovering and developing a new compound. Some form of market exclusivity or market barrier to easy imitation has been essential in this industry to allow pioneers to appropriate enough of the benefits from new drug innovation to cover their large R&D costs and earn a risk-adjusted return on their overall portfolio of R&D programs.

The importance of patents to pharmaceutical innovation has been demonstrated in several studies by economists.²³ By contrast, these studies found that many other research-intensive industries, such as computers and semiconductors, placed greater stress on factors like lead time and efficiencies in the production of new products accruing to first movers.²⁴ This reflects the fact that R&D costs and

²¹ In a recent paper, Scherer also has focused on the relationship between pharmaceutical industry profits and R&D outlays. He found a high degree of correlation between the deviations in trends from these series, suggesting that R&D outlays are affected significantly by changes in profitability. He also found that the growth rates on gross margins were substantially lower than the growth rates for R&D outlays, leading to the possibility that growth rates for R&D could lessen in the future. F.M. Scherer, *The Link Between Gross Profitability and Pharmaceutical R&D Spendings*, 20 HEALTH AFF. 216 (2001).

²² See Richard D. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783 (1987).

²³ Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGMT. SCI. 173 (1986). Edwin Mansfield surveyed the chief research officers of 100 U.S. corporations and found that 60 percent of the innovations commercialized in 1981–1983 by the pharmaceutical firms would not have been developed without patent protection. His findings are consistent with more recent studies. See Levin et al., above n. 22; Wes Cohen et al., *Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector*, Carnegie-Mellon University Working Paper (1997).

²⁴ In the Levin study, only 3 of 130 industries studied had a higher score than drugs (6.5 out of 7) on the importance of product patents. Conversely, computers and semiconductors had scores of 3.4 and 4.5 respectively on the importance of patents. See the comparative analysis of their computer file containing industry aggregates presented in F.M. SCHERER, *INDUSTRY STRUCTURE, STRATEGY AND PUBLIC POLICY* 361–362 (Harper Collins 1996).

investment periods are larger than average in pharmaceuticals while imitation costs are lower than in other high-technology industries.

The importance of patent protection in pharmaceuticals is further supported by comparing innovative performance of the pharmaceutical industries in countries with and without strong patent protection. In another study, I found that strong systems of patent protection exist in all countries with strong innovative industries in pharmaceuticals.²⁵ This is a major finding from analyzing the distribution of important new global drug introductions categorized by the nationality of the originating firms for the period 1970 to 1985. Similarly, longitudinal studies on the growth of R&D expenditures and foreign direct investment in Canada and Japan associated with changes in their patent systems for pharmaceuticals support the significance of intellectual property rights as incentives for innovation.²⁶

3. The Orphan Drug Act of 1983

In this section I review the nature of the Orphan Drug Act (ODA) of 1983 and its impacts on drug development.

3a. Push and pull incentive programs

Given the economics of new drug development, strategies for stimulating R&D on orphan drugs and neglected diseases must work either to lower the costs of development (“push programs”), enhance the expected revenues after market launch (“pull programs”), or utilize a combination of both approaches. In the push category, prominent strategies include R&D cost sharing or subsidy programs, which can be accomplished through tax credits, research grants, and related economic incentives. Another potentially powerful push incentive involves programs designed to accelerate drug development and approval by the FDA and other regulatory bodies.

Pull programs work to increase the size of the benefits to innovators after market launch. Three types of pull programs are important. The first is

²⁵ Henry Grabowski, *Innovation and International Competitiveness in Pharmaceuticals, in EVOLVING TECHNOLOGY AND MARKET STRUCTURE* 167 (Arnold Heertje & Mark Perlman eds., University of Michigan Press 1990). See also Robert E. Evenson & Sunil Kanwar, Does Intellectual Property Protection Spur Technological Change?, Yale Economics Growth Center Discussion Paper No. 831 (2001).

²⁶ B. Pazderka, *Implications of Recent Changes in Pharmaceutical Patent Legislation in Canada, in OECD, DIRECTORATE FOR SCIENCE TECHNOLOGY AND INDUSTRY, ECONOMIC ASPECTS OF BIOTECHNOLOGIES RELATED TO HUMAN HEALTH – PART II: BIOTECHNOLOGY, MEDICAL INNOVATION AND THE ECONOMY: THE KEY RELATIONSHIPS* 159 (1998); Ian Neary, *Japanese Industrial Policy and the Pharmaceutical Industry, in INDUSTRIAL POLICY AND THE PHARMACEUTICAL INDUSTRY* 12 (Adrian Toswe ed., OHE 1995).

guaranteed market exclusivity for undertaking the costs and risks of developing a new medicine. This can be important in the case of medical compounds that have no or little patent protection remaining. It is also relevant to situations where the compound's patent protection is subject to uncertainty. The second pull mechanism is a guaranteed purchase agreement. This is relevant where there are no established markets for new medicines or where the resources to pay for these medicines are far below the cost of developing and producing them. This case is particularly relevant to the problem of drug research for diseases in developing economies, as discussed in the next section.

Another kind of pull program would grant firms a transferable right for developing a socially desirable but unprofitable medicine. For example, the firm could obtain the right to additional exclusivity on a drug compound of its choice in the U.S. market for undertaking development of a drug for diseases of poverty. Under the Food and Drug Administration Modernization Act (FDAMA) of 1997,²⁷ U.S. firms can obtain six months of added market exclusivity on approved medicines in exchange for doing additional clinical investigations to gain FDA approval for pediatric indications. The idea of a transferable or floating exclusivity right is a logical extension of this concept. Alternatively, the right could be structured around priority regulatory review status on a new drug application of the firm's choice. These concepts are explored later in this chapter.

3b. *Characteristics of the Orphan Drug Act*

In the case of the 1983 ODA, the incentives involve both push and pull elements.²⁸ First, the law established a 50-percent tax credit on clinical trials for orphan drug indications undertaken in the United States. Second, this was combined with a clinical research grants program, administered by the FDA, which focused on early clinical development (Phase I and II) and involved grants of between \$150,000 and \$300,000. A third important cost incentive involved providing FDA advice and counseling to sponsors on the characteristics of orphan-drug protocols. As discussed below, many orphan drugs have received priority review and fast-track development status, and FDA approval has been granted based on fewer total clinical subjects than for the average new drug introduction.

The ODA also includes one important pull incentive, which is a guaranteed seven-year market exclusivity period.²⁹ The FDA has characterized this as the most sought-after incentive. While this exclusivity runs concurrently with the regular patent term, it was a critical factor to many biotechnology drugs. Many of the original biotechnology compounds were natural substances that were not eligible

²⁷ Food and Drug Modernization Act of 1997, Pub. L. 105-115, 111 Stat. 2296 (1997) [hereinafter FDAMA].

²⁸ Sheila R. Schulman et al., *Implementation of the Orphan Drug Act: 1983-1992*, 47 *FOOD & DRUG L.J.* 363 (1992).

²⁹ *Id.*

for patents on the molecule itself. Several of these drugs also were targeted to diseases of low prevalence. Given the uncertainty that surrounded biotechnology patents during this period, the seven-year exclusivity period was an important market incentive to many biopharmaceutical firms.³⁰ This period of exclusivity was also important in the case of some older chemical entities that were found to be useful for orphan drug indications. In this regard, the first approved therapy for AIDS in 1987, Zovirax (AZT), was a compound that had previously been investigated as a cancer therapy in the 1960s. It received orphan drug status as well as a use patent.³¹

Orphan drug legislation was also enacted in Japan in 1993 and the European Union in 1999. These laws incorporate many of the push and pull incentives incorporated into the United States law.³² Since the ODA has been in effect much longer than the corresponding acts in Japan and Europe, the focus of my analysis in this paper will be on the U.S. case.

3c. Orphan drug designation and approvals

The FDA concludes that the “ODA has been very successful – more than 200 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to the market.”³³ While a simple pre-ODA and post-ODA time series analysis does not prove causation, the more than tenfold increase in the rate of orphan drug approvals since 1983 is indicative that the Act has indeed been a powerful stimulus to increased R&D investment on rare illnesses.

As of May 2003, the FDA had granted 1,238 orphan drug designations to drug firms and organizations developing medicines for rare illnesses.³⁴ Furthermore, 238 of these orphan-designated drugs have received marketing approval.³⁵ Figure 2 shows the annual number of orphan drug approvals for the period 1983–2002.³⁶ Almost half (46 percent) of all orphan drug approvals were for new drug molecular entities or new biopharmaceuticals. The data in Figure 2 also imply that a large number of previously approved drugs received approval for orphan drug indications. There has been a tendency for the number of orphan drug approvals to decline in the last three years. This decline mirrors a similar decrease in new approved drug applications for pharmaceuticals since 2000. However the number of new orphan drug designations has remained relatively stable.

³⁰ Sheila R. Schulman & Michael Manocchia, *The U.S. Orphan Drug Programme 1983–1995*, 12 PHARMACOECONOMICS 313 (1997).

³¹ Willis Emmons & Ashok Nimgade, *Burroughs Wellcome and AZT*, Case 9–792–004, Harvard Business School (1991).

³² For a discussion of the specific features of each country’s law, see Hannah E. Kettler, *Narrowing the Gap Between Provision and Need for Medicines in Developing Countries* (Office of Health Economics 2000).

³³ www.fda.gov/orphan/history.htm.

³⁴ www.fda.gov/orphan/designat/allap.rtf. ³⁵ *Id.* ³⁶ *See id.*

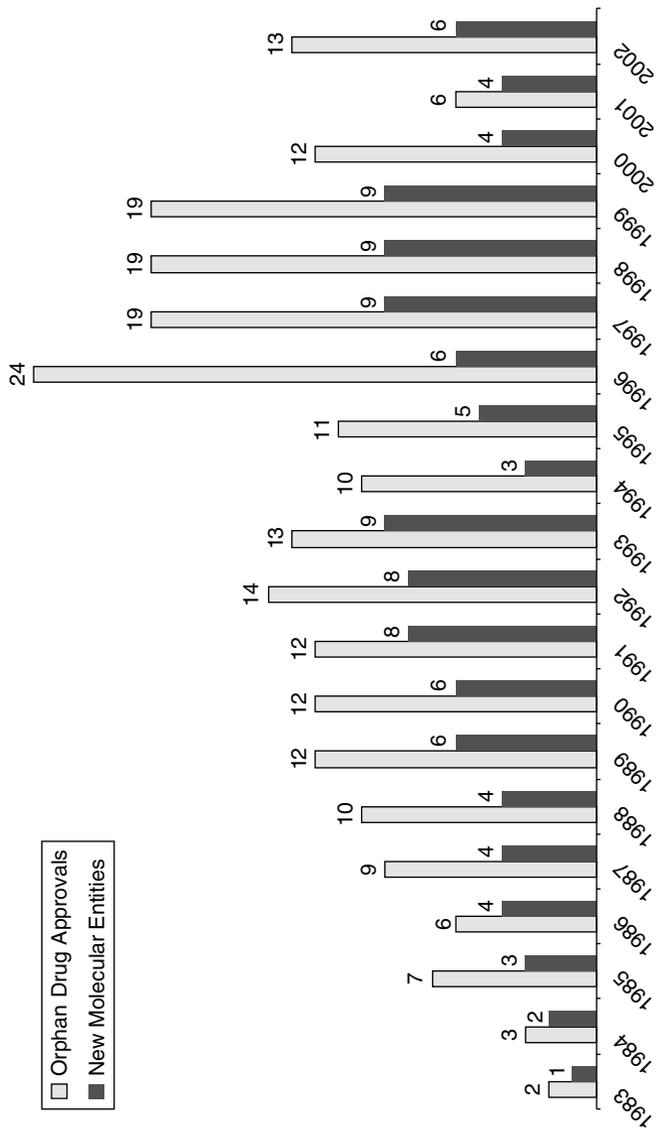


Figure 2. Orphan Drug Approvals, 1983–2002

3d. *Costs of orphan drugs*

A 1993 study of the pharmaceutical industry by the Office of Technology Assessment (OTA) noted that the economics of orphan drug development and approvals may be different from that applicable to other new drug candidates. "These products (orphan drugs) may have a different cost structure from other New Chemical Entities (NCEs), not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs."³⁷ Available data sources for the number of subjects enrolled in trials and subsequent market sales suggest that the R&D cost structure for orphan drugs is indeed different from that of other NCE introductions.

In addition to protocol assistance from the FDA, many orphan drugs are also eligible for other FDA programs instituted in the 1980s and 1990s.³⁸ These include priority review, accelerated approval, and fast-track status. Under priority review, the FDA goal is to review new drug and biologics applications in six months or less. Priority review is reserved for new drugs that provide a significant improvement in safety or effectiveness. Most orphan drugs qualify for priority review. Accelerated approval was instituted in 1992 to speed the approval of new treatments for serious or life-threatening diseases. It allows approval to be granted at the earliest phase of development at which safety and efficacy can be reasonably established. This is often done on the basis of a single Phase II trial involving hundreds rather than thousands of patients.

The FDA's fast-track program was established under the FDAMA.³⁹ It consolidated and expanded the FDA's expedited development and accelerated approval regulations to allow for fast-track designation for drugs with the potential to address unmet medical needs for serious or life-threatening conditions. Fast-track development programs can take advantage of accelerated approval based on surrogate end points, rolling submissions of applications for marketing approval and priority review. A study by Tufts University's Center for the Study of Drug Development found that three years after the program was initiated, half of the 65 fast-track designated products in their analysis also had orphan designations.⁴⁰

An analysis of orphan drug designations in the early 1990s found that nearly half of all orphan drugs up to that time were concentrated in three broad

³⁷ See, e.g., OFFICE OF TECHNOLOGY ASSESSMENT, PHARMACEUTICAL R&D: COSTS, RISKS, AND REWARDS 71 (U.S. Gov't Printing Office 1993).

³⁸ Sheila R. Schulman & Jeffrey Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503 (1995); Christopher Paul Milne, *Fast Track Designation Under the Food and Drug Modernization Act: The Industry Experience*, 35 DRUG INFO. J. 71 (2001).

³⁹ See FDAMA, above n. 27.

⁴⁰ FDA's Fast Track Program Results in 62% Approval Rate After First 3 Years, Tufts Center for the Study of Drug Development Impact Report vol. 3, No. 1 (Jan./Feb. 2001).

therapeutic areas – cancer, AIDS and genetic diseases.⁴¹ These are generally life-threatening diseases of high unmet medical needs. To the extent that orphan drugs continue to be directed to therapeutic areas with these characteristics, they would become eligible for the FDA's accelerated approval and priority review and fast-track programs. Even if orphan drugs are not formally enrolled in these programs, those compounds that address high unmet medical needs could expect to undergo an accelerated development process, given that the FDA is charged with facilitating orphan drug approvals under ODA. Moreover, because orphan drugs are targeted to rare diseases and illnesses, it may be infeasible to enroll large numbers of patients in clinical trials in most instances.

Janice Reichert has examined the total number of subjects enrolled in trials for 12 new biopharmaceuticals that received FDA approval in the period 1994 to 2000.⁴² The sample included seven orphan designated entities. She found that biopharmaceuticals as a group have a significantly lower number of clinical subjects than new drug entities. However, the biopharmaceuticals approved for orphan designated indications had a much smaller number of subjects than the non-orphans. In particular, the mean number of subjects for the seven orphan designated compounds was 576. The average non-orphan biopharmaceutical in her sample had three times as many participants in the trials.

Some data assembled from 1999 FDA marketing approval letters by T. Balasubramaniam are also consistent with the view that the total number of subjects for orphan drug approvals is much smaller than the average for all drugs. In particular, he found that the seven orphan drug marketing approvals in 1999 had a mean sample of 588 patients, with a range of between 152 and 1281 total patients.⁴³ This compares with an average of more than 5,000 subjects for the typical new drug introduction in the late 1990s.⁴⁴

⁴¹ Schulman et al., above n. 28.

⁴² Janice M. Reichert, *Clinical Development of Therapeutic Medicines: A Biopharmaceutical Versus Pharmaceutical Product Comparison*, 35 *DRUG INFO. J.* 337 (2001).

⁴³ James Love, *What Do U.S. IRS Tax Returns Tell Us About R&D Investment?*, Consumer Project on Technology Presentation (16 Jan. 2003) (citing data and analysis provided by T. Balasubramaniam), available at www.cptech.org. Love also concludes that orphan drug costs are much lower based on aggregate IRS Form 8820 filings for the orphan drug tax credit. While these data are also supportive of OTA's hypothesis, it is important to note they understate firm R&D expenditures on a number of grounds. First, an analysis of FDA data for orphan compounds indicates that many firms file for orphan drug designation within a year before receiving marketing approvals. This would make most or all of their clinical expenditures ineligible for the credit. In addition, more than half of the orphan drug marketing approvals are for drugs already approved for non-market indications. Supplemental drug approvals would be expected to have significantly lower costs than those of new drug introductions. Finally, foreign clinical trials are not eligible for the credit unless they receive an exception based on insufficient subjects in the United States.

⁴⁴ Data collected by Parexel for a large number of molecular entities approved in the period 1998 to 2000 found that the mean number of patients per new drug approval (NDA) was over 5,000. See PAREXEL, *PHARMACEUTICAL R&D STATISTICAL SOURCEBOOK* (2001).

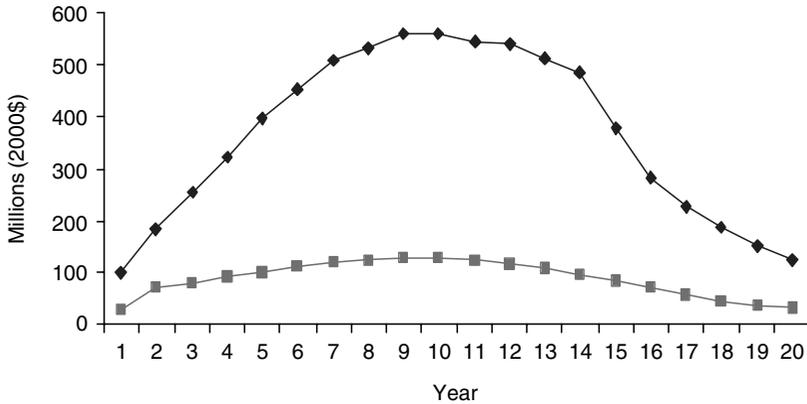


Figure 3. Average Sales of 1990–94 Orphan vs. Non-Orphan New Drug Introductions

3e. Revenues from marketed orphan drugs

In Figure 3, I have plotted sales life cycle profiles for new orphan and non-orphan drug introductions in the 1990–1994 cohort.⁴⁵ As one can see from this figure, the sales peak for the average orphan drug is in the neighborhood of \$100 million compared with \$500 million for the mean, non-orphan new drug introduction. While this is a large difference, it is important to keep in mind that sales of the average pharmaceutical are strongly influenced by a few high-volume compounds. In fact, the distribution of sales for orphan drugs is even more skewed than is that for non-orphan compounds.

Figure 4 shows the distribution of tenth-year sales for 1990–94 new orphan drug introductions.⁴⁶ There were 27 new orphan drugs launched in this period. The top quintile earned over \$500 million in its tenth year on the market (which corresponds to the peak year for most orphan drugs). By contrast, the median quintile had tenth-year sales of only \$29.5 million, and most of the drugs in the lower two quintiles had tenth-year sales of less than \$10 million. Clearly, there is tremendous heterogeneity in the sales of orphan drugs. Most of these compounds have modest sales, but there are a few “wealthy orphans.” The latter consist of some very expensive biopharmaceuticals that have revenues comparable to the pharmaceutical and biological products in the top-selling decile.⁴⁷

The sales data in Figures 3 and 4 are strongly supportive of the conjecture of the Office of Technology Assessment that the R&D cost structure of orphan drugs is very different in nature from that of other drugs.⁴⁸ Even allowing for the possibility of a 50-percent tax credit, the sales of most orphan drugs would not support large-scale clinical trials involving several thousand patients, which

⁴⁵ Grabowski et al., above n. 7. ⁴⁶ *Id.*

⁴⁷ See Grabowski & Vernon, above n. 19, at 25.

⁴⁸ See OFFICE OF TECHNOLOGY ASSESSMENT, above n. 37.

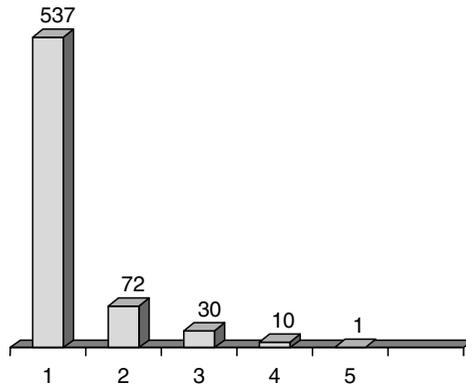


Figure 4. Distribution of 1990–94 Drug Sales by Quintiles

can cost hundreds of millions of dollars for the typical new drug approval. Based on available information on orphan-product sales and the number of subjects listed in the available new drug application (NDA) approval letters, it is reasonable to conclude that the representative orphan drug has R&D costs that are significantly lower than non-orphan compounds.

Clearly, FDA actions and programs under the ODA have been a major factor in the rapid growth in the number of drugs targeted to diseases of low prevalence. The application of the R&D tax credit has also significantly reduced the net costs for many orphan compounds, especially those of smaller biopharmaceutical firms. Finally, the exclusivity provision has also been critical for many compounds with expired or weaker patent protection.

3f. *Health benefits of orphan drugs*

In a recent paper, two authors investigated the health benefits to individuals suffering from rare illnesses in both the pre-ODA and the post-ODA periods.⁴⁹ For this purpose, they employed data on disease prevalence, prescription drug consumption, and longevity by three-digit ICD-9 disease codes in 1979 and 1998.⁵⁰ The measure of longevity used in their analysis is the percentage of individuals dying young, defined as dying before age 55.

⁴⁹ Frank R. Lichtenberg & Joel Waldfoegel, *Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act*, National Bureau of Economic Research Working Paper 9750 (June 2003).

⁵⁰ ICD-9 disease codes are a standard method to classify medical conditions for mortality data in death certificates. The related ICD-9-CMs are used to code morbidity data in inpatient and outpatient medical records. For more information, see the National Center for Health Statistics, *The International Classification of Diseases, Ninth Revision (1996)*, available at www.cdc.gov/NCHS/icd9.htm.

Table 1 *FDA Approved Orphan Drugs for Neglected Diseases*

Disease	Drug	Sponsor	Designation Date	Approval Date
Malaria	Halofentrine	SKB	Nov. 1991	July 1992
	MefloquineHCL	HL Roche	April 1988	May 1989
Leishmaniasis	Liposomal AmphotericinB	Fujisawa	Dec. 1996	Aug. 1997
Meningitis	Cytarabine liposomal	DepoTech	June 1993	April 1999
	Liposomal AmphotericinB	Fujisawa	Dec. 1996	Aug. 1997
Tuberculosis	Aminosalicyclic Acid	Jacobus Pharm Co	Feb. 1992	June 1994
	Rifampin	HMR	Dec. 1985	May 1989
	R, I, P	HMR	Dec. 1985	May 1994
	Rifapentine	HRM	June 1995	June 1998
Trypanosoma	Eflornithine HCL	HMR	April 1986	Nov. 1990
Leprosy	Clofazimine	Novartis	June 1984	Dec. 1986
	Thalidomide	Celgene	Jul 1995	July 1998

Source: FDA, Office of Orphan Products Development, website (<http://www.fda.gov/orphan>), 1 July 2003; Kettler (2000), above n. 32, pp. 44–45

The analysts found that the percentage of individuals dying young from relatively rare illnesses (conditions existing for diseases at the 25th prevalence percentile) fell from 22 percent in 1979 to 16 percent in 1998, or six full percentage points.⁵¹ By contrast, the percentage of individuals dying young from more common disease conditions (i.e., those in the 75th prevalence percentile) had fallen only two percentage points, from 13 to 11 percent over the same period. Moreover, the greatest percentage decline in individuals dying young occurred for disease categories in which there were greater availability and consumption of orphan drugs. This indicates that the availability of novel therapies for rare diseases had a statistically significant effect on the longevity of people suffering from these conditions.

That analysis provides evidence that the aggregate health effects of ODA for individuals suffering from rare diseases have been positive. Their analysis is

⁵¹ Lichtenberg & Waldfoegel, above n. 49.

also consistent with the fact that a large number of new molecular entities in the orphan drug category have been given priority ratings by the FDA (indicating they are significant advances over available therapies.)⁵² Clearly, the Orphan Drug Act has been successful in encouraging many new therapies for rare diseases and illnesses that have provided significant health benefits to patients in terms of both quality of life and longevity.

3g. *The ODA and new drugs for the neglected diseases of poor countries*

There have been relatively few drugs developed under the ODA for tropical diseases and other neglected diseases of poor countries. As of July 2003, there were only twelve orphan drug approvals in the United States targeted specifically at tropical diseases, as shown in Table 1.⁵³ This group represents approximately five percent of the 238 market approvals for orphan designated indications. Moreover, most of these drugs are for conditions that either have some market in the developed countries or in the travelers' market (tuberculosis, malaria and meningitis) or have other approved indications with a market in developed economies.

Diseases that predominately affect poor countries are technically eligible for all the incentives of the ODA, given their low prevalence in the United States. However, there is a lack of market pull incentives in poor countries corresponding to the prevailing insurance reimbursement available in developed economies. In the case of the U.S. health system, most orphan drugs, once they receive FDA approval, are reimbursed by insurance companies as well as by the Medicare and Medicaid programs.⁵⁴

The primary barrier to R&D investment in neglected diseases of poor countries is the low ability to pay in developing countries.⁵⁵ Many of these countries devote as little as \$2 per capita per year to health care, reflecting their low GDP per capita.⁵⁶ Furthermore, there has been a reluctance of developed countries to

⁵² See, e.g., CDER Report to the Nation for the years 2000 to 2003, at www.fda.gov/cder/reports. For earlier years, the March edition of *Pharmacy Times* gives a list of all new molecular entities' approvals for the prior year with their FDA ratings.

⁵³ AIDS-related drugs are excluded from this table. The sources for Table 1 are FDA, Office of Orphan Products Development, website: <http://www.fda.gov/orphan> (last visited 1 July 2003), and H. Kettler, above n. 32, at 44–45.

⁵⁴ Even in the case of very expensive orphan medicines, such as Ceredase for Gaucher's Disease, which can cost more than \$100,000 per year for the initial treatment, this drug was covered by Medicare, Medicaid and private insurance companies. In addition, Genzyme provided the drug free to approximately five percent of patients without insurance. See Genzyme Corporation: Strategic Challenges with Ceredase, Harvard Business School Case 9–793–120 (17 May 1994). See also Christopher-Paul Milne, *Orphan Products – Pain Relief for Clinical Development Headaches*, NATURE BIOTECHNOLOGY, 20 Aug. 2002, at 780.

⁵⁵ See Kremer, above n. 6; Lanjouw, above n. 6. ⁵⁶ See WHO, above n. 4.

come to their aid for health care, at least until recently. The ability-to-pay barrier is compounded by other barriers, including the lack of patent protection in many developing countries as well as an inadequate medical and political infrastructure to insure efficient and timely delivery of prescription drugs.⁵⁷

Some drugs targeted to neglected diseases have been developed under the philanthropic programs of major pharmaceutical firms. The most notable of these programs is Merck's donation of the drug Mectizan (ivermectin) for river blindness. Merck has provided medical infrastructure support as well as free medicines for the treatment of this disease since 1987. More than 200 million individuals in 33 countries have been treated for river blindness under Merck's program.⁵⁸ Other important current initiatives include Glaxo SmithKline's drug albendazole for filariasis, and the anti-trachoma program of Pfizer and Novartis' multi-drug regimen for leprosy.⁵⁹ While drug-donation programs have made a strong contribution to eradicating the health threats for many significant diseases of poor countries, the problems are too broad in scope and R&D development costs are too large in scale to rely primarily on philanthropic donations from a handful of private firms and their non-governmental organization (NGO) partners.

A number of public-private partnerships (PPPs) also have emerged in recent years that target the development of new vaccines and medicines for diseases, such as malaria, tuberculosis (TB), and AIDS, that have a high burden in developing countries.⁶⁰ Under these arrangements, non-profit foundations and organizations plan to support many R&D projects at different stages of the development process. They also seek out both public and private institutions as research partners, using a variety of novel contractual relationships. Many of these agreements specify explicit price and volume requirements. For example the International AIDS Vaccine Initiative (IAVI) has provided research grants to support development of an AIDS vaccine targeted to African strains of the disease. The participating firms retain international patent rights to the technology, but must agree to supply any approved vaccines to the public sector in developing countries at reasonable prices and

⁵⁷ Keith E. Maskus, *Ensuring Access to Essential Medicines: Some Economic Considerations*, 20 WIS. INT'L L.J., 563 (2002).

⁵⁸ Private correspondence with Jeff Kempecos and Jeff Sturchio at Merck (on file with the author).

⁵⁹ Discussions with James Russo, Executive Director of the Partnership for Quality Medical Donations, available at www.pmq.org. See also Peter Wehrwein, *Pharmacophilanthropy*, Harvard University (1993), available at http://www.hsph.harvard.edu/review/summer_pharmaco.shtml.

⁶⁰ For an economic analysis of these public-private partnerships, see Hannah Kettler & Adrian Towse, *Public Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty*, Office of Health Economics Report (Dec. 2002).

in sufficient quantities.⁶¹ Similarly, the Global Alliance for TB Development has recently reached a licensing agreement with Chiron for the development of a new TB drug for which no royalties would be earned on sales in less-developed countries.⁶²

At the present time, there is much experimentation with intellectual property rights and contractual terms. It is too soon to evaluate the success or feasibility of the basic financial model of the various partnership programs. Even if these highly targeted programs ultimately prove to be successful, it is still desirable that government bodies also consider a broad-based program of decentralized market incentives for developing treatments of neglected diseases. This task will be important for disease targets that are not part of the targeted donation programs of large multinational firms or the emerging partnerships described above. Furthermore, the targeted PPPs have an ambitious set of goals and may fall short of their funding plans. In any case, targeted PPP programs are likely to benefit from some complementary push and pull side incentives when they enter the later and more expensive part of the development distribution stage.

4. An amended Orphan Drug Act for neglected diseases

As discussed earlier, most of the cost-saving provisions of the ODA already apply to R&D investment for neglected diseases. While the R&D tax credit is specifically designed to cover domestic clinical trials, a firm can obtain the credit for foreign trials if the number of available subjects is too limited in the United States.⁶³ Neglected diseases would also be eligible for clinical research grant programs and priority reviews at the FDA.

It would help enhance these cost-side incentives if a list of designated diseases of high unmet needs in poor countries would automatically qualify for these tax credits and priority review without requiring firms to apply for such coverage. Because grants currently cover only clinical development trials, it would also be beneficial to earmark some grant funds specifically for basic research on these diseases to involve participation of university researchers and smaller biopharmaceutical firms in the discovery phase. This change would be particularly desirable given recent advances in biotechnology genomics and the understanding of the molecular basis of pathogenesis, which has enhanced the

⁶¹ While agreements are tailored to each party, all define reasonable price based on income level of the country and other relevant factors. See www.iavi.org/pdf/ipagreements.pdf.

⁶² See www.tballiance.org; Aimee Dingswell, *Chiron: Parsing the TB Universe*, BIOCENTURY, 4 Feb. 2002.

⁶³ See Chris Milne et al., *Orphan Drug Laws in Europe and the U.S.: Incentives for the Research and Development of Medicines for the Diseases of Poverty*, WHO Commission on Macroeconomics and Health Working Paper No. WG 2:9, at 6 (2002), available at http://www.cmhealth.org/docs/wg2_paper9.pdf.

scientific opportunities for developing significant new vaccines and therapies for many infectious and tropical diseases.⁶⁴

The basic challenge at the present time, however, is to add a significant market-pull incentive for neglected diseases, which can be combined with the R&D cost incentives that are, for the most part, already in place. Again, a key barrier causing low levels of R&D investment in the neglected diseases of poor countries is the lack of sufficient market revenues to undertake the high fixed costs of R&D. The existing R&D cost incentives in the ODA are not sufficient where markets for new drugs are so limited that even subsidized R&D costs cannot be covered.

This new incentive program needs to balance several objectives. First, the market-pull incentive must be large enough to overcome the barrier raised by insufficient market revenues. Second, the medicines should be distributed in poor countries at a price that is consistent with broad access. Third, the programs should be structured in such a manner that they receive support from important constituent groups and funding from policymakers. I next examine three policy options in this regard: transferable patent exclusivity, transferable priority review rights, and purchase funds or guarantees.⁶⁵

4a. Transferable patent exclusivity rights

One idea that has been proposed by Kettler and others is a roaming or transferable patent exclusivity right.⁶⁶ Specifically, companies would be allowed to extend the patent life of a product of their choice for a pre-specified amount of time in high-income markets in exchange for developing and obtaining market approval for a neglected disease in poor countries. The process could work as follows. First, a list of qualifying disease categories would be prepared by a group of experts under the auspices of an international body, such as the WHO or World Bank. This group also would approve applications from companies for special neglected disease designations and possibly also set a price guideline that would facilitate access. When the product is approved by a public-health regulatory body and begins distribution in developing-country markets, the firm would receive the transfer exclusivity rights in the participating developed-country's market.

The program could incorporate a fixed extension period like the six-month exclusivity extension for pediatric indications under FDAMA. This would be the simplest case to administer from a bureaucratic standpoint. It also would

⁶⁴ See, e.g., *MICROBIAL THREATS TO HEALTH: EMERGENCE, DETECTION, AND RESPONSE* 184 (Mark S. Smolinski et al. eds., National Academies Press 2002) (discussing these new technologies); see also World Health Organization, *World Health* (2002), available at www.who.int/genomics.

⁶⁵ For a further discussion of how a modified orphan drug program might affect the R&D effort for specific diseases, see Milne et al., above n. 63.

⁶⁶ See Kettler, above n. 32.

send clear signals to firms on how much benefit they might expect from participation. Alternatively, firms could engage in negotiations on the number of extra months of exclusivity with a government regulatory agency, such as the U.S. Department of Health and Human Services, on a case-by-case basis at the time that the firm receives approval for their R&D program on a neglected disease.

Under the negotiated exclusivity scenario, the length of the extensions in the United States and other countries could be a function of the expected R&D costs and extra returns as well as the expected social value of a new medicine for the designated disease. However, this scenario would open a complex regulatory negotiation process in which all of the key variables would be subject to a high level of uncertainty. This would be especially the case for products at early stages of the R&D processes. Nevertheless, if authorities waited until a drug were successfully developed and much of this uncertainty had been reduced, issues of credibility would arise for the innovating firms. Once the drug was developed, government regulators would have a strong incentive to minimize the added exclusivity time in order to keep the costs of the program low. For these reasons, time period fixed up front, with a possible market cap on additional earnings, would appear to be a more feasible approach than a negotiated exclusivity approach.

Using the experience with the pediatrics exclusivity program as a guide, transferable exclusivity would likely become a powerful incentive program for increased R&D investment on diseases of poverty.⁶⁷ A major disadvantage with this proposal, however, is that the cost burden would be borne by consumers and payers of the drug granted the extended exclusivity. Given current concerns about escalating health care and prescription drug expenditures in the United States and other sponsoring countries, the proposal would likely face stiff opposition from insurance payers and patient groups. Indeed, recent proposed legislation on prescription drugs in the United States actually has moved in a different direction. In the Medicare Prescription Drug Improvement and Modernization Act of 2003, Congress has included various provisions to facilitate generic competition, and there are a number of federal and state legislators now pushing for drug importation as a cost containment measure.⁶⁸ Hence, the prospects for legislative passage of a proposal increasing the market exclusivity of existing patented drugs, even for such a worthy cause as more R&D for neglected diseases, would not appear to be great at the present time.

⁶⁷ According to PhRMA, in the four years from 1997 to 2001, pharmaceutical companies had launched 400 pediatric studies for about 200 drugs that were eligible for the six-month exclusivity. PhRMA, *Pharmaceutical Industry Profile 2002*, at 17 (PhRMA 2002).

⁶⁸ Medicare Prescription Drug Improvement and Modernization Act, Pl. 108–173 (2003). See Wendy Schacht & John Thomas, *The Hatch Waxman Act: Proposed Legislation Affecting Pharmaceutical Prices*, Congressional Research Services Issue Brief for Congress, IB10105 (5 Jan. 2004). For a discussion of the drug importation provision proposed by the House in July 2003, see *Would Prescription Drug Importation Reduce U.S. Drug Spending?*, Congressional Budget Office Economic and Budget Issue Brief (29 Apr. 2004). See also Ceci Connolly, *Drug Reimportation Plan Saves City \$2.5 Million*, WASH. POST, 15 July 2004, at A03.

4b. Transferable priority review rights

An alternative to the transferable exclusivity proposal would be a transferable right of priority review by the regulatory authorities. If a firm had the option to elect priority review for one of its products designated for standard review by the FDA, this could also be a powerful incentive to undertake an R&D investment program on diseases affecting poor countries. Currently, the average time to review a non-priority new drug application by the FDA is 18 months. On the other hand, priority drugs take an average of around six months. Using the findings from my analysis of returns on pharmaceutical R&D for drugs introduced between 1990 and 1994, a reduction of one year in FDA review time would be worth approximately \$300 million in increased present value for the average product in the top decile of compounds and more than \$100 million for a product in the second decile.⁶⁹

A potential problem with transferable priority review rights is that they could slow down the approval of other drugs in the United States, which are addressed to equally deserving or even more pressing needs. Like all government agencies, the FDA operates under budgeting and manpower constraints. The program should be configured to avoid such adverse consequences. In particular, the transferable priority review drugs could be put in a new review category and allocated resources from a separate budget funded by general revenues or new user fees.

The overall costs to society to fund a program of transferable priority review rights in exchange for firms developing new therapies for neglected diseases are likely to be much smaller than a transferable exclusivity rights program. Moreover, priority review rights are likely to be more valuable to smaller biotech firms that have no established products, but expect to launch new medicines in the near future. Finally, a government incentive program where the costs basically would be incurred to get drugs on the market sooner in both developed and developing countries is likely to be more acceptable politically than an incentive program that delayed patent expiration and generic entry for leading drug products.

4c. Purchase guarantees

Another pull mechanism that has been discussed extensively in the recent literature is the establishment of funds to purchase a pre-specified amount of new vaccine or drug that meets a given therapeutic profile for a neglected disease.⁷⁰ The idea is to overcome the ability-to-pay barrier to R&D investment

⁶⁹ Grabowski et al., above n. 7.

⁷⁰ See, e.g., Michael Kremer & Jeffrey Sachs, *A Cure for Indifference*, THE FINANCIAL TIMES, 5 May 1999, at 14.

by committing in advance to a level of market purchases that would allow a reasonable return on expected R&D outlays to firms that successfully developed new products. Products that exceed the established profile in terms of efficacy could be given a bonus payment. Compared to extended exclusivity or transferable priority review rights, purchase funds are a more novel approach without any real precedent in providing incentives for pharmaceutical R&D funding.

The purchase fund policy option has been elaborated in most detailed form by Michael Kremer in the context of the development of vaccines for the diseases of malaria, tuberculosis and HIV-AIDS.⁷¹ Under this proposal, a sizeable fund, on the order of \$250 to \$500 million or more, would be established to purchase the new vaccines. Candidate vaccines would need to be approved by a regulatory agency, such as the FDA. They would be distributed at a low, affordable cost in eligible countries. Distribution would, however, be subject to a modest co-payment to insure that vaccines met a market test in terms of acceptability. In this way, the access issue would be addressed. Intellectual property rights would also be protected since the commitment would be to purchase only from original producers and licensees. Government purchasers in the developing countries would also have incentives to adhere to intellectual property rights in order to receive the highly subsidized price that came with participation in the program.

While purchase funds have a number of attractive features on economic grounds, there are also some basic problems that would need to be overcome. Foremost is the issue of credibility. As discussed earlier, pharmaceutical R&D typically spans a period of ten years or so. It can take another decade or more for firms to recoup the R&D costs and earn a competitive rate of return on this investment. Given the long time spans, firms would be concerned that the funding agencies either would renege or be unable to deliver on their commitments once a drug was successfully developed and approved. The leaders and priorities of governments and donor groups are subject to substantial changes over a 20-year period. Given that future government politicians and purchasers would have a strong incentive to try to obtain medicines as cheaply as possible once they became available, a creditable long-term purchase commitment is absolutely essential for this incentive program to work. Kremer has presented some ideas and options for enhancing credibility in the context of vaccine purchases for AIDS and malaria.⁷²

Kremer, using information from industry analysts, estimates that a \$250 to \$500 million real annual market would be required to motivate substantial research for new vaccines in these disease areas.⁷³ In fact, this number seems

⁷¹ Michael Kremer, *Creating Markets for New Vaccines – Part I: Rationale, and Part II: Design Issues*, in *INNOVATION POLICY AND THE ECONOMY* (Adam B. Jaffe et al. eds., 2001).

⁷² *Id.* ⁷³ See Kremer, above n. 6, at 85.

low unless R&D costs can also be kept below average for the industry through use of orphan-drug tax credits, fast-track approval, and other means discussed above. At the same time, the high social value that would be associated with a vaccine against AIDS, malaria, or TB implies that a purchase fund of considerably larger size would still be an extremely cost-effective investment if it resulted in an effective vaccine against these diseases.

In the United States, Senators Frist and Kerry and Representatives Palosi and Dunn have advocated a tax credit on the sales of vaccines for AIDS, tuberculosis, and malaria to non-profit and international organizations serving developing countries.⁷⁴ Each dollar of sales would be matched by a dollar of tax credit. This would be a market-pull mechanism corresponding in spirit to the purchase fund concept. A similar measure was endorsed by the Clinton Administration in its fiscal year 2001 budget, but was not passed by Congress.⁷⁵

The purchase fund approach would seem best suited, at least initially, to high profile diseases, such as AIDS, malaria and TB, with the largest disease burden in developing countries. These are diseases for which policymakers in developed countries and international donor organizations may be able to raise substantial earmarked funds. If so, purchase funds could be a natural complement to an expanded orphan drug program along the lines discussed. For example, an amended ODA that includes a transferable right of priority review would be a significant pull incentive applicable to all neglected diseases. Purchase funds then could be an option for certain diseases of high visibility and burden. Since pull programs do not become effective until a firm actually meets the requirements set out for the neglected disease, successful enterprises could choose between a purchase fund and transferable priority review if both options were available. Alternatively, policymakers could stipulate that certain high profile diseases with large purchase funds would not be eligible for transferable rights of priority review, but the diseases without designated purchase funds would have such option rights.

5. Summary and conclusions

The U.S. Orphan Drug Act has been a great success in encouraging the development of new drugs for rare diseases. Unfortunately, while new medicines for the neglected diseases of poverty are technically eligible for the incentives embodied in the Act, less than five percent of the orphan drug marketing approvals have been for such indications. The basic problem is insufficient expected revenues associated with the low ability to pay for health care in poor countries, coupled with the high fixed costs of R&D. In developed countries, orphan drugs are typically covered under national and employer

⁷⁴ The Vaccines for the New Millennium Act, HR 1504, 107th Cong. (2001).

⁷⁵ See Kremer, above n. 6, at 85.

health insurance plans, so this barrier has been surmounted in many cases, given the other incentives incorporated in the Orphan Drug Act: tax credits and grants, FDA accelerated review programs, and market exclusivity.

The focus of this chapter is to suggest means for extending the Orphan Drug Act to include a strong market-pull mechanism applicable to neglected diseases in poor countries. Prior authors have focused on transferable or roaming exclusivity rights and purchase funds as incentive mechanisms. In this chapter, the concept of a transferable right of priority review was developed as an alternative to transferable exclusivity rights. Transferable rights of priority review have advantages as a decentralized market incentive mechanism. In particular, they are likely to be more cost-effective and acceptable politically compared to transferable exclusivity incentive programs. Furthermore, they could be designed to complement government and private donor purchase funds targeted to specific conditions with high disease burdens, such as malaria and tuberculosis.