

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

Edited by

KEITH E. MASKUS

AND JEROME H. REICHMAN



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INTERNATIONAL PUBLIC GOODS AND
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PROPERTY REGIME

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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PREFACE

In recent years the world has moved sharply toward successive strengthening – and harmonization – of intellectual property protection. There has emerged, at an unprecedented level, both a globalized regime of private rights in information and new foundations for a basic international system of innovation. This new system will have profound implications for the nature of such processes as innovation, technology transfer, market competition, and economic development. It also raises essential and sometimes disturbing questions about potential impacts on the ability of governments to provide critical public goods, both within and across countries. Such goods include public health, nutrition, education, environmental protection, cultural identity, and other elements of social importance that must rely increasingly on the exercise of private rights over technical inputs.

It is possible that the globalized intellectual property regime will improve markets for trading information internationally by encouraging invention and resolving inherent failures in technology transactions. It is also conceivable that the system will throw up high roadblocks in the path of follow-on innovation, competition, and the attainment of public goods. These questions are deep and complex and require sustained analysis.

The clear difficulties of this task constitute one of the main reasons that the editors of this volume decided to organize the Conference on International Public Goods and Transfer of Technology under a Globalized Intellectual Property Regime in April 2003 at Duke University.¹ This was a major attempt to subject the complex conceptual foundations of the changing worldwide intellectual property regime to systematic legal and economic analysis.

The conference brought together a distinguished group of economists, political scientists, and legal experts to assess the public processes and inputs they deemed likely to become indispensable in a transnational system of innovation that, while still dependent on territorial law, must aim to promote technical progress, economic growth and welfare for all participants. The

¹ Conference on International Public Goods and Transfer of Technology under a Globalized Intellectual Property Regime, held at Duke University School of Law, Durham, North Carolina on 24–26 April 2003. Oral presentations are available at: <http://www.law.duke.edu/trips/webcast.html>.

contributors were also urged to think broadly and to propose means to minimize the social costs and enhance the benefits that might ensue from the TRIPS Agreement and related standard-setting initiatives by deliberately taking into account the promotion of public goods.

Their responses constitute the contributions to this volume. They have been organized under four major rubrics. Part I is entitled “International Provision of Public Goods under a Globalized Intellectual Property Regime.” In the first section of this part, framework papers and associated commentaries analyze the concept of public goods in the expanding knowledge economy. A second section turns directly to issues of preserving the public commons in the areas of science, access to information, and agricultural technologies.

Part II of the volume addresses the general theme of “Innovation and Technology Transfer in a Protectionist Environment.” In the first section of this part, framework papers focus on obstacles to the transfer of technology under international intellectual property standards and the impacts of those standards on the means of information transfer. Additional analysis focuses on implications of stronger private rights in information for moving technology into the public domain. A second section is aimed at understanding how the new system might affect incentives for local innovation in developing countries and how the system might be improved for that purpose.

Part III, entitled “Sectoral Issues: Essential Medicines and Traditional Knowledge,” first takes on the critical problem of ensuring that access to medicines is not worsened by the international intellectual property system via the exercise of patents and protection of clinical test data. Various contributors offer both positive and negative assessments of the potential for the new regime to improve innovation and distribution of medicines and to meet the needs of poor countries. The second task is to offer comprehensive analysis of basic problems of protecting traditional knowledge in the new environment of globalized intellectual property systems.

The volume turns last, in Part IV, to numerous contributions gathered under the general theme of “Reform and Regulation Issues.” A first section deals with balancing public and private interests in the specific intellectual property regimes, including reforms of the global patent regime. A second section fully explores the role of competition law in a worldwide market for knowledge goods. A final set of papers, dealing with dispute settlement at the WTO and intellectual property rights, emphasizes the need for WTO panels to take public goods into account.

The editors of this volume wish to thank the Rockefeller Foundation, the John D. and Catherine T. MacArthur Foundation, the McGuire Center for International Studies at the University of Colorado, the Center for the Study of the Public Domain at Duke University, and the Center for the Public Domain for their generous support of the conference in April 2003. In organizing the conference and preparing this volume, the editors also received considerable

assistance from a variety of people, including Jennifer Jenkins, Aaron Lang, Heather Ritch, Jeff Wasikowski, Debbie Upchurch, and, especially, Patricia Reichman. We are extremely grateful for their contributions, counsel, and hard work. We also thank Finola O'Sullivan, Jane O'Regan and Anna-Marie Lovett, and others at Cambridge University Press for their advice and patience as we edited the large and diverse set of chapters in this volume.

Finally, we wish to acknowledge the willingness of Cambridge University Press and Oxford University Press to work together on this project. Oxford University Press is the publisher of *Journal of International Economic Law*, whose editor, John Jackson, agreed to publish a selection of the chapters appearing in this volume in the June, 2004 issue (Volume 7, number 2). Early versions of the chapters published in that issue include Maskus and Reichman, "The Globalization of Private Knowledge Goods and the Privatization of Global Public Goods" (pages 279–320); Drahos, "The Regulation of Public Goods" (pages 321–340); Barton, "Issues Posed by a World Patent System" (pages 341–358); Branstetter, "Do Stronger Patents Induce More Local Innovation?" (pages 359–370); Cottier and Panizzon, "Legal Perspectives on Traditional Knowledge: The Case for Intellectual Property Protection" (pages 371–400); Ullrich, "Expansionist Intellectual Property Protection and Reductionist Competition Rules: A TRIPS Perspective" (pages 401–430); Dinwoodie and Cooper Dreyfuss, "WTO Dispute Resolution and the Preservation of the Public Domain of Science under International Law" (pages 431–448); Ethier, "Intellectual Property Rights and Dispute Settlement in the World Trade Organization" (pages 449–458); and Shaffer, "Recognizing Public Goods in WTO Dispute Settlement: Who Participates? Who Decides?" (pages 459–482). Revised and expanded versions of those contributions appear in this volume, and we are deeply grateful to both Presses for permitting us to circulate them as widely as possible.

KEITH E. MASKUS and JEROME H. REICHMAN

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

HENRY GRABOWSKI*

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 - 4a. Transferable patent exclusivity rights
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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

* Henry Grabowski is Professor of Economics, Duke University.

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.*

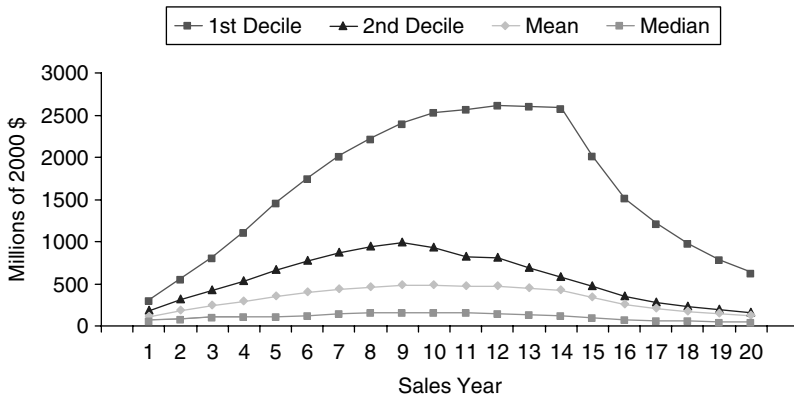


Figure 1. Worldwide Sales Profiles of 1990-94 New Chemical Entities

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.*

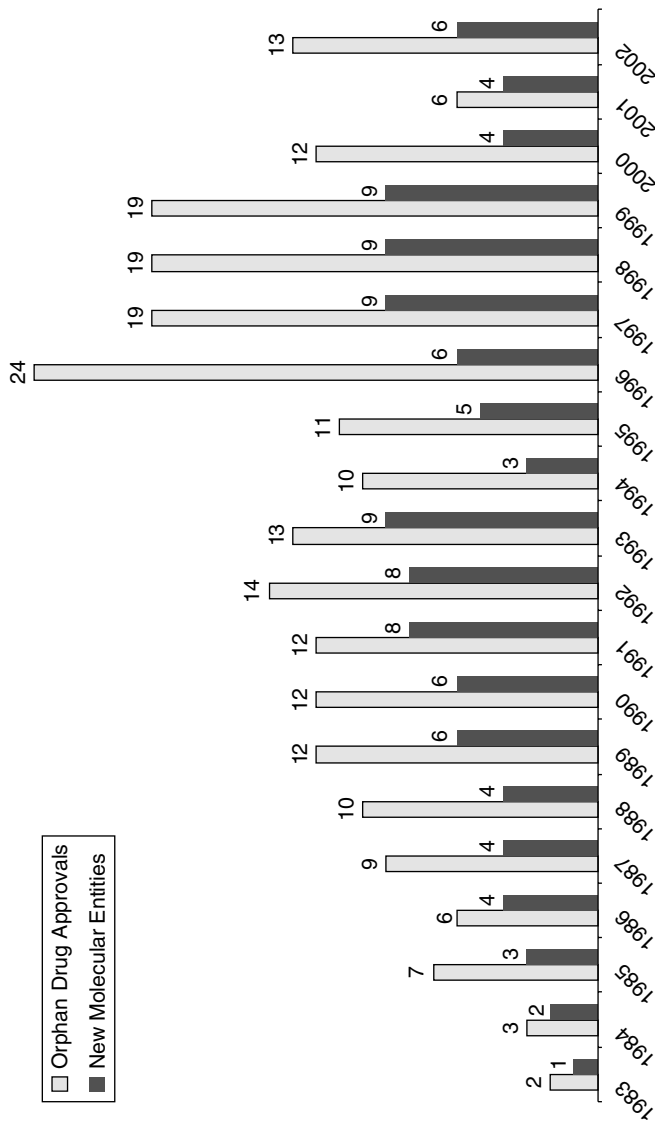


Figure 2. Orphan Drug Approvals, 1983–2002

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).

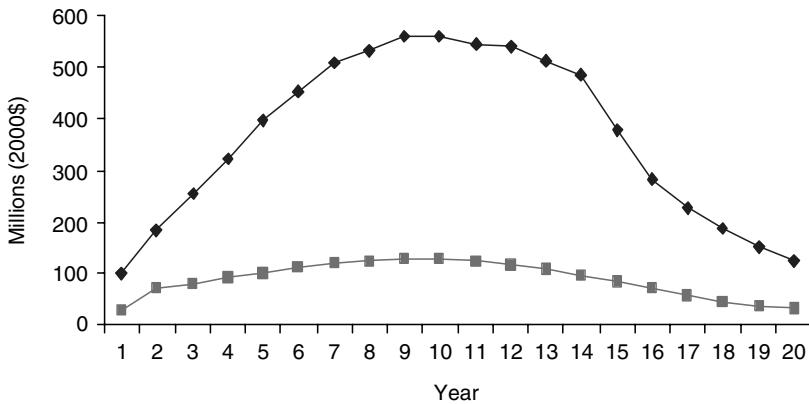


Figure 3. Average Sales of 1990–94 Orphan vs. Non-Orphan New Drug Introductions

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.

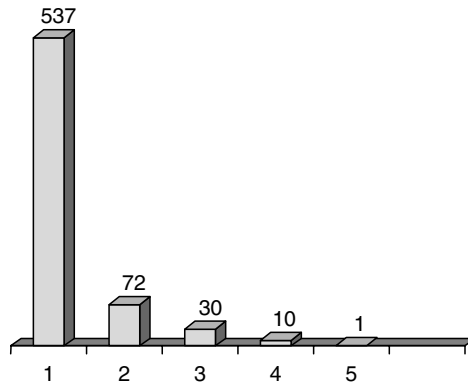


Figure 4. Distribution of 1990–94 Drug Sales by Quintiles

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.

Comment: Access to essential medicines – Promoting human rights over free trade and intellectual property claims

HEINZ KLUG*

1. Introduction

Over the past five years, there has been an intense international debate, negotiations at the World Trade Organization (WTO) and a variety of political and legal struggles in various jurisdictions over access to affordable medicines in developing countries. Until recently, the debate focused on the ability of the existing medical infrastructure to address the HIV/AIDS pandemic; but more recently the focus has shifted to questioning whether the heightened patent protection of the TRIPS Agreement¹ allows countries sufficient flexibility to deal with domestic health crises.² This question has been increasingly driven by the impact of the global HIV/AIDS pandemic and the threat it poses to economic and political stability, particularly in Africa,³ and it has motivated two new WTO agreements – at Doha and just before Cancun – aimed at providing flexibility under the terms of the TRIPS Agreement.⁴ Most recently, the World

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¹ Agreement on Trade-Related Aspects of Intellectual Property Rights, 15 Apr. 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS – RESULTS OF THE URUGUAY ROUND vol. 31, 33 I.L.M. 81 (1994) [hereinafter TRIPS Agreement].

² Carlos Correa, *Implementing the TRIPS Agreement in the Patents Field – Options for Developing Countries*, 1 J. WORLD INTELL. PROP. 75 (1998); C. CORREA, *INTELLECTUAL PROPERTY RIGHTS, THE WTO AND DEVELOPING COUNTRIES: THE TRIPS AGREEMENT AND POLICY OPTIONS* (Zed Books 2000). See also Frederick Abbott, *Managing the Hydra: The Herculean Task of Ensuring Access to Essential Medicines* [this volume].

³ A. De Waal, *Why the HIV/AIDS Pandemic is a Structural Threat to Africa's Governance and Economic Development*, 27 FLETCHER F. OF WORLD AFF. 6 (2003).

⁴ WTO Doha Ministerial Declaration on the TRIPS Agreement and Public Health, WT/MIN(01)/DEC/2 (14 Nov. 2001) [hereinafter Declaration on TRIPS and Public Health]; WTO Council for TRIPS, Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, IP/C/W/405 (30 Aug. 2003) [hereinafter WTO, Implementation of Paragraph 6].

Health Organization (WHO), which has been at the forefront of these negotiations, declared that the “failure to deliver AIDS drugs to impoverished people is so grave that it has become a global health emergency.”⁵ With thousands of people dying each day, the question of access to affordable medicines can no longer be treated as a predominately intellectual property or trade-related issue. Rather, it requires the assertion of a human rights perspective to facilitate access to public goods, particularly when dealing with rights to the knowledge required to produce medicines that combat life-threatening diseases.⁶

Placing public health – in this case the global HIV/AIDS pandemic – at the center of this debate exposes the inherent tensions between the law and policies affecting free trade, intellectual property rights, development, and public health. Instead of debating whether the protection of intellectual property rights (IPRs) will eventually lead to increased innovation and foreign investment in developing countries,⁷ or whether current drug prices are justified by the need for future research and development,⁸ issues which presuppose a hierarchy of values dominated by free trade and IPRs, advocates of a human rights approach insist on the primacy of public health concerns. This position is supported by an approach to interpreting international agreements that takes the broad goals of the post-World War II United Nations system, particularly the emphasis on human rights reflected in the Universal Declaration,⁹ as guiding principles. While this approach does not resolve the real policy debates over economic development, trade and the protection of intellectual property, it does raise questions about the relative importance of the so-called “soft law” set out in the preambles and general principles clauses of relevant treaties as opposed to the so-called “hard law” of specific treaty provisions that purport to

⁵ Press Release, WHO, World Health Organization Says Failure to Deliver AIDS Medicines is a Global Health Emergency: Global AIDS Treatment Emergency Requires Urgent Response – No More Business as Usual (2003), available at <http://www.who.int/mediacentre/releases/2003/pr67/en/print.html> (visited 26 Sept. 2003).

⁶ See I. Kaul & R.U. Mendoza, *Advancing the Concept of Public Goods*, in PROVIDING GLOBAL PUBLIC GOODS: MANAGING GLOBALIZATION 78, 84 (Inge Kaul et al. eds., Oxford 2003).

⁷ Robert Sherwood, *A Larger Context for Considering Pharmaceutical Patents in Developing Countries*, 15 WORLD BULL. 76 (Jan.-Dec. 1999) (Institute of International Legal Studies, University of Philippines Law Center).

⁸ H.E. Bale, *Patent Protection and Pharmaceutical Innovation*, 29 N.Y.U. J. INT’L L. & POL. 95 (1997); International Federation of Pharmaceutical Manufacturers Associations (IFPMA), *TRIPS, Pharmaceuticals and Developing Countries: Implications for Health Care Access, Drug Quality and Drug Development* (2000), available at [http://www.ifpma.org/admin/MediaServer.jsr?@_ID=431&@_MODE=GLB%20\(2000\)](http://www.ifpma.org/admin/MediaServer.jsr?@_ID=431&@_MODE=GLB%20(2000)). See also Henry Grabowski, *Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act* [this volume].

⁹ Universal Declaration of Human Rights, G.A. Res. 217A (III), U.N. GAOR, UN Doc A/810, at 71 (10 Dec. 1948).

guarantee free trade and protect the rights of property claimants against attempts by national governments to address pressing social needs.¹⁰

International law, however, provides no institutional mechanism for resolving these tensions. Instead, this failure in global governance leaves each negotiating or interest community to rely upon its own expertise and assumptions about subject matter and priority to define the parameters of its debate and feasible outcomes. Trade negotiators and their allied professionals, including some economists and trade lawyers, balance and barter concessions – greater IP protection for increased access to agricultural and textile markets¹¹ – while IP lawyers and other economists focus on increasing the likelihood of innovation and foreign investment.¹² While each arena is guided by its own constituting principles, the range of fora provides opportunities for powerful interests to shape the terrain upon which the rules governing particular issues, such as intellectual property, are formed.¹³ However, the emergence of non-government organizations (NGOs) operating within the global system as observers and activists is providing a counter-weight to organized business, particularly in the context of the HIV/AIDS pandemic; NGOs have been campaigning and vocally raising concerns about the impact that policies tailored to suit organized business might have on the health of marginalized populations.¹⁴ Furthermore, so long as the ministries of trade, industry and commerce were the only national authorities conducting the negotiations – whether at the WTO or World Intellectual Property Organization (WIPO) – the relationship between the exploding HIV/AIDS pandemic, access to essential medicines and the developing global trade regime remained in the background.

An effective human rights approach must not, however, be limited to the mere counter-assertion of rights – especially if it takes the form of a simple recitation of the long list of United Nations resolutions or other formal commitments to improving health in general, or even statements and resolutions specifically designed to address the HIV/AIDS pandemic. Rather, it should begin by defining the legal and institutional terrain on which multiple claims, norms and strategic interventions accumulate, with a view to either facilitating or hindering attempts to make public health the first level of concern. Such an approach must also recognize the ways in which different

¹⁰ See generally, Laurence R. Helfer, *Regime Shifting: The TRIPS Agreement and New Dynamics of International Intellectual Property Lawmaking*, 29 YALE J. IN'TL L. 1 (2004).

¹¹ JAYASHREE WATAL, *INTELLECTUAL PROPERTY RIGHTS IN THE WTO AND DEVELOPING COUNTRIES* (Kluwer Law International 2001).

¹² *INTELLECTUAL PROPERTY RIGHTS IN EMERGING MARKETS* (Clarisa Long ed., AEI Press 2000).

¹³ Peter Drahos & John Braithwaite, *INFORMATION FEUDALISM: WHO OWNS THE KNOWLEDGE ECONOMY?* (New Press 2002). See also SUSAN SELL, *PRIVATE POWER, PUBLIC LAW: THE GLOBALIZATION OF INTELLECTUAL PROPERTY RIGHTS* (Cambridge University Press 2003).

¹⁴ See, e.g., Helfer, above n. 10; Abbott, above n. 2.

fora have provided alternative loci for competing normative and strategic interventions. These have ranged from the international to the domestic; from WIPO and the WTO to WHO, UNAIDS and the United Nations Conference on Trade and Development (UNCTAD); and from national trade offices to domestic courts. These fora have been used by all sides: those attempting to protect intellectual property, those working to facilitate the transfer of technology, and those trying to ensure affordable access to essential medicines. Although there have been formal links between some of these fora – with UNCTAD and WHO being invited to attend TRIPS Council meetings on the subject – and even more intensive informal interactions involving negotiators, drug companies, experts and NGOs, so long as these have remained within the rubric of trade negotiations and intellectual property rights, the legal framework has remained dominated by the prerogatives of the WTO agreements.

Focusing on the different sources of law governing human rights, trade, and intellectual property rights, I will argue that, in the debate over access to medicines, there is a need to view the relationship between them in terms of the broader normative goals of the international legal order, rather than simply treating them as bases for contending claims.¹⁵ To do this, it is important to understand the recent and socially-constructed nature of the system of intellectual property rights guaranteed by the TRIPS Agreement and to recognize the implications of characterizing the rules as more or less flexible, or as subject to determination under a particular international or national regime. While much of the excellent academic work on this issue has focused on the construction of the TRIPS Agreement, its implementation, interpretation, or even the growing opposition to it, little attention has been paid to the legal assumptions and implications of the different sources and forms of rights and obligations being deployed by the different participants. Finally, I will focus primarily on the implications of choosing particular legal tools or approaches and the impact these choices have on the question of access to medicines and public health more generally.

2. Public health and access to medicines

Until recently, public health has been understood only in terms of measures that are necessary to prevent large-scale epidemics. This preventive approach is evident in the development of the idea of primary health care which “is a blend of essential health services, personal responsibility for one’s own health and health-promoting action taken by the community.”¹⁶ The most effective means for achieving these goals have been the provision of clean water, good sanitation and more recently, widespread vaccination. While these remain the most

¹⁵ Cf. JOOST PAUWELYN, *CONFLICT OF NORMS IN PUBLIC INTERNATIONAL LAW: HOW WTO LAW RELATES TO OTHER RULES OF INTERNATIONAL LAW* 158–236 (2003).

¹⁶ World Health Organization (WHO), *Concepts of Health Development*, WHO 50TH (1998), at www.who.int/archives/who50/en/concepts.htm.

cost effective and broadly applicable ways to protect public health, the revolution in pharmaceuticals during the twentieth century has blurred the line between treatment and prevention. In the context of the HIV/AIDS pandemic, where prevention on its own has proven extremely difficult, the most effective approach seems to lie in the combination of preventive education, treatment, and the lowering of individuals' viral loads. Effective prevention must include treatment and today, particularly in developing countries, this requires access to affordable medicines, which are now understood to be integral to the achievement of public health goals.

At the beginning of the twentieth century, "aspirin was the only widely available modern medicine,"¹⁷ but by the 1970s modern pharmaceuticals existed for nearly every major illness known to medical science. The problem was clearly one of access. According to Dr. Michael Scholtz, WHO's Executive Director of Health Technology and Pharmaceuticals, "one third of the world's population still lacks access to essential drugs while in the poorest parts of Africa and Asia, over fifty percent of the population do not have regular access to the most vital essential drugs."¹⁸ It was in response to this situation that the idea of identifying a list of essential medicines arose and led to the launch of the WHO's essential medicines program in 1977. The program produced model lists of essential drugs that national governments use to make their own local lists; these lists make the task of providing prescribed medications more manageable by limiting the thousands of available medicines to approximately 200 essential ones.

By the turn of the century, over 160 countries had adopted essential drug lists and clinical treatment guidelines based on the WHO's model lists and selection criteria, which effectively doubled access to essential medicines. The criteria laid out for compiling these lists reflect a synergetic amalgam of public health and human rights concerns, with an emphasis on equal access and medical effectiveness. Drugs chosen for an essential medicines list must "satisfy the health needs of the majority of the population; be available at all times in adequate amounts and appropriate dosage forms; and be available at a price that individuals and the community can afford."¹⁹ When it comes to choosing between different available drugs there are five key criteria: relative efficacy, safety, quality, price and availability. Reliance on these criteria has led to an emphasis on off-patent or generic drugs, which

¹⁷ Dr. M. Scholtz, *International Trade Agreements and Public Health: WHO's Role*, Paper Presented at the Conference on Increasing Access to Essential Drugs in a Globalized Economy, at 1 (Amsterdam, 25–26 Nov. 1999), available at http://www.who.int/medicines/docs/WTO_Public_Health_Amsterdam_MS.html.

¹⁸ *Id.*

¹⁹ World Health Organization, *WHO 50th: Concepts of Health Development* (1998), at www.who.int/archives/who50/en/concepts.htm (last visited 3 Oct. 2003).

still comprise more than 90 percent of the medicines included on the model list.²⁰

While the price of pharmaceuticals varies significantly between different markets,²¹ the cost of most patented medicines remains beyond the reach of the bulk of the population in developing countries. This reality is starkly evident in the case of HIV/AIDS, where the emergence of drug regimes to manage the disease in the mid-1980s created a bifurcated epidemic. Opening the Thirteenth International AIDS Conference in Durban, South African High Court Judge Edwin Cameron claimed to embody “the injustice of AIDS in Africa because, on a continent in which 290 million Africans survive on less than one US dollar a day, I can afford medication costs of about \$400 per month.”²² Accusing manufacturers of imposing prices that made drugs “unaffordably expensive,” Cameron argued that the international patent and trade regime prevents the production and marketing of affordable drugs, despite earlier experience in India, Thailand and Brazil, that demonstrates the feasibility of producing key drugs at costs within reach of the developing world.²³

Still today, despite a dramatic drop in the price of antiretrovirals, victims of the HIV/AIDS pandemic may be divided into those for whom contraction of HIV remains a death sentence and those for whom the disease is a chronic illness they are able to manage. The disparity in access to antiretrovirals that creates this divide is heightened by the lack of generic alternatives, which has fueled the demand for access to medicines in general and generic drugs in particular. Using affordability as one of the relevant criteria, the essential drug program promoted the use of generic drugs, a strategy which allowed the program to both limit costs and reduce conflict with the global patent-based pharmaceutical industry, which opposes generic substitution (particularly for products originating from countries that did not recognize the companies product patents). The inclusion of twelve antiretrovirals on the WHO’s model essential medicines list in 2002²⁴ brought this tension to the fore and

²⁰ World Health Organization, *The Use of Essential Drugs*, Ninth Report of the WHO Expert Committee (including the Tenth Model List of Essential Drugs), Technical Report Series, No. 895 (2000).

²¹ See, e.g., P. Danzon & A. Towse, *Theory and Implementation of Differential Pricing for Pharmaceuticals* [this volume].

²² Justice Edwin Cameron, First Jonathan Mann Memorial Lecture: The Deafening Silence of AIDS, XIIIth International AIDS Conference, Durban, South Africa, 9–14 July 2000, available at <http://www.tac.org.za/newsletter/2000/ns000717.txt>

²³ *Id.*

²⁴ WHO, Department of Essential Medicines, *Updating and Disseminating the WHO Model List of Essential Drugs: The Way Forward*, draft (22 June 2001), available at <http://www.who.int/medicines/organization/par/edl/orgedldev.html>. See also WHO, *Essential Drugs and Medicines Policy Department, WHO Medicines Strategy: 2000–2003*, WHO Policy Perspectives on Medicines, No. 1 (Dec. 2000). Geneva.

made it clear that the program's primary reliance on generics for the effective delivery of affordable drugs was no longer tenable.

Research-oriented pharmaceutical manufacturers are involved in a relatively risky business, in which an average of only one "commercially viable drug emerges from every 4,000 to 10,000 compounds screened in a development process that may involve ten years of testing and clinical trials for efficacy and safety."²⁵ Compounding the high costs of development, however, are the relatively low costs of product imitation – through reverse engineering – and production, which creates what economists refer to as the appropriability problem. Patent law, which aims to reward innovation by providing a limited monopoly to the patent holder, provides intellectual property-intensive industries, such as the pharmaceutical industry, with one means of attaining profitability. But the fruits of medical innovation raise questions that go beyond profitability. As the WHO points out, medicines are "not simply just another commodity," but rather a public good.²⁶

Access to essential drugs, from this perspective, becomes a critical part of the fundamental human right to health.²⁷ While WHO accepts that "patent protection stimulates development of needed new drugs," it argues that "countries must ensure a balance between the interests of the patent holders and the needs of society."²⁸ Advocating that "generic competition should begin promptly upon patent expiration" and that "preferential pricing is necessary for lower-income countries and should be actively pursued,"²⁹ WHO also argues that because the research and development priorities of the pharmaceutical industry do not necessarily respond to the needs of the bulk of the world's population, there should be public involvement to "ensure development of new drugs for certain priority health problems."³⁰ Thus, although WHO does not reject the idea of pharmaceutical patents, its position seems to question the unbridled power of private decision-making in the research effort and to claim some level of exception to the rights of patent holders for essential drugs. This prioritization of health over specific property rights becomes the key to a human rights approach.

²⁵ M. RYAN, *KNOWLEDGE DIPLOMACY: GLOBAL COMPETITION AND THE POLITICS OF INTELLECTUAL PROPERTY* 5 (Brookings Institution 1998). See also Grabowski, above n 8.

²⁶ Dr. G.H. Brundtland (Director-General of the WHO), *International Trade Agreements and Public Health: WHO's Role*, presented by video at the Conference on Increasing Access to Essential Drugs in a Globalized Economy (Amsterdam, 25–26 Nov. 1999), at 1, available at http://www.who.int/medicines/docs/WTO_Public_Health_Amsterdam_GHB.html.

²⁷ See Jonathan Mann et al., *Health and Human Rights*, in *HEALTH AND HUMAN RIGHTS* 7 (J. Mann et al. eds., Routledge 1999). See also Rebecca Cook, *Gender, Health and Human Rights*, in *HEALTH AND HUMAN RIGHTS* 262 (J. Mann et al. eds., Routledge 1999).

²⁸ Scholtz, above n. 17, at 3. ²⁹ *Id.* ³⁰ *Id.*

3. Towards a legal regime that promotes public health

Since the Second World War, it may have been assumed that public health issues, particularly those with transnational effects, would be coordinated by WHO as the relevant body within the United Nations system. The WHO constitution empowered the organization's governing body, the World Health Assembly, to adopt conventions as well as other international legal instruments, including binding regulations.³¹ In practice, however, WHO has, until very recently relied more on the adoption of standards, principles and models supplemented by the body's annual reports and occasional declarations such as the Alma-Ata Declaration, which called upon countries and international organizations to adopt a system of primary health care.³² When it came to the regulation of pharmaceuticals, the essential medicines program exemplified WHO's choice of standards rather than rules. Any binding legal rules controlling the availability of medicines remained rooted in two independent legal processes within national jurisdictions, one regulatory and the other based on the laws of the market, including the relevant intellectual property rules of each country.

Despite a long history of the international regulation of drugs,³³ the availability of any particular medicine still depends on its registration by the health authorities or other agencies empowered to decide which products meet the required standards of safety and effectiveness. Even after registration, access to these drugs depends on their affordability in the market and, for the vast majority of patients in the developing world, on whether the state is able to make the drug available through the public health system. In this latter case, states have mostly relied on the availability of generic substitutes or used their relative market power to bargain for sustainable public sector prices. Despite the state's formal status as sovereign power, many developing countries, particularly in Africa, in the era of structural adjustment and neoliberal fiscal constraints, have lost the capacity to keep their public hospital dispensaries well stocked. The implementation of national essential drugs programs that rely to a large extent on the model lists produced by WHO had provided one mechanism for governments to manage the supply, use and cost of pharmaceuticals.

By the 1990s, however, initiatives affecting health care, particularly within individual nations, seemed to have shifted away from reliance on WHO standards and towards incorporation of decisions made by a range of other

³¹ D. FIDLER, *INTERNATIONAL LAW AND PUBLIC HEALTH: MATERIALS ON AND ANALYSIS OF GLOBAL HEALTH JURISPRUDENCE* 118 (Transnational Publishers 2000).

³² WHO & UNICEF, *Declaration of Alma-Ata, Report of the International Conference on Primary Health Care* (1978).

³³ J. BRAITHWAITE & P. DRAHOS, *GLOBAL BUSINESS REGULATION* 360–98 (Cambridge University Press 2000).

international bodies, including the World Bank and the WTO.³⁴ Fueled by the debate over access to medicines in the context of the HIV/AIDS pandemic, the question of the relationship between health and trade policies began to complicate the WTO's trade agenda in the late 1990s. The adoption of the TRIPS Agreement as part of the world trade regime in 1994 fundamentally changed the global legal environment for the production and supply of medicines.³⁵

Despite these and other successes, the pharmaceutical industry's goal of having intellectual property rights enforced through the international trade regime continued to face strong opposition, especially from developing and newly industrialized countries.³⁶ Launching the Doha Round of Multilateral Trade Negotiations in November 2001 was made possible only after Members agreed to adopt the Doha Declaration on the TRIPS Agreement and Public Health.³⁷ Despite concerted opposition from multinational pharmaceutical corporations and a group of developed countries led by the United States, Switzerland and Japan, the 140 trade ministers gathered in Doha, Qatar, agreed that the TRIPS Agreement "does not and should not prevent Members from taking measures to protect public health . . . [and] that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' rights to protect public health and, in particular, to promote access to medicines for all."³⁸

At first blush, this seemed to be a major negotiating success for the developing world. Not only was this interpretation extended to all aspects of public health, not just pharmaceuticals, but it also emphasized the need to interpret the WTO agreements in more holistic ways. In essence, it accepted that an interpretation reducing barriers to free trade is not automatically the sole or correct understanding of the relevant agreements.

Despite opposition by the United States and Canada to any broad public health exception, their own threats to override Bayers' Cipro patent – in response

³⁴ G. WALT, *HEALTH POLICY: AN INTRODUCTION TO PROCESS AND POWER* (University of the Witwatersrand Press 1994); G. Walt, *Globalization of International Health*, 351 *LANCET* 434 (7 Feb. 1998).

³⁵ See, e.g., Abbott, above n. 2. At the GATT Ministerial Meeting in 1982, intellectual property rights were discussed in the context of international trade relations for the first time. This was an early indication of the impact of a group of United States corporate leaders who, in the late 1970s, had "devised a strategy to improve intellectual property protection internationally until American standards became the international norm, especially in developing countries." RYAN, above n. 28, at 68. See also *THE PHARMACEUTICAL CORPORATE PRESENCE IN DEVELOPING COUNTRIES* 198 (L.A. Travis & O.P. Williams eds., University of Notre Dame Press 1993).

³⁶ See Abbott, above n. 2. See also Ruth Gana, *Prospects For Developing Countries Under the TRIPS Agreement*, 29 *VAND. J. TRANSNAT'L L.* 735 (1996); M. Adelman & S. Baldia, *Prospects and Limits of the Patent Provision in the TRIPS Agreement: The Case of India*, 29 *VAND. J. TRANSNAT'L L.* 507 (1996).

³⁷ Declaration on TRIPS and Public Health, above n. 4. ³⁸ *Id.* para. 4.

to the mailed Anthrax attacks³⁹ – weakened their official claims that the strong protection of patents was the most effective means of securing access to required medicines. The Doha Declaration specifically recognizes the right of a Member to grant compulsory licenses, to determine what constitutes a national emergency or other circumstance of extreme urgency, and to establish its own regime for the exhaustion of intellectual property rights.⁴⁰ It also encourages developed countries to promote technology transfer to the least-developed countries, and it extends the initial transition period, with respect to pharmaceutical products, until 1 January 2016.⁴¹ The understanding of the TRIPS Agreement reached in Doha constituted a major shift in the rhetoric about the protection of intellectual property rights; yet, given the realities of pharmaceutical production and distribution, little progress has been made towards actually ensuring access to urgently needed HIV/AIDS related medications.⁴²

Despite acknowledging that many countries have “insufficient or no manufacturing capacities in the pharmaceutical sector” and thus cannot make effective use of compulsory licensing,⁴³ the declaration failed to accept the developing countries’ claim that they have the right to grant compulsory licenses to producers in countries with greater manufacturing capacity in order to gain access to medicines. Instead, the declaration instructed the TRIPS Council to find a solution and to report to the WTO General Council by the end of 2002. Without the capacity to produce under compulsory licenses or to import generic equivalents of necessary medications, the problem of access for the millions infected with or suffering from life-threatening diseases in developing countries remained unresolved.

It took the TRIPS Council twenty-one more months to finally reach agreement in late August 2003 on the problem of access to medicines for countries that lack manufacturing capacity.⁴⁴ Heralded at first as the solution to the problem of lack of capacity, the pre-Cancun agreement has since been criticized as being unworkable for placing so many prerequisites on its implementation.⁴⁵ Before it can benefit from the decision, a country must prove that it

³⁹ See Paul Blustein, *Drug Patents Dispute Poses Trade Threat; Generics Fight Could Derail WTO Accord*, WASH. POST, 26 Oct. 2001, Sec. F, at E1. See also, Kavaljit Singh, *Anthrax, Drug Transnationals and TRIPS: Profits Before Public Health*, Z Magazine (December 2001), 39–42.

⁴⁰ Declaration on TRIPS and Public Health, above n. 4, para. 5.

⁴¹ *Id.* para. 7. ⁴² See, e.g., Abbott, above, n. 2.

⁴³ Declaration on TRIPS and Public Health, above n. 4, para. 6.

⁴⁴ WTO, Implementation of Paragraph 6, above n. 4.

⁴⁵ See Carlos M. Correa, *Implementation of the WTO General Council Decision on Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health* (Draft, December 2003). See also, Carlos M. Correa, *Implications of the Doha Declaration on the TRIPS Agreement and Public Health*, Health Economics and Drugs, EDM Series No. 12, WHO/EDM/PAR/2002.3 (WHO June 2002).

lacks production capacity and access to affordable medicines, and that it has an existing health emergency. While the Canadian government has taken steps to change Canadian law to make the export of medicines produced under these compulsory licenses possible, the international brand-name pharmaceutical industry has begun to raise questions about whether the NAFTA Agreement precludes Canada from supplying these medicines. Even the Canadian government itself seems to be limiting its proposals to drugs designed to address HIV/AIDS, malaria and Tuberculosis, a restriction rejected by the developing countries and the pre-Cancun agreement.⁴⁶

Once again, it seems that the question of access to essential medicines is being displaced by an assertion of prior legal commitments. The uncompromising principle of *pacta sunt servanda* is used to elevate notions of unrestricted trade above the health needs of millions of people around the world. While all participants in the debate deny any intention to restrict access or even to indirectly create such an effect,⁴⁷ it seems hard to deny that the failure to resolve the issue of compulsory licensing, since it was first raised by the international pharmaceutical industry in its 1997 case against the South African law implementing an essential drugs program, has in fact frustrated attempts to broaden access.

Even if it is accepted that the TRIPS Agreement was initially unsuited to accommodating the complexities of a global health emergency such as HIV/AIDS, it is hardly unreasonable to suggest that, in light of both new understanding of the magnitude of the pandemic and the emergence of effective medicines to address it, the principle of adapting to changed circumstances – or *rebus sic stantibus* – should have been applied to interpretations of the Agreement in order to facilitate attempts to address this exploding crisis. At the least, such an approach would justify the assertion of an article 30 exception under the TRIPS Agreement.⁴⁸ Instead, there has been a constant emphasis on the rather unique protection of private rights contained in the TRIPS Agreement and a denial of the legal effect of the so-called soft-law exceptions and principles of interpretation, which are also part of international trade law and essential to realizing public health goals.

4. Conclusion

After twenty years, the HIV/AIDS pandemic has finally been recognized as a global health crisis, yet the debates over access to public goods that are essential

⁴⁶ See, Press Release, 28 Apr. 2004, Canada Proceeds with Bill C-9 on Cheaper Medicines Exports: NGOs Say Initiative is Important, and Urge Other Countries to Avoid the Flaws in the Canadian Model, available at www.aidslaw.ca/Media/press-release/e-press-apr2804.pdf.

⁴⁷ International Intellectual Property Institute, Patent Protection and Access to HIV/AIDS Pharmaceuticals in Sub-Saharan Africa, Report prepared for WIPO (2000).

⁴⁸ See TRIPS Agreement, above n. 1, art. 30.

to defeating this scourge continue to be shaped less by concerns about public health than by principles of unrestricted trade and intellectual property rights protection. Within the legal field, the claims of the international patent-based pharmaceutical corporations are framed as rights to property, while the claims of NGOs and developing country governments seeking access to affordable medicines are characterized as legal exceptions to free trade or as the soft law principles contained in general preambular statements. These formal legal distinctions, based upon the interpretation of international agreements created in a context of asymmetrical power, are now relied upon to delay and avoid recognizing the urgent needs of those whose lives and futures are at stake.

Asserting a human rights perspective, from which the health impact of any particular interpretation is seen as an equally legitimate consideration in evaluating the validity of any particular legal option, could dissolve the stifling distinction between so-called hard law obligations and soft law principles or commitments. Introducing such a perspective might facilitate access to medicines by encouraging private investors to reconcile the need for compulsory licenses or other exemptions with their own investment calculus, including investments in generic production. It could also provide developing countries with a means to justify decisions to privilege policies securing access to medicines over concerns about their international trade commitments or threats from patent holders. Instead of relying on thin strands of legal flexibility, NGOs, international organizations, countries and governments attempting to address the global HIV/AIDS pandemic should promote a human rights-based interpretation that places public health ahead of economic claims.