

INCREASING R&D INCENTIVES FOR NEGLECTED DISEASES –

LESSONS FROM THE ORPHAN DRUG ACT

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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 diseases. They found pharmaceutical innovations have provided significant net benefits to patients across a wide spectrum of conditions such as heart disease, cancer, and depression.² 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 which are specific to and concentrated in developing countries. 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

¹ See, for example, David M. Cutler and Mark McClellan, “Is Technological Change in Medicine Worth It?” *Health Affairs*, Vol. 20 (Sept/Oct 2001), pp. 11-29; Frank R. Lichtenberg, “Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS,” *ibid*, p. 241-251; Jack E. Triplett, Editor, *Measuring the Prices of Medical Treatments*, (The Brookings Institution: Washington, DC, 1999).

² Cutler and McClellan, *ibid*, pp. 11-29

income and ability to pay for health care that exists in developing countries. Insufficient revenues on the demand side of the market is 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. 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% tax credit on their clinical development expenses. Other incentives include development grants, counseling and guidance from the 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.” In this paper 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 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 paper I investigate the feasibility of developing an orphan drug-type program oriented to the neglected diseases of developing countries.³ The plan of the paper is as follow. 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 managed to alter 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.

ECONOMICS OF PHARMACEUTICAL R&D PROCESS

Competition in the research-based segment of the pharmaceutical industry is centered around 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. 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

³ In particular, I expand on ideas first presented in the paper, "Patents, Innovation and Access to New Pharmaceuticals," *Journal of International Economics Law*, Vol. 5, No. 4, December 2002, pp. 849-860.

and commercial risks associated with the pharmaceutical R&D process and the tremendous variability in the economic returns of new drug introduction.

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. Of these, only about twenty percent of the compounds entering clinical trials survive the development and FDA approval process. 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.⁴

In a study published in the 2003 *Journal of Health Economics*, Joe DiMasi, Ron Hansen, Lou Lasagna, and I examined the representative costs for new drugs whose mean

⁴ Joe DiMasi, Ronald Hansen, and Henry Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, Vol. 22, 2003, pp. 151-85

introduction date was in the late 1990s.⁵ 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. 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% above general inflation when compared to the costs for new drug introductions of the 1980s. A major factor accounting for this growth in costs is the size of and number of clinical trials which have 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.

R&D Returns

In a paper published in the *PharmacoEconomics*, John Vernon, Joseph DiMasi, and I examined the distribution of returns for 1990-94 new drug introductions.⁶ A key finding was that the sales and returns of new drugs exhibit tremendous variability. In

⁵Ibid, pp. 161-167. 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.

⁶Henry Grabowski, John Vernon and Joseph DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *PharmacoEconomics*, Vo. 20, Suppl. 3, 2002, pp. 11-29.

particular, we found that a small number of drugs provide a disproportionate share of overall revenues. The search for these exceptional compounds, which generally involves significant therapeutic advances over establishing therapies, is a key driver of R&D competition in pharmaceuticals.

The life cycle of sales profiles for the top few deciles and the mean and median drugs are presented in Figure 1. 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 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.⁷

The highly skewed outcomes observed in Figure 1 reflect the dynamic nature of the R&D process and the large risks that surround the process from a scientific, regulatory and commercial perspective. The long time lags, the need to obtain regulatory approval from the FDA, and the new drug introductions of competitors compound the various scientific and technical risks. These factors help to explain the great variability in market sales and profitability that has been observed in every time cohort that we have examined since the 1970s.⁸ Even the very largest pharmaceutical firms, with extensive

⁷ F. M. Scherer has shown in recent work that many industrial R&D activities are characterized by skewed outcome distributions. This is especially the case for venture capital investments; F. M. Scherer, "New Perspectives on Economic Growth and Technological Innovation," Washington, D.C., *Brookings Institute Press*, 1999, Chapter 5, pp. 71-80.

⁸ See Grabowski, et. al., "Returns on Research and Development", *PharmcoEconomics*, 2002, pp. 23-28.

pipelines of new drug candidates, exhibit great variability in the number of approvals and sales from their R&D investment in a given period.⁹

John Vernon and I have performed two studies on the factors that influence the size of a company's total R&D expenditures.¹⁰ 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 will be directed toward increased R&D expenditures.¹¹ The cash flows from successful new products are therefore very important to funding R&D for future new product innovations.

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. 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,

⁹Henry Grabowski and John Vernon, "The Distribution of Sales Revenues from Pharmaceutical Innovation," *PharmcoEconomics*, Vol. 18, Suppl. 1, 2000, pp. 21-32.

¹⁰Henry Grabowski and John Vernon, "The Determinants of R&D Expenditures in the Pharmaceutical Industry," in R. Helms, ed., *Drugs and Health*, (Washington, D.C.: AEI), 1981; "The Determinants of Pharmaceutical Research and Development Expenditures," *Journal of Evolutionary Economics*, Vol. 10, 2000, pp. 201-215.

¹¹In 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 also 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," *Health Affairs*, Vol. 20 (Sept./Oct. 2001), pp. 216-220.

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.¹² 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.¹³ This reflects the fact that R&D costs and investment periods are larger than average in pharmaceuticals while imitation costs are lower than in other high tech 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. Strong systems of patent protection exist in all

¹² Edwin Mansfield, "Patents and Innovation: An Empirical Study," Management Science, Vol. 32, No. 2, 1986, pp. 173-181. 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 Richard D. Levin, et al, "Appropriating the Returns from Industrial Research and Development," Brookings Papers on Economic Activity No. 3, 1987, pp. 783-820; Wes Cohen, et al, "Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector," Working Paper (Carnegie-Mellon University, Pittsburgh), 1997.

¹³ 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.

countries with strong innovative industries in pharmaceuticals. This is a major finding of an analysis that I performed of the distribution of important new global drug introductions categorized by the nationality of the originating firms for the period 1970 and 1985.¹⁴ 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.¹⁵

THE ORPHAN DRUG ACT OF 1983

Push and Pull Incentive Programs

Given the economics of new drug development, strategies for stimulating R&D on orphan drugs and neglected diseases must either work to lower the costs of development (“push programs”), enhance the expected revenues after market launch (“pull programs”), or utilize a combination of both approaches. Table 1 provides examples of prominent push and pull strategies. In the push category, one has R&D cost sharing or subsidy programs. These can be done 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.

¹⁴ Henry Grabowski, “Innovation and International Competitiveness in Pharmaceuticals,” in Arnold Heertje and Mark Perlman (eds.), *Evolving Technology and Market Structure* (Ann Arbor, MI: University of Michigan Press 1990), pp. 167-185. See also, Robert E. Evenson and Sunil Kanwar, “Does Intellectual Property Protection Spur Technological Change?” Yale Economics Growth Center Discussion Paper No. 831.

¹⁵ B. Pazderka “Implications of Recent Changes in Pharmaceutical Patent Legislation in Canada,” in OECD, Directorate for Science Technology and Industry, *Economics Aspects of Biotechnologies Related to Human Health—Part II: Biotechnology, Medical Innovation and the Economy: The Key Relationships*, 1998, OECD: Paris, 159-191; Ian Neary, “Japanese Industrial Policy and the Pharmaceutical Industry” in Adrian Toswe (editor), *Industrial Policy and the Pharmaceutical Industry*, (London: OHE 1995), pp. 12-29.

Pull programs work to increase the size of the benefits to innovators after market launch. Three types of pull program are listed in Table 1. The first is 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 listed 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 developing market economics 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 FDAMA Act, 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 further in the third section of this paper.

Characteristics of the Orphan Drug Act

In the case of the 1983 Orphan Drug Act (ODA), the incentives involved both push and pull type incentives.¹⁶ 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. This grants program focused on early clinical development (Phase I and II) and involved grants of between \$150,000 to \$300,000. A third important cost side incentive involved FDA advice and counseling with sponsors on orphan drug protocols. As discussed below, many orphan drugs have received priority review and fast track development status and FDA approval has been granted on fewer total subjects than for the average new drug introduction.

The ODA also includes one important pull side incentive. This is a guaranteed seven year market exclusivity period. The FDA has characterized this as the most sought after incentive. While this seven year exclusivity runs concurrently with regular patent term exclusivity, it was a critical factor to many biotech drugs. Many of the original biotech compounds were natural substances that were not eligible for patents on the molecule itself. Several of these drugs also were targeted to diseases of low prevalence. Given the uncertainty that surrounded biotech patents during this period, the seven year exclusivity period was an important market incentive to many biopharmaceutical firms.¹⁷ This seven year exclusivity was also important in the case of some older chemical entities

¹⁶ Shelia R. Schulman, et. al., "Implementation of the Orphan Drug Act: 1983 – 1992," *Food and Drug Law Journal*, Vol. 47, 1992, pp. 363-403.

¹⁷ Sheila R. Schulman and Michael Manocchia, "The U.S. Orphan Drug Programme 1983-1995," *PharmcoEconomics*, Vol. 12, No. 3, 1997, pp. 313-326.

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.¹⁸

Orphan Drug legislation has also been enacted in Japan (1993) and the European Union (1999). These laws incorporate many of the push and pull incentives incorporated in the United States law.¹⁹ 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.

Orphan Drug Designation and Approvals

The FDA has concluded 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.”²⁰ While a simple pre and post ODA time series analyses 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.

¹⁸ Willis Emmons and Ashok Nimgade, “Burroughs Wellcome and AZT,” Case 9-792-004, Harvard Business School, 1991.

¹⁹ 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, London, February, 2002.

²⁰ www.fda.gov/orphan/history.htm

As of May 2003, the FDA has granted 1238 orphan drug designations to drug firms and organizations developing medicines for rare illnesses. Furthermore, 238 of these orphan designated drugs have received marketing approval.²¹ Figure 2 shows the annual number of orphan drug approvals for the period 1983-2002. Almost half (46%) of all orphan drug approvals have been for new drug molecular entities or new biopharmaceuticals. The data in Figure 2 also imply that a large number of previously approved drugs have 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.

Costs of Orphan Drugs

A 1993 study of the pharmaceutical industry by the Office of Technology Assessment noted that the economics of orphan drug development and approvals may be different than other new drug candidates. “These products (orphan drugs) may have a different cost structure from other NCEs, not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs.”²²

Available data sources the number of subjects enrolled in trials and subsequent market

²¹ www.fda.gov/orphan/designat/allap.rtf

²² Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards*, Washington, D.C., U.S. Government Printing Office, February 1993, p. 71.

sales suggest that the R&D cost structure for orphan drugs is indeed different than 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. 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 FDA Modernization Act of 1997. It consolidated and expanded 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 CSDD found that three years after the program was

initiated, half of the 65 fast track designated products in their analysis also had orphan designations.²³

An analysis of orphan drug designations by Schulman, et. al. in the early 1990s found that nearly half of all orphan drugs up to that time were concentrated in three broad therapeutic areas – cancer, AIDS and genetic diseases.²⁴ These are generally life-threatening diseases of high unmet medical need. To the extent that orphan drugs continue to be directed to therapeutic areas with these characteristics, they would be 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 receive an accelerated development process, given that the FDA is charged with facilitating orphan drug approvals under ODA. Also, 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 2000.²⁵ The sample included seven orphan designated entities. She found that biopharmaceuticals as a group have significantly lower number of 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

²³ Tufts Center for the Study of Drug Development Impact Report, “FDA’s Fast Track Program Results in 62% Approval Rate After First 3 Years,” Vol. 3, No. 1, January/February 2001.

²⁴ Shelia R. Schulman, “Implementation of the Orphan Drug Act,” 1992, (see footno53 15).

²⁵ Janice M. Reichert, “Clinical Development of Therapeutic Medicines: A Biopharmaceutical Versus Pharmaceutical Product Comparison,” *Drug Information Journal*, Vol. 35, 2001, pp. 337-346

the seven orphan designated compounds was 576 subjects. The average non-orphan biopharmaceutical in her sample had three times as many subjects.

Some data assembled from 1999 FDA marketing approval letters by T. Balasubramaniam is 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 the seven orphan drug marketing approvals in 1999 had a mean of 588 patients with a range between 152 and 1281 total patients.²⁶ This compares with an average of more than 5,000 subjects for the typical new drug introduction in the late 1990s.²⁷

Revenues of Marketed Orphan Drugs

In Figure 3 I have plotted sales life cycle profiles for new orphan and non-orphan new drug introductions in our 1990-1994 cohort²⁸. As one can see from this figure, the sales peak for the average orphan drug is in the neighborhood of \$100 million compared for \$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 mean pharmaceutical is

²⁶ Presentation of James Love, "What Do U.S. IRS Tax Returns Tell Us About R&D Investment?" January 16, 2003 (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.

²⁷ 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 NDA was over 5,000. See Parexel's *Pharmaceutical R&D Statistical Sourcebook*, Waltham, Mass, 2001.

²⁸ Grabowski, Vernon, and Di Masi, "Returns on Research and Development," 2002. See footnote 4.

strongly influenced by few large selling compounds. In fact, the distribution of sales for orphan drugs is even more skewed than non-orphan compounds.

Figure 4 shows the distribution of tenth year sales for 1990-94 Orphan new drug introductions. 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 10th 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 very modest sales, but there are a few “wealthy orphans.” These consist of some very expensive biopharmaceuticals that have revenues comparable to the very top selling decile pharmaceutical and biological products.

The sales data in Figures 3 and 4 are strongly supportive of OTA’s conjecture that the R&D cost structure of orphan drugs is very different in nature from other drugs. Even allowing for the possibility of a 50 percent tax credit, the sales of most orphan drugs would not support the large scale clinical trials involving several thousand patients and which can cost hundreds of millions for the typical new drug approval. Based on available information on orphan product sales and the number of subjects listed in the available 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 for smaller biopharmaceutical firms. Finally, the exclusivity provision has also been critical for many compounds with expired or weaker patent protection.

Health Benefits of Orphan Drugs

In a recent paper Lichtenburg and Waldfogel have investigated the health benefits to individuals suffering from rare illnesses in both the pre and post ODA period. For this purpose, they employ data on disease prevalence, prescription drug consumption and longevity by three digit ICD-9 disease codes in 1979 and 1998. The measure of longevity used in their analysis is the percentage of individuals dying young or dying before age 55.²⁹

Lichtenberg and Waldfogel found that the percent of individuals dying young for relatively rare illnesses (conditions at the 25th prevalence percentile) has fallen from 22 percent in 1979 to 16 percent in 1998, or six full percentage points. 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 occurs for disease categories in which there is greater availability and consumption of orphan drugs. This indicates that the availability of novel therapies for

²⁹Frank R. Lichtenberg and Joel Waldfogel, "Does Misery Love Company? Evidence From Pharmaceutical Markets Before and After the Orphan Drug Act," Working Paper 9750, National Bureau of Economic Research, Cambridge, MA, June 2003.

rare diseases has had a statistically significant effect on the longevity of people suffering from these conditions

Lichtenberg and Waldfogel's analysis provides evidence that the aggregate health effects of ODA for individuals suffering from rare diseases have been very positive. Their work is complemented by a number of medical studies of individual drugs that reach similar conclusions.³⁰ Clearly, the Orphan Drug Act has been very 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.

The ODA Act and New Drugs for the Neglected Diseases of Poor Countries

There have been relatively few drugs developed under the ODA Act for tropical diseases and other neglected diseases of poor countries. As of July 2003, there have been only twelve orphan drug approval in the United States targeted specifically to tropical diseases (Table 2).³¹ This represents approximately five percent of the 238 market approvals for orphan designated indications. Moreover, the majority of the drugs are for conditions that either have some market in the developed countries or the travelers' market (TB, 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 U.S. However, there is a

³⁰ These studies have been performed for various orphan drugs including important biopharmaceuticals like Ceredase, Avonex and Pulmozyme

³¹ AIDS related drugs are excluded from this table.

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 are reimbursed by insurance companies once they receive FDA approval. In developed countries with broad health care insurance coverage, orphan drugs are typically covered under the national health insurance plans.

The largest barrier to R&D investment in neglected diseases of poor countries is the low ability to pay in developing countries. Many of these countries devote as little as \$2 per capita per year on health, reflecting their low per GDP per capita. Furthermore, there has been a reluctance of developed countries to come to their aid for health care, at least until recently. The ability to pay barrier is compounded by other barriers – 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.³²

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 drug Mectizan (ivermectin) for river blindness. Merck has provided medical infrastructure 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.³³ Other important current initiatives include

³² With respect to the issue of patent protection, Lanjouw has proposed a bifurcated system of patent protection for global and neglected diseases. Her approach is designed to facilitate access in developing countries to new products directed toward global diseases, while preserving the incentives for R&D on neglected diseases. For a detailed discussion, including potential issues involving parallel importation and international reference pricing, see Jean O. Lanjouw, "Intellectual Property and the Availability of Pharmaceuticals in Poor Countries," *Innovation Policy and the Economy*, Vol 3, 2002.

³³ Private correspondence with Jeff Kempecos and Jeff Sturchio at Merck.

Glaxo SmithKline's drug albendazole for filariasis, the anti-trachoma program of Pfizer and Novartis' multi drug regimen for leprosy.³⁴ 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 too large in scale to rely primarily on philanthropic donations from a handful of firms and their NGO partners.

A number of public-private partnerships (PPPs) also have emerged in recent years that are targeting the development of new vaccines and medicines for diseases that have a high burden in developing countries, such as malaria, TB and AIDS.³⁵ These 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 under the Gates Foundation support, 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 have agreed to supply any approved vaccines developed under this program at a small margin over cost to developing countries. Similarly, the Global Alliance for TB Development has recently reached a licensing agreement with Chiron for the

³⁴Discussions with James Russo, Executive Director of the partnership for Quality Medical Donations, (www.pmd.org).

³⁵For an economic analyses of these public private partnerships see Hannah Kettler and Adrian Towse, *Public Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty*, Office of Health Economics, London, December 2002.

development of a new TB drug for which no royalties would be earned on sales in less developed countries.

At the present time there is much experimentation with IP 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 neglected diseases. This will certainly be important for disease targets that are not part of the targeted donation programs of large multinational firms or the emerging partnerships. Furthermore, the targeted PPP programs have a very 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.

AN AMENDED ORPHAN DRUG ACT FOR NEGLECTED DISEASES

As discussed, most of the cost savings provision of the ODA already apply to R&D investment for neglected diseases given their low incidence in the United States. While the R&D tax credit is specifically designed to cover domestic clinical trials, a firm can obtain the credit for foreign trials covered if the number of available subjects is too limited in the United States. 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 the need for firms to apply for such coverage. In addition, it would also be beneficial to have some grant funds specifically earmarked for basic research on these diseases to involve participation of university researchers and smaller biopharmaceutical firms in the discovery phase. Currently, grants only cover the clinical development trials. This would be particularly desirable given recent advances in genomics which enhance the scientific opportunities for developing significant new vaccines and therapies for many infectious and tropical diseases that are concentrated in poor countries.

The basic challenge at the present time, however, is to add a significant market pull incentive for neglected diseases that can be combined with the R&D cost side incentives that are, for the most part, already in place. As discussed, 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 saving push incentives in the ODA will not be 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, this market pull incentive must be large enough to overcome the insufficient market revenues barrier. Second, the medicines need to be distributed in poor countries at a price that is consistent with broad access. Third, the programs need to be structured in such a manner that they receive support from important constituent groups, and funding from policymakers. I

examine three policy options in this regard - transferable patent exclusivity, transferable priority review rights, and purchase funds or guarantees.³⁶

Transferable Patent Exclusivity Rights

One idea that has been proposed by Kettler and others is a roaming or transferable patent exclusivity right.³⁷ 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: 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 regulatory body and begins distribution in the developed 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 send clear

³⁶For a further discussion of how a modified orphan drug program might affect the R&D effort for specific diseases, see Chris Milne, Ken Kathin, and E. Ranchi, "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," CMH Working paper No. WG 2:9. This is available online at http://www.cmhealth.org/docs/wg2_paper9.pdf.

³⁷ Hannah E. Kettler, *Narrowing the Gap Between Provision and Need for Medicines in Developing Countries*, Office of Health Economics, London, February 2002, Chapter 4.

signals to firms on how much benefit they might expect from participation.

Alternatively, firms could engage in negotiations on the amount of extra months exclusivity with a government regulatory agency such as HHS 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 size of the extension in the U.S. 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 case opens a complex regulatory negotiation process in which all of the key variables are subject to a high level of uncertainty. This would be especially case for products at early stages of the R&D processes. Nevertheless, if one waits until a drug is successfully developed and much of this uncertainty has been reduced, issues of credibility arise for the innovating firms. At that point in time, government regulators have a strong incentive to minimize the added exclusivity time to keep the costs of the program low. For these reasons, a fixed time period, 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 could likely be a powerful incentive program for increased R&D investment on diseases of poverty. A major disadvantage with this proposal however, is that the cost burden will 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 U.S. and other sponsoring countries, this proposal is likely to face stiff opposition from insurance payers and patient groups. Recent

proposed legislation on prescription drugs in the United States is actually moving in a very different direction. The Senate recently passed, by a nearly unanimous vote, legislation to facilitate increased generic competition as a principal strategy in containing health care costs. Hence, the prospects of legislative passage of a proposal increasing the market exclusivity of existing patented drugs, even for a worthy cause like more R&D for neglected diseases, would not appear to be very great at the present time.

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 1990-94 introductions with John Vernon and Joe DiMasi, 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.³⁸

A potential problem with transferable priority review rights is that it could potentially slow down the approval of significant drugs designated for priority review in

³⁸Grabowski, Vernon, and DiMasi, "Returns on Research and Development," 2002 (see footnote 5).

cancer and other disease areas of high unmet need. The program would have to be configured so that doesn't occur. In particular, the transferable priority review drugs could be put in a separate category and allocated resources from a separate budget.

The overall costs to society to fund a program of transferable priority review rights in exchange for a firm 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 are basically incurred to get drugs on the market sooner in both developed and developing countries is likely to be much more acceptable politically than an incentive program that delays patent expiration and generic entry for leading drug products with its attended consequences of higher expenses for payers and patients.

Purchase Guarantees

Another pull mechanism that has been discussed extensively in the recent literature by Michael Kremer, Jeff Sachs, and others, 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.³⁹ The idea is to overcome the ability to pay barrier to R&D investment by committing in advance to a level of market purchases that would

³⁹ See for example Michael Kremer and Jeffrey Sachs, "A Cure for Indifference," *The Financial Times*, May 5, 1999.

allow a reasonable return on expected R&D outlays to firms that successfully develop new products for neglected diseases. Products that exceed the established profile 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 incentivizing pharmaceutical R&D funding.

The purchase fund policy option has been developed in most detailed form by Michael Kremer in the context of the development of vaccines for the diseases of malaria, tuberculosis and HIV.⁴⁰ Under their proposal, a sizeable fund, on the order of \$250 – \$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. They would, however, be subject to a modest co-payment to insure that they met a market test. 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 legitimate producers. Government purchases in the developing countries would also have incentives to adhere to the 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 associated with them that would need to be addressed and overcome. Foremost is the issue of credibility. As discussed in Section II,

⁴⁰ Michael Kremer, “Creating Markets for New Vaccines – Part I: Rationale, and Part II: Design Issues: in *Innovation Policy and the Economy*, editors Adam B. Jaffe, Josh Lerner and Scott Stein, 2001. Available at <http://post.economics.harvard.edu/faculty/kremer/vaccine.html>

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 will be concerned that the funding agencies will either renege or be unable to deliver on their commitment once a drug is 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 have a strong incentive to try to obtain a product as cheaply as possible once it is 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 the credibility in the context of vaccine purchases for AIDS, malaria and HIV.⁴¹

Kremer and others estimate that a \$250 to \$500 million real annual market would be required to motivate substantial research by several firms. In fact, this number seems low unless R&D costs can also be kept below average for the industry through use of orphan drug type 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 considerably larger in value would still be an extremely cost effective investment if it results 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

⁴¹ Kremer, *op. cit.*

malaria, to non-profit and international organizations serving developing countries. Each dollar of sales would be matched by a dollar of tax credit. This is a market pull mechanism corresponding in spirit to the purchase fund concept. A similar measure was endorsed by the Clinton Administration in its FY 2001 budget, but was not passed by Congress.

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 market 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 firms could choose between a purchase fund or 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.

SUMMARY AND CONCLUSIONS

The U.S. Orphan Drug Act has been a great success in encouraging the development of new drugs for rare diseases. 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 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 paper is how to amend 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 market pull incentive mechanisms. In this paper, 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 burden such as malaria and tuberculosis.