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13

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PATENTS, INNOVATION AND ACCESS TO NEW PHARMACEUTICALS

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ABSTRACT

This paper considers the role of intellectual property rights in the development of, and access to, new pharmaceuticals. A number of studies have found patents are significantly more important to pharmaceutical firms in appropriating the benefits from innovation compared with other high tech industries. The reason for this is because the costs of drug innovation are very high while the costs of imitation are relatively low. Hence the industry is subject to significant free-rider problems. The paper discusses the economics of the innovative process and considers how patent policies have evolved in response to these characteristics in several developed countries with research-intensive drug firms. One area currently receiving policy attention is the effect of patents on the development of, and access to, new medicines for developing countries. The final section of the paper focuses on this issue and discusses the need for an orphan drug type programme to stimulate more R&D on diseases specific to third-world countries.

INTRODUCTION

As Roy Levy and Abraham Wickelgren of the Federal Trade Commission observe in a recent article: 'It is hard to think of many industries that have contributed as much to human welfare as the pharmaceutical industry. The importance of the industry makes the job of competition authorities that much more difficult and important.'[1]

There is accumulating empirical evidence that new drug introductions have indeed played a central role in increased longevity, enhanced quality of life and improved labour force participation and productivity. A number of benefit-cost analyses using very different data sets and methodologies have found that there are typically large positive externalities and net social benefits from

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[1] Roy Levy and Abraham Wickelgren, 'Competition Policy Issues for Regulators: A US Perspective on Pharmaceutical Industry Cases Before the Federal Trade Commission' in Hannah Kettler (ed), *Consolidation and Competition in the Pharmaceutical Industry* (London: Office of Health Economics 2001) 106–17.

drug innovation.[2] In a recent survey, Cutler and MacClellan conclude: 'in most of the cases we analyzed, technological innovations in medicine are on net positive. Technology often leads to more spending, but outcomes improve by even more'.[3]

It has also been shown in the literature that public policy actions can have a strong effect on the rate of technological progress in this industry.[4] The focus of this paper is on the role of intellectual property rights and patents in the development of and access to new pharmaceuticals. The next section discusses why patents are a more critical stimulus factor for pharmaceutical innovation compared with their impacts in other high-tech industries. Section II considers the evidence on this point emerging from the international experiences of countries that have implemented very different patent policies with respect to pharmaceuticals. The final section considers the special case of developing countries, where patent protection of pharmaceuticals has received increased attention in recent years with the expanding global AIDS crises and the enactment of TRIPS.

I. THE IMPORTANCE OF PATENTS FOR PHARMACEUTICAL INNOVATION

The importance of patents to pharmaceutical innovation has been demonstrated in several studies by economists. Richard Levin *et al.*, and Wes Cohen *et al.*, have undertaken surveys of US R&D managers in a large cross-section of industries to identify which factors are most important and necessary in appropriating the benefits from innovations.[5] These factors included the competitive advantages of being first in the market, superior sales and service efforts, secrecy and complexity of production and product technology, as well as patents. Both studies found that the pharmaceutical industry placed the highest importance on patents. By contrast, many other research-intensive industries, such as computers and semiconductors, placed greater stress on factors like lead-time and learning by doing efficiencies in production accruing to first movers.

The findings of these studies are in accordance with an earlier study per-

[2] See for example, Frank R. Lichtenberg, 'Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS', 20 Health Affairs (September/October 2001) 241–51; Jack E. Triplett (ed), *Measuring the Prices of Medical Treatments* (Washington, DC: Brooking Institution 1999).

[3] David M. Cutler and Mark McClellan, 'Is Technological Change In Medicine Worth It?' 20 Health Affairs (September/October 2001) 21.

[4] Adrian Towse (ed), *Industrial Policy and the Pharmaceutical Industry* (London: Office of Health Economics 1995).

[5] Richard D. Levin *et al.*, 'Appropriating the Returns from Industrial Research and Development', *Brookings Papers on Economic Activity* (1987) 783–820; Wes Cohen *et al.*, 'Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector', Working Paper (Pittsburgh: Carnegie-Mellon University 1997).

formed by the British economists Taylor and Silberston. Based on a survey of UK R&D managers, they estimated that pharmaceutical R&D expenditures would be reduced by 64% in the absence of patent protection. By contrast, the corresponding reduction was only 8% across all industries. Similar findings were reported by Edwin Mansfield from a survey of the research directors of 100 US corporations.[6]

The explanation for why patents are more important to pharmaceutical firms in appropriating the benefits from innovation follows directly from the characteristics of the pharmaceutical R&D process. In essence, it takes several hundred million dollars to discover, develop, and gain regulatory approval for a new medicine. Absent patent protection, or some equivalent 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 for discovering and developing a new compound.

One of the reasons R&D is so costly in pharmaceuticals is that most new drug candidates fail to 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, fewer than 1% of the compounds examined in the pre-clinical period make it into human testing. Only 22% of the compounds entering clinical trials survive the development process and gain FDA approval.[7] Furthermore, the full R&D process from synthesis to FDA approval involves undertaking successive trials of increasing size and complexity. The pre-clinical and clinical testing phases generally take more than a decade to complete.[8]

In a recently completed study, Joe DiMasi, Ron Hansen and I have examined the average R&D cost for drugs introduced into the market in the late 1990s. We found the representative new product approval incurred out-of-

[6] C. T. Taylor and Z. A. Silberston, *The Economic Impact of the Patent System* (Cambridge, UK: Cambridge University Press 1973). In a follow-on study, Silberston categorized three groups of industries for when patents are essential, very important or less important based on both survey responses and objective analyses (patent and R&D intensity). He concluded that 'the first category consists of one industry only, pharmaceuticals'. Z. A. Silberston, *The Economic Importance of Patents* (London: The Common Law Institute of Intellectual Property 1987); Edwin Mansfield surveyed the R&D directors of 100 US corporations on what fraction of the inventions they introduced between 1981 and 1983 would not have been developed without patent protection. For pharmaceuticals, the value was 60%, while the average across all industries was 14%. Edwin Mansfield, 'Patents and Innovation: An Empirical Study', 32 Management Science (1986) 175.

[7] Joseph A. DiMasi, 'Success Rates for New Drugs Entering Clinical Testing in the United States', 58 Clinical Pharmacology and Therapeutics (1995) 1–14.

[8] Joseph A. DiMasi, 'Trends in Drug Development Costs, Times and Risks', 29 Drug Information Journal (1995) 375–84; Kenneth I. Kaitin and Joseph A. DiMasi, 'Measuring the Pace of New Drug Development in the User Fee Era', 34 Drug Information Journal (2000) 673–80.

pocket costs of over $400 million.[9] This includes money spent in the discovery, pre-clinical and clinical phases as well as an allocation for the cost of failures. R&D costs were shown to have increased at an annual rate of 7.4% above general inflation when compared to the costs of 1980s introductions. A major factor driving this increase is the current size and number of clinical trials, which have increased significantly in the 1990s compared to the earlier period.[10]

By contrast, the development costs of generic compounds are relatively modest. In the United States, and most other countries, generic compounds must only show that they are bio-equivalent to the pioneering brand to receive market registration. This process only takes a few years and costs $1–2 milllion.[11] The probability of success is also very high, as reflected by the fact that many generic firms typically receive FDA approval and enter the market within a short time of the patent expiration of the pioneer brand.

Effective patent life, defined as the patent time remaining at the time of product launch, is important from an economic incentive standpoint to innovators. This is because it takes many years for firms to recoup the high costs involved in drug R&D and earn a positive return.[12] Since 1994, the USA grants a patent term of 20 years from the date of patent application. However, the core patents in pharmaceuticals are typically applied for in the pre-clinical period. This means a significant loss in actual patent life will occur by the time of market launch as it takes many years for a product to pass through the different phases of clinical trials and regulatory review.[13]

In light of this, most countries with innovative industries – the USA, Europe, and Japan – have all enacted patent term restoration laws. These laws provide a partial restoration of patent times lost during clinical testing and regulatory period. Taking account of these patent restoration benefits,

[9] When R&D costs are capitalized to the date of market launch at an 11% discount rate, capitalized R&D costs are equal to $802 million. Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs* (Boston, MA: Tufts University Center for the Study of Drug Development 2002). For an earlier study using the same methodology for 1980s new drug introductions, see Joseph A. DiMasi *et al.*, 'The Cost of Innovation in the Pharmaceutical Industry', 10 Journal of Health Economics (1991) 107–29.

[10] Ibid.

[11] US Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (Washington, DC: US Government Printing Office 1998); David Reiffen and Michael Ward, 'Generic Drug Dynamics,' Bureau of Economics, Federal Trade Commission Working Paper 248 (February 2002).

[12] Henry Grabowski and John Vernon, 'Returns to R&D on New Drug Introductions in the 1980s', 13 Journal of Health Economics (1994) 383–406; 'A New Look at the Returns and Risks to Pharmaceutical R&D', 36 Management Science (1990) 804–821.

[13] Henry Grabowski and John Vernon, 'Longer Patents for Increased Generic Competition: The Waxman Hatch Act After One Decade', 10 Pharmaco Economics (1996) 110–23; Henry Grabowski and John Vernon, 'Effective Patent Life in Pharmaceuticals', 19 International Journal of Technology Management (2000) 98–120.

the representative new drug introduction in the USA during the mid-1990s, had an average effective lifetime of approximately 12 years.[14]

These patent term restoration laws are also structured to facilitate regulatory approval of generic products. The intensity of generic competition has grown significantly in the USA and other world markets during the 1990s. In an analysis of generic competition in the US market performed by John Vernon and myself, we found that the initial generic products enter the market at a significant discount to the originating brand and this discount grows larger as the number of generic competitors increases over time. For a sample of commercially significant products coming off patent in the early to mid-1990s, we found that after one year of generic competition, generic products were being offered at an average discount of over 50% relative to the originating brand, and had captured a total market share of 64%.[15] More recent time cohorts were characterized by even more intensive generic competition.

In summary, competition in pharmaceuticals centres around the introduction of new molecular entities as well as imitative drug therapies. The family of medicines in a given therapeutic class passes through a well delineated life cycle. There is dynamic competition involving breakthrough, as well as incremental advances, among branded products within a given class. This dynamic competition, in turn, produces substantial consumer surplus and social returns as discussed in the Introduction. When the patents for established products expire, consumers also benefit from imitative competition from generic entrants, which provide social benefits in terms of significantly lower prices.

The patent system is the public policy instrument designed to balance the tradeoffs inherent between these dynamic and generic forms of competition. Without a well-structured system of patent protection, neither the research pharmaceutical industry nor the generic industry would be able to grow and prosper, as the rate of new product introductions and patent expirations would decline significantly.

II. INTERNATIONAL COMPARATIVE STUDIES

Insights on the importance of patent protection in pharmaceuticals also can be obtained by comparing the innovative performance of the pharmaceutical industries in countries with and without strong patent protection. Strong systems of patent protection exist in all countries with strong innovative industries in pharmaceuticals. This is reflected in Figure 1, which shows the distribution of consensus new drug introductions in global markets categorized by the nationality of the originating firms for the period 1970–85. The USA accounts for the largest share of consensus drugs with

[14] Ibid.

[15] Grabowski and Vernon, 'Effective Patent Life in Pharmaceuticals', see above n 13.

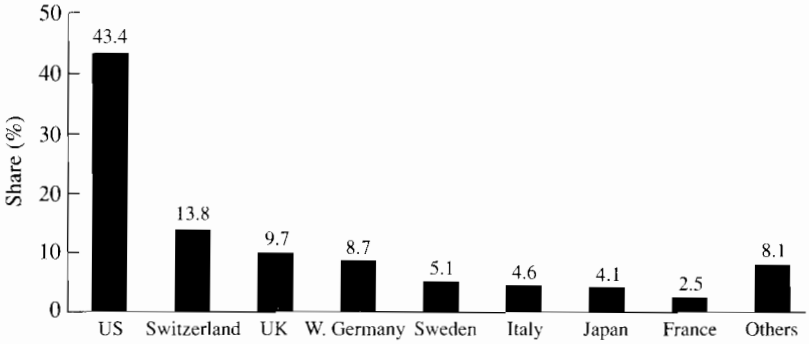

Figure 1. Consensus new drug introductions: nationality or originating firm.

43%, followed by several countries of Western Europe and Japan. All of the countries with innovative industries have significant patent protection for new drug introductions in terms of both the coverage and the length of effective patent life.[16]

Japan provides an interesting case study. Until 1976, patent protection for pharmaceuticals was relatively weak. Only process protection was available. Their system did not encourage investment into real innovation. Instead, the energies of Japanese firms were primarily devoted to copying new drug innovation from abroad for sale within Japan. There was no development of an innovative industry and limited export potential associated with this system.

In 1976, Japan decided that it was in its long-term interests to change these policies. In that year, the patent system was amended to allow full product patent protection for terms of 15 years. In the two decades since the change, Japan has emerged as one of the leading areas of international R&D activity in pharmaceuticals. The Japanese industry has evolved from an imitative entity to an innovative one.[17]

[16] The data for Figure 1 were compiled from US FDA and Paul de Haen databases. Consensus NCEs are defined as new drugs approved for marketing in at least six of eleven major country markets over the period 1970–1985. See Henry Grabowski, 'Innovation and International Competitiveness in Pharmaceuticals' in Arnold Heertje and Mark Perlman (eds), *Evolving Technology and Market Structure: Studies in Schumpeterian Economics* (Ann Arbor, MI: University of Michigan Press 1990), P. E. Barral has expanded on this analysis for the 1975–94 period using different criteria to measure the innovative importance of new drugs emanating from the pharmaceutical industry in different countries. His analysis also indicates a strong concordance between innovating performance in a country and its degree of patent protection. P. E. Barral, *Twenty Years of Pharmaceutical Research Results Throughout the World (1975–94)* (Paris: Foundation Rhone-Poulenc Sante 1995).

[17] Ian Neary, 'Japanese Industrial Policy and the Pharmaceutical Industry', in Adrian Towse (ed), *Industrial Policy and the Pharmaceutical Industry* (London: Office of Health Economics 1995) 12–29.

Canada is another country that has changed its patent laws. The Canadian system historically featured a compulsory licensing approach to drug patents. This strongly discouraged investment in its domestic industry. Canada discontinued the practice in 1987 and adopted a system of strong patent protection for drugs. It has experienced a dramatic growth in R&D investment in its domestic pharmaceutical industry since making this policy change in 1987.[18]

In a recent paper, Evenson and Kanwar perform an econometric study of the relationship between R&D investment and the strength of a country's patent protection.[19] This study also considers several other control variables involving country-specific characteristics. In this study, Evenson and Kanwar utilize a cross-country panel of 32 countries over the period 1981–90. The strength of a country's patent protection is measured by an index which incorporates five aspects of patent laws: extent of coverage, observance of international patent agreements, provision for loss of protection, enforcement mechanisms, and the duration of protection. Evenson and Kanwar find that there is a strong positive association between countries' intellectual property protection and their R&D investment expenditures. The relationship continues to hold even when several relevant control variables are present in the regression model. Hence, they conclude that 'the evidence unambiguously indicates the significance of intellectual property rights as incentives for innovation'.[20]

Overall the strong association between patent protection and R&D investment suggests that an interactive dynamic process is at work. In particular, countries that wish to encourage R&D investment and innovation have industrial policies that feature strong patent protection approaches. These policies in turn play an important role in incentivizing firms in industries like pharmaceuticals and biotechnology to undertake the long, costly, and risky investments that characterize the innovative process in these industries.[21]

[18] Compulsory licensing in Canada was replaced with a system of drug pricing controls administered by the Canadian Patented Medicine Review Board. As part of this change, the pharmaceutical industry agreed to locate in Canada drug R&D activities roughly proportional to Canada's share of their world sales. For an analysis of the Canadian situation, see S. R. Shulman, 'The Canadian Patented Medicine Review Board: New Rules and New Statues', 6 Pharmaco Economics (1994) 71–79. See also Patricia M. Danzon, *Pharmaceutical Price Regulation* (Washington: American Enterprise Institute 1997).

[19] Robert E. Evenson and Sunil Kanwar, *Does Intellectual Property Protection Spur Technological Change* (New Haven: Yale Economic Growth Center Discussion Paper, No 831; June 2001.)

[20] Ibid.

[21] For an analysis of the scope of relevant industrial policies pursued in several leading countries and their impact on pharmaceutical innovation, see Adrian Towse (ed), *Industrial Policy and the Pharmaceutical Industry*, previously cited above in n 4.

III. PHARMACEUTICAL PATENTS AND DEVELOPING COUNTRIES

A. Barriers to innovation and access

The patent system has played a critical role in incentivizing R&D investments for global diseases like AIDS, cardiovascular illnesses, and cancer. At the same time, relatively little public or privately supported R&D investment is currently directed to diseases specific to developing countries such as malaria, tuberculosis and schistosomiasis, even though these diseases currently afflict millions of individuals. This lack of strong interest is illustrated by the fact that only 13 of the more than 12,000 new drugs introduced globally, between 1975 and 1997, were specifically directed to tropical diseases.[22] The basic problem, from a return on investment perspective, is the low income and low expected potential sales in developing country markets. The problem is compounded by the lack of patent protection in many developing countries, the fact that developing countries devote as little as $2 per capita per year on health, and the reluctance of developed nations to come to their aid.

A different, but related issue involves access to new medicines developed in high income countries for global diseases like AIDS and hepatitis, cancer and cardiovascular illnesses. It must be noted that more than 90% of the drugs on the World Health Organization's (WHO) List of Essential Drugs are not patent protected, and are sold at comparatively low prices. Nevertheless, the extremely low per capita spending on medicines in those nations suggests that low prices on essential drugs do not, on their own, result in adequate utilization. In the case of patented drugs, their comparatively higher prices can serve as an additional barrier to many individuals in gaining access to the newest medicines. The development of several new medicines to treat AIDS in the 1990s has brought the access issue to the fore in sub-Saharian Africa and other developing countries experiencing this global epidemic.

Recent events have shown that developing countries, when confronting epidemics and national health emergencies, do possess some viable options for gaining access to patented medicines. Under the TRIPS Agreement, countries retain various policy instruments such as compulsory licensing and price controls for gaining access to new medicines in the case of national health emergencies and various other circumstances.[23,24] Furthermore, the goodwill

[22] Bernard Pecoul, *et al.*, 'Access to Essential Drugs in Developing Countries: A Lost Battle?', 281 Journal of the American Medical Association (1999) 361–67.

[23] F. M. Scherer and Jayashree Watal, *Post-TRIPS Options for Access to Patented Medicines in Developing Countries*, WHO, Commission on Macroeconomics and Health, available as Working Group 2 Papers on the web at www.cmhhealth.org/cmh_papers&reports.htm.

[21] Jean Lanjouw also provides a recent analysis of the benefits and limitations of these various options. In her paper, she advocates a new mechanism of differential patent protection. This mechanism is designed to facilitate access in developing countries to new products targeted toward global diseases, while preserving the incentives for R&D on diseases specific to third-world countries. See Jean O. Lanjouw, *Intellectual Property and the Availability of Pharmaceuticals in Poor Countries*, Center for Global Development, Working Paper no 5, April 2002 (forthcoming in *Innovation Policy and the Economy*, vol 3, 2002).

benefits from corporate philanthropy as well as the critical glare of unfavourable international publicity can be powerful carrot-and-stick forces for facilitating access to these new medicines at a reasonable cost. In the case of AIDS, many of the drug manufacturers have agreed to provide their medicines at cost, and some now provide their products without charge as charitable donations to these countries.[25]

The provision of products at cost or below cost raises other trade-related issues. One of the major issues from the standpoint of the companies is the possibility that these products will be pirated and illegally diverted to high-income countries where they can be sold at the higher prices prevalent in these countries. Parallel exportation of drugs from low- to high-income countries could undermine the willingness of pharmaceutical firms to continue to provide these products at low prices, since this kind of arbitrage would adversely affect the return on their investment in major markets.[26] If parallel exportation becomes a serious problem, an international agreement barring parallel exports from developing countries to high income countries may be necessary to avoid these adverse consequences. Such an international agreement would serve patient interests in developing countries.[27]

In most cases, even the marginal costs of most AIDS drugs, whether supplied by large pharmaceutical firms or generic entities, far exceed the total per capita health expenditures of these countries.[28] Hence charity and donations from many sources – including foreign governments, non-profit foundations and corporate entities – will be essential if the global community is to deal effectively with this and other epidemics.[29] As discussed further below, some pharmaceutical firms have an impressive history of in-kind donations to developing countries and this is something that should be encouraged as part of the overall solution to this crisis.[30]

Under current US tax law, firms can deduct charitable donations on their corporate income tax and thus recover part of the costs associated with donating the products.[31] They also receive corporate goodwill from such donations. As the tax laws are currently constructed, US firms cannot deduct more than twice their inventory cost of donated product. In a recent paper commissioned for the WHO, Scherer and Watal show that the incentives for firms to

[25] Mark Schoofs and Michael Waldholz, 'Price War Breaks Out Over AIDS Drugs in Africa as Generics Present Challenge', *Wall Street Journal*, 7 March 2001.

[26] Controls over illegal division are generally more feasible when non-governmental organizations (NGOs) play a primary role in the distribution of the drug products.

[27] Scherer and Watal, above n 23.

[28] Jeffrey Sachs, 'The Best Possible Investment in Africa', *New York Times*, 10 February 2001.

[29] Hans Binswanger, *How to Make Advanced HIV Treatment Affordable for Millions in Poor Countries*, US Conference on AIDS, Atlanta, GA, October 2000.

[30] Peter Wehrwein, 'Pharmacophilanthropy' (1993) available at http://www.hsph.harvard.edu/review/summer_pharmaco.shtml

[31] Scherer and Watal, above n 23.

undertake these donations of product could be increased if US tax laws were re-interpreted or modified to impose no net cost on the donor.[32] In this case the burden would be shifted to the US taxpayers. Some would argue that if this is to be done, it should be done directly as part of American foreign aid policy rather than indirectly through tax incentives. As a response to this argument, Scherer and Watal point out that charity via non-transparent tax expenditures is often more politically feasible than direct governmental subsidies. Accordingly, they argue that tax-*incentivized* grants should be aggressively pursued as an important approach to increase the supply of life-saving drugs to the world's poor.[33]

B. Encouraging drug innovation for third world diseases

While access to patented medicines in less affluent nations presents many thorny policy issues, the more long-run and to-date intractable problem involves the need for greater R&D investment and drug innovation devoted to diseases endemic in these countries. These diseases have no viable markets in more affluent countries to spur such investment efforts. The remainder of this paper is devoted to a discussion of this issue.

From an economic incentives perspective, the problem of developing medicines for tropical diseases like malaria and tuberculosis is similar in nature to the 'orphan drug' problem concerning new medicines for rare illnesses. In both cases, there are inadequate incentives for companies to bear the high costs and risks of new drug development. In the case of orphan drugs, this problem is similar: Small numbers of patients afflicted with rare diseases, such as Wilson's disease or Huntington's disease, make R&D programs that might help these afflicted patients economically infeasible. In the case of diseases endemic in developing countries, a mirror-image problem exists: a lack of economic resources resulting from low per capita health spending discourages research, even though in this case the number of patients is enormous. One could thus categorize these tropical diseases as 'orphan diseases' even though the afflicted patient populations are very large.

As mentioned above, some pharmaceutical firms have developed medicines for particular tropical diseases and made them available under drug donation programmes. This has included medical infrastructure support as well as free medicines. The most notable of these programmes is Merck's donation of its

[32] Ibid, Section 6.4, 54–59. Since the US corporate income tax rate is 34%, a deduction of twice the cost would only cover 68% of a firm's overall costs. Scherer and Watal point out that inventory costs include some fixed costs and hence are greater than a firm's marginal cost of production. But this is not usually sufficient for firms to fully cover marginal costs under existing law. For that to occur, one would need to increase the cost basis for tax deductions or medicines. Senator Lugar has introduced a bill to increase the cost basis for in-kind donations of food supplies (S37IS, Good Samaritan Hunger Relief Tax Incentive Act, introduced into the US Senate on 22 January 2001).

[33] Scherer and Watal, Section 7, 63.

drug Mectizan® (*ivermectin*) for river blindness, beginning in 1987.[34] Since that year, more than 200 million individuals have been treated for this disease in 33 countries.[35] Other significant drug donation programmes include the anti-filariasis drug, *albendazole*, by Glaxo Smith-Kline, the anti-trachoma initiative sponsored by Pfizer, and Novartis' donation of multi-drug therapy to eliminate leprosy. Importantly, each of these corporations has made a commitment to sustain the projects until the target diseases are eradicated as health threats.[36]

While drug donation programmes can make a strong contribution to patient welfare in less affluent countries, one cannot expect them to be the cornerstone to solving the orphan disease problem of these countries. The problems posed by these diseases are too broad in scope to rely primarily on charitable donations from a relatively small number of private sector entities and their NGO partners. A broader public-private partnership approach to the issue is necessary. The case of the US Orphan Drug Act is instructive in this regard.

In 1983, Congress passed the Orphan Drug Act, which provided a variety of incentives to undertake R&D on orphan drug indications (defined in a subsequent law as diseases or medical conditions which affect fewer than 200,000 patients).[37] The economic incentives included in the Act involved R&D tax credits, a clinical research grants programme, accelerated reviews at the FDA, and a guaranteed market exclusivity period of 7 years from the date of FDA approval (this was separate from any normal patent protection that might also apply to these products). Funding for R&D has also been provided by various non-profit foundations focused on particular rare illnesses.

The effect of these incentives on the development of new orphan drugs has been impressive. In the period between 1983 and 1999, more than 200 drugs and biologicals for rare diseases have been introduced.[38] This represents more than a 12-fold annual increase compared to the decade prior to the enactment of the law, when fewer than 10 such products came to the market for the entire 10-year period. In a recent paper, Professor Frank Lichtenberg has shown that the Act has had a favourable effect on mortality from rare illnesses. While the number of deaths from rare diseases had been increasing faster than those from other diseases in the 5-year period prior to 1983, the number

[34] Wehrwein, above n 30.

[35] Wehrwein, above n 30, and correspondence with Jeff Kemprecos and Jeff Sturchio at Merck.

[36] Wehrwein, above n 30, and private communication with James Russo, Executive Director of the Partnership for Quality Medical Donations (www.pqmd.org).

[37] Sheila R. Schulman *et al.*, 'Implementation of the Orphan Drug Act: 1983–1991', 47 Food and Drug Law Journal (1992) 363–403.

[38] Frank R. Lichtenberg, *The Effect of New Drugs on Mortality from Rare Disease and HIV* (New York: Columbia University 2001).

of deaths from rare diseases declined, both in absolute terms and relative to other deaths, in the post-1983 period.[39]

To attack the 'orphan disease' problem confronting third world countries for diseases like malaria and leprosy, one needs an international counterpart to the US Orphan Drug Act. From a scientific standpoint, it is an auspicious time to proceed with such a programme, given the recent advances in genomics which enhance the possibility of developing significant new vaccines and therapies for infectious diseases prevalent in less affluent countries. As in the case of the Orphan Drug Act, a multifaceted approach is necessary including R&D subsidies to firms with promising new technologies. These could be funded through government as well as non-profit charitable entities and public-private partnerships. Given the low-income base of third world markets, success of these programmes might well hinge upon guarantees to purchase amounts of economically sustainable products that are successfully developed. The purchase agreements could be tied to up-front commitments from the firms on the product's price within third-world markets. Michael Kremer has characterized R&D incentive programmes based on purchase guarantees as 'pull' programmes and analyzed how they could be designed in the context of new vaccines for third-world diseases.[40]

A variety of risk- and reward-sharing arrangements between pharmaceutical firms and funding sponsors could be envisioned. The objectives would be to provide incentives for new R&D programmes for diseases in developing countries. For example, under the Gates Foundation-sponsored International AIDS Vaccine Initiative (IAVI), firms have received grants to partially support development of AIDS vaccines targeted to African strains of the disease. The firms retain international patent rights to the technology, but have agreed to supply any approved vaccines developed from this programme at a small margin over cost to developing countries. Such terms can be particularly attractive to earlier stage biotech firms seeking funding for proof of principle for a new technology with multiple applications. Similarly, the Global Alliance for TB Drug Development has recently announced a memorandum of understanding with Chiron for the development of a new TB drug for which no royalties would be due on sales in less-developed countries.[41]

In summary, the success of the US Orphan Drug Act in stimulating R&D investment and innovation for diseases with low expected market potential provides a useful model for the orphan disease problem confronting less industrialized countries. While the characteristics of particular programmes may differ significantly from those employed in the case of the US Orphan Drug Act, the basic principle of public and private risk sharing within the context of a system of market incentives would appear to be a fruitful guiding principle.

[39] Ibid.

[40] Michael Kremer, 'Creating Markets for New Vaccines', 1 Innovation Policy and the Economy (2001): 35–118.

[41] Details of the agreement can be found on the Alliance website www.tballiance.org.