Chapter **6**

Product Development Priorities

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The overall goal of this chapter is to introduce the multistep process that leads to new product development and use and to outline the economic and institutional context for products developed specifically for major global diseases. In addition, it attempts to define the major financial efforts under way to help stimulate the process. Because product development is integrally related to intellectual property issues and to regulatory and liability concerns, these topics are also included. Data on product development for the developing countries are not systematically available. We have, therefore, used information based on analyses for developed countries and, when possible, made comparisons.

INTRODUCTION

In recent decades, scientific advances in many disciplines, particularly molecular biology, genomics, and medicinal chemistry, opened the way for developing new therapeutic agents, several vaccines, and enhanced diagnostic capabilities. The central questions for the purpose of this chapter are what drives research, discovery, and development and what institutional and financing arrangements are necessary to promote research and development (R&D) for global diseases? Medical needs and public health imperatives constitute the logical answer to the first question; however, our armamentarium for combating major global diseases suffers from certain fundamental gaps. Innovation or discovery in the health fields is the process whereby the findings of many sciences are translated from basic findings into approaches to protect health (vaccines) or reverse disease (therapeutic and diagnostic products).

Even though investigators have explored the conceptual framework for understanding how knowledge may be translated into products over the years, consensus is lacking on the specific drivers of the process or on the effects of alternative institutional arrangements.

Several features of the innovation process and its environment are essential for product development (Hilleman 2000; Nederbragt 2000; Schmid and Smith 2002). Innovation advances through a sequence of steps from discovery, through process development, to animal and human testing—a sequence with many overlapping features. Discovery may come in two ways: in a nonlinear, quantum-leap fashion that results in findings of an unexpected or unpredictable nature or in a linear fashion that builds on existing knowledge. Nonlinear processes are characteristically random despite many efforts to inject varying degrees of predictability or goal definitions (Webber and Kremer 2001). By contrast, the goal of linear innovation is defined improvement of a known process or mechanism.

Discovery

Product development is fundamentally anchored to the discovery process. In modern societies, discovery represents a societal capability that involves multiple institutions and constituents. The concept of networks of innovation has been introduced to describe one of the processes of discovery that leads to the development of pharmaceutical products or vaccines (Galambos and Sewell 1995, 272). Original scientific observations are made in organizations widely distributed across society, such as academic environments, government laboratories, biotechnology companies, or the large organizations dedicated

to R&D. Because of the multiplicity of these settings and the traditions of open scientific communications, combined with the high costs of research and the importance of incentives, intellectual property issues must be taken into account.

The outcome is appreciably complex. Therefore, prescribing in a systematic way how to develop products along a planned pathway—particularly those intended for use in developing countries—is challenging. Recent decades have witnessed many attempts to develop specific drugs or vaccines to meet developing countries' needs, and the process has been difficult. Examples include pharmaceuticals to treat major global killers such as malaria and African trypanosomiasis and vaccines for most of the diarrheal diseases and respiratory infections (Nossal 2000).

Development Cycles

Discovery may set in motion a series of steps that eventually leads to the deployment of a product suitable for human use. The next step following discovery is process definition to map the steps of manufacturing and scalability to optimize the size of manufacturing. This process involves translating an idea discovered anywhere in the multiplicity of settings defined earlier, including mobilizing the energies of many sciences, to come up with a product. For instance, for a discovery in the therapeutic field to be translated into a drug, the sciences of medicinal chemistry, structural biology, and structure-function relationships are fundamental to the process. More recently, the product development process has begun using genomics and proteomics to bring about a more focused approach to defining clinical candidate products. Only then are pharmacology, toxicology, and bioavailability used in the next phase of therapeutic evaluation.

The capabilities for process definition and scalability have traditionally been concentrated in the research-based pharmaceutical industry, but several recent successful efforts in public-private partnerships (PPPs) have expanded these capabilities, such as the Medicines for Malaria Venture (MMV) and Global Alliance for TB Drug Development (GATB). Developing countries such as Brazil, India, and the Republic of Korea are now undertaking major efforts to achieve similar capabilities (Biehl 2002; Lohray 2003).

Therapeutic evaluation may begin at an in vitro or molecular level before proceeding to animal testing and the usual three phases of human assessment (Hilts 2003). The scientific disciplines of clinical research, epidemiology, and biostatistics have progressed at a significant pace in recent decades. In parallel, ethical and societal concerns about research involving human subjects and its standards, particularly across countries, cultures, and capabilities, are being extensively debated (Agre and Rapkin 2003; Barrett and Parker 2003; Emanuel and others 2004; McMillan and Conlon 2004).

The engineering aspects of product development are the next major step. Optimizing manufacturability and assessing market needs to determine the level of investment required for plant construction and operation are the two fundamental components of this phase.

One important feature of discovery and development is the length of time it takes. Estimates indicate that the average time for a new chemical entity (NCE) or vaccine to proceed from discovery through preclinical testing, human clinical trials, and regulatory approval is longer than a decade (Garber, Silvestri, and Feinberg 2004; Hilleman 1996; Rappuoli, Miller, and Falkow 2002), including the time spent on unsuccessful attempts. This timeline imposes certain pressures on how decisions are made, on the investment needed, and on competing priorities.

Development Institutions

As indicated previously, innovation and discovery occur in a multiplicity of settings. Although these settings have been concentrated in developed counties and have served the process of product development well, the challenges of developing new products for the developing world are considerable. Many countries, such as Brazil, India, and Singapore, are initiating a new wave of fundamental research institutions (Ahmad 2001; Jayaramann 2003). Their involvement in the discovery of products necessary for the health needs of developing countries is a fundamental paradigm shift. Along with the developing world's emerging biotechnology industry, a movement toward product discovery and development is under way. In addition, multiple PPPs—for example, the MMV (2002) and the GATB (2001)—are adding to the total global effort (Lyles 2003; Widdus 2001). The major feature of these new settings is their ability to focus on the immediate needs of developing countries. The challenge, however, lies in sustaining their funding and ensuring their ability to proceed from discovery to development and manufacturing, possibly with appropriate partners.

Finally, the evaluation of a product's pharmacological, biological, and toxicological properties may be carried out in developed or developing countries. Indeed, the evaluation of the safety and efficacy of products intended for developing countries should occur in those settings. Although quality control standards should be applied globally (Milstien and Belgharbi 2004), specific efforts must be directed at protecting the rights of human subjects (Agre and Rapkin 2003; Barrett and Parker 2003; Emanuel and others 2004; McMillan and Conlon 2004). In general, clinical development is heavily regulated in developed countries, and additional mechanisms exist for monitoring other aspects of product development, such as animal experimentation, use of controlled substances, and so on, but the global situation varies considerably. The time is ripe to consider the development of a global coordinated effort that involves uniform standards and reciprocity.

The analysis in the following sections focuses on the costs of developing drugs, vaccines, and diagnostics. The emphasis on

drugs and vaccines reflects both the available evidence and the fact that regulatory requirements and costs are much greater for drugs and vaccines than for devices and diagnostics.

PHARMACEUTICAL PRODUCTS

The costs of developing new medicines and diagnostics reflect both the technical complexities of product development and costs related to regulatory approval, which requires clinical trials to establish product safety and efficacy. Although the relative contributions of these two components are difficult to distinguish empirically—and even conceptually—there is general consensus that increasing regulatory requirements have contributed to the rising costs of new product development in the United States. In considering the costs of new product development for diseases prevalent in low-income countries (LICs), we attempt to identify those costs that might be influenced by regulatory policy as opposed to the unavoidable costs resulting from the hard science of new product development.

R&D Costs for Drugs for Industrial Countries

The most detailed evidence on the cost of developing new drugs is from DiMasi, Hansen, and Grabowski (2003), who estimate the cost of bringing a compound to market at US$802 million in 2000 dollars. Their estimate is based on U.S. data from 10 major companies for a randomly selected sample of 68 compounds that entered human testing between 1983 and 1994 and reached approval between 1990 and 2001. The 68 compounds include 61 small molecule chemical entities, 4 recombinant proteins, 2 monoclonal antibodies, and 1 vaccine. Together, the 10 companies accounted for 42 percent of R&D by U.S. companies. The cost estimates are based on project-level data obtained from the companies for the period 1980–99. The sample was restricted to compounds that originated within these companies to avoid omitted costs of in-licensed products.

Earlier studies using similar data and methods found significantly lower R&D costs for drugs launched in the 1970s and 1980s (DiMasi and others 1991; Hansen, 1979). For the 1980s drug cohort, the estimate was US$359 million per NCE (U.S. Congress, Office of Technology Assessment 1993). Thus, the estimate for the 1990s drug cohort of US$802 million represents a significant increase over and above inflation.

Three main factors contribute to this high and rising cost of R&D. Understanding the contribution of each of these factors is important to understanding whether drug R&D costs might be lower in developing countries.

First, the inputs into pharmaceutical R&D are costly, including highly trained scientists, highly specialized capital equipment, expensive animal studies, and clinical trials involving thousands of human subjects that are often coordinated across multiple countries. Clinical trial out-of-pocket costs reflect expenditures on patients' medical treatment and monitoring, data collection, and analysis. In the study by DiMasi, Hansen, and Grobowski (2003), the average expected clinical cost, adjusted for the probability of entering each clinical phase, was US$60.6 million per compound entering human trials. In addition, the authors estimated that the out-of-pocket costs of drug discovery and preclinical development account for 30 percent of overall R&D costs, raising the total expected out-of-pocket cost to US$86.8 million per compound entering clinical trials. The average number of clinical trial patients per compound was 5,303, and the average cost per patient was US$23,500 before adjusting for the probability of entering each clinical phase.

Second, in the United States, the Food and Drug Administration (FDA) approves only roughly one in five compounds that enter human clinical trials.[1] The costs incurred for the four out of five compounds that failed must be included as costs of bringing one new compound to market. Failures occur because of safety concerns, lack of significant efficacy, and poor economic prospects. Even though the new technologies of drug discovery should eventually improve predictive accuracy for both safety and efficacy, success rates were no better in the 1990s than in the 1980s (DiMasi, Hansen, and Grabowski 2003; DiMasi and others 1991). Adjusting for failure rates raises the total out-of-pocket cost from US$86.8 million to US$403 million per approved compound.

Third, the US$802 million total cost estimate includes the opportunity cost of capital over the roughly 12-year investment period. Using an 11 percent real (net of inflation) cost of capital, DiMasi, Hansen, and Grabowski (2003) estimate the total cost of capital at US$399 million. This figure represents the return that shareholders would have received had they invested in activities that yielded immediate returns rather than in the lengthy drug discovery process. If pharmaceutical R&D is financed by—and hence must compete for—private equity capital, shareholders must be compensated for this opportunity cost. Thus, the cost of capital is appropriately included as a cost of R&D if the R&D is undertaken in commercial firms and financed by equity capital. As discussed later, if not-for-profit organizations finance R&D, the opportunity cost of capital may be lower. If we assume financing by private equity, adding the US$399 million cost of capital to the US$403 million out-of-pocket cost yields US$802 million as the capitalized cost at launch, before taxes, per approved compound. The after-tax estimate is considerably lower because, like any business expense, R&D expenses are tax deductible, plus R&D tax credits may be available in certain circumstances. However, for purposes of comparing the costs of R&D to the revenues a commercial firm would require to cover these costs, if costs are measured net of tax, then revenues must also be measured net of tax, in which case adjusting for tax makes little difference. Hereafter we use the before-tax R&D cost estimates to facilitate

comparison with other estimates of R&D costs. The before-tax estimates are also most relevant to not-for-profit firms and PPPs that are not subject to taxes.

If commercial firms facing a commercial cost of capital and with no in-kind contributions (see the next section) undertake R&D, they might be able to save roughly 10 to 20 percent of their costs by conducting trials in developing countries and possibly more if they adhere to the countries' regulatory requirements, which may permit fewer and shorter trials than are normal for the FDA. Whether firms could realize those potential savings may be a matter of judgment depending on perceived liability risks. If commercial firms conduct R&D for LIC diseases in not-for-profit spinoffs, they may realize tax advantages and a lower cost of capital, which would further reduce their cost below the US$802 million estimate.

R&D Costs for Drugs for Developing Countries

Recent studies by two PPPs that focus on new product development for diseases in developing countries yield much lower cost estimates for drugs in their portfolios than those in the previous section. The GATB and the MMV estimate the costs of R&D at US$150 million (MMV 2002) and US$178 million (midpoint of the range of US$115 million to US$240 million) (GATB 2001, 101) or less than a quarter of DiMasi, Hansen, and Grabowski's (2003) estimate of US$802 million. The reasons for these large differences are instructive.

First, the GATB and MMV estimates reflect only out-of-pocket costs, with no allowance made for the opportunity cost of capital. Nevertheless, the estimates of out-of-pocket cost are less than half of the US$403 million out-of-pocket cost estimated by DiMasi, Hansen, and Grabowski (2003). This difference in out-of-pocket costs primarily reflects two factors: (a) fewer clinical trials and, hence, fewer patients in trials—namely, 1,368 patients per drug for the GATB compared with 5,303 in the DiMasi, Hansen, and Grabowski (2003) study—and (b) lower costs per patient of US$1,000 to US$3,000 for the GATB for trials run in developing countries compared with US$23,500 per patient in the DiMasi, Hansen, and Grabowski (2003) study.

Some drugs for LICs may require fewer trials, fewer patients, or both per trial because of differences in drug types and trial objectives and different regulatory requirements. For example, some of the drugs in the two PPPs' portfolios are modifications of existing drugs for which some data have been established. R&D costs for LIC drugs may also be lower to the extent that these drugs are tested for fewer indications, with less within-sample stratification by patient subgroup and less need to test for drug interactions. Clinical effects for infectious and parasitic diseases may also be greater than for chronic diseases, which permit smaller trial sizes.[2] The lower trial cost per patient for LIC drugs partly reflects the lower costs of conducting trials in developing countries, with much lower costs of medical care and

personnel than in the United States. The trial duration may also be shorter because the target diseases are acute rather than chronic. To the extent that the lower out-of-pocket clinical costs in the GATB and MMV studies reflect fewer patients in trials and lower cost per patient, such savings could, in principle, apply to LIC drugs regardless of whether these drugs are developed by not-for-profit or commercial enterprises.[3]

Another factor contributing to the lower out-of-pocket costs reported by the MMV and the GATB is that these PPPs benefit from in-kind contributions of personnel, technologies, and other resources supplied by their industry and academic partners. The MMV estimates these in-kind contributions as equivalent to its own incurred costs. Thus, if these in-kind contributions are included, the full social cost for developing LIC drugs increases to US$250 million to US$300 million per compound, or only 25 to 35 percent less than the DiMasi, Hansen, and Grabowski (2003) estimate of US$403 million. However, as long as such in-kind contributions are available without charge to PPPs, the actual budget cost to PPP funders is only US$150 million to US$178 million, or less than half DiMasi, Hansen, and Grabowski's (2003) estimate.[4]

The second major determinant of R&D costs is failure rates. The GATB and MMV estimates show overall drug failure rates similar to those in DiMasi, Hansen, and Grabowski's (2003) study. Indeed, there is no obvious reason to expect significant differences in failure rates if LIC drugs face similar scientific challenges and are reviewed by the FDA or the European Medicines Evaluation Agency applying the same safety, efficacy, and risk-benefit tradeoff standards as are applied to drugs for the industrial countries. However, if the regulatory review of LIC drugs uses risk-benefit tradeoffs that reflect conditions in developing countries, then success rates might be higher, implying a lower budget cost per approved compound for LIC drugs.

Finally, the third major contributor to R&D costs is the opportunity cost of capital, which accounts for US$399 million, or almost half of DiMasi, Hansen, and Grabowski's (2003) US$802 million cost per compound. The GATB and MMV estimates do not include the cost of capital. Whether the cost of capital should be included in estimating the cost of R&D for LIC drugs depends on the circumstances and the perspective. If LIC drugs are to be developed by commercial firms that must generate a competitive return for their shareholders, then the cost estimates appropriately include a cost of capital at roughly 11 percent, as in the DiMasi, Hansen, and Grabowski (2003) study. However, if LIC drugs are developed by PPPs or other not-for-profit institutions with financing from philanthropic or governmental agencies, the opportunity cost of capital may be lower if these funders typically do not require a rate of return on their investment to compensate them for the forgone alternative uses of the funds during the investment period. For example, government investments sometimes assume a social opportunity cost of capital of about 5 percent. Using a 5 percent cost of

capital for financing from philanthropic or governmental agencies implies a roughly 50 percent markup over out-of-pocket R&D costs to reflect the cost of capital rather than the roughly 100 percent estimated by DiMasi, Hansen, and Grabowski (2003), assuming the same time flow of investments.

Applying this markup to the US$150 million to US$178 million estimated out-of-pocket R&D cost for the MMV and the GATB yields a total capitalized R&D cost of roughly US$250 million for LIC drugs if they are developed by PPPs with foundation or government funding, assuming that in-kind contributions are at current levels and that trials are conducted in developing countries. Alternatively, these funders might choose to use a zero cost of capital, reflecting the importance that they attach to developing new medicines to treat currently untreatable diseases and to replace existing drugs that are increasingly ineffective because of resistance. In that case, the appropriate capitalization cost is zero, and the out-of-pocket costs of US$150 million to US$178 million are the full R&D costs per new compound for LIC diseases.

Economics of Vaccine Discovery and Development

In discussions of the economics of vaccine development, comparing the findings with those obtained for pharmaceuticals is useful. Note, however, that the two product categories are different in many fundamental and practical aspects. Pharmaceuticals are used to treat an existing clinical condition with the ultimate aim of reversing the course of disease. By contrast, vaccines are used to prevent a future threat. In addition, pharmaceuticals may be administered over a prolonged time frame and, in many chronic conditions, may be taken from the time of diagnosis for the rest of the patient's life, whereas most vaccines are administered once or a few times.

The costs of vaccine production consist of the traditional components of discovery, process development, scale-up, and manufacturing, as well as the costs pertaining to regulatory requirements, liability, and postlicensing studies (Andre 2002; Grabowski 1997). Furthermore, the economic framework for disease prevention (Kou 2002) raises many questions that are less clear than calculating the cost of treatment of a specific pathological condition in an individual or setting priorities for government budgets. Finally, the financing of vaccine purchasing and immunization programs has traditionally been separated from the totality of health care financing. Although this practice may have appeared to be advantageous at some point globally or in individual countries, the current outcome is less than satisfying in that the financing of vaccines is fragmented (Institute of Medicine 2004) and competes at a less favorable level with other budgetary priorities.

Costs of Vaccine R&D

The decision to develop a new vaccine is usually based on medical need, scientific feasibility, and market conditions. Because most currently available vaccines have been developed over relatively long periods and multiple organizations have been involved in their discovery, our cost estimates are based on historical data and on many assumptions that are probably changing rapidly (Agre and Rapkin 2003; Barrett and Parker 2003; Emanuel and others 2004; McMillan and Conlon 2004). The cost elements are similar to those for pharmaceutical R&D except for the specific regulatory procedures for vaccines, such as the completion of plant construction before phase 3 trials.

As noted earlier, estimates indicate that an NCE costs US$403 million to US$802 million in 2000 dollars (DiMasi, Hansen, and Grabowski 2003). Clarke (2002) estimates that a vaccine costs approximately US$700 million by the time the product is marketed, including not only the actual costs of products, but also such items as the cost of failures and the cost of funds (Grabowski 1997). In addition, the size of phase three clinical trials has recently escalated along with costs.

The Institute of Medicine (2004) estimates that total expenditure on vaccine R&D in 1995 was US$1.4 billion. The large pharmaceutical companies accounted for approximately 50 percent of the total (Mercer Management Consulting 1995). However, the current situation is more complex for vaccine research than for drug R&D. In 2004, only five major multinational companies were investing in vaccine R&D and production (Institute of Medicine 2004). In addition, a multitude of smaller, new biotechnology organizations in both developed and developing countries are pursuing multiple vaccine targets that are of considerable value (Nossal 2004). Since September 11, 2001, U.S. government funding for microbial threats that can be used as agents of terror has increased: Project Bioshield is devoting more than US$5 billion during the next 10 years to discovering and producing vaccines and other therapeutics (Herrera 2004). These initiatives may have spillover benefits for vaccines and therapeutics for developing countries.

Another barrier, in addition to complexity and costs that may directly or indirectly affect investment in vaccine R&D, is the condition of the vaccine market. Even though experts anticipate healthy growth in the total global vaccine market from approximately US$6 billion in 2004 to US$20 billion in 2009, the number of large private pharmaceutical companies involved in vaccine research is down to five (Mercer Management Consulting 2002). As a recent Institute of Medicine report (2004) demonstrates, other significant barriers also stand in the way of a well-functioning vaccine research and production system. These barriers include the difficulties of entering the field and of financing research, plus in the United States they include the government's role in determining pricing in relation to the government's purchase of a significant proportion of vaccines. Similar situations arise in other countries. All lead to an underappreciation of the value of vaccines and reduce the incentives for investment in future vaccine products.

As noted earlier, whether the cost of R&D for drugs or vaccines intended for use in developing countries is less than for products targeted to high-income markets is questionable. Certainly, developing vaccines for LICs requires investment from both industrial and developing countries and participation by scientists from both industrial and developing countries. In the case of vaccines, discovery similar to pharmaceuticals is a costly process. Therefore, a research infrastructure has to be supported in academic institutions and private sector and government laboratories for new ideas to emerge and to be tested. The capabilities needed to discover a new HIV or malaria vaccine are different and far more complex than those used to manufacture traditional vaccines such as whole-cell pertussis. Indeed, the technological know-how needed to discover new vaccines is embedded in the advancing edge of science.

Alternative mechanisms of financing and managing the development of new vaccines for the developing world must be identified and may require governmental, international, and philanthropic funding. Appropriate new institutions or alliances could evolve from the multiple PPPs now being pursued. The case has repeatedly been made for a massive infusion of funds and global coordination if vaccines against great killer diseases such as HIV/AIDS are to be developed (Klausner and others 2003).

Effect and Cost of Vaccination Programs

The major societal and health effect of vaccines are realized mainly when immunization programs reach a significant proportion of individuals in a society (Mahmoud 2004). The effect of vaccines in interrupting or preventing the transmission of infectious agents depends on two concepts: inducing resistance in healthy individuals before exposure and extending the umbrella of prevention to the majority of the target population to achieve herd immunity (Anderson and May 1990). When deciding to mount a vaccination program, health professionals face scientific, public health, and financial considerations. The ultimate outcome is a cost structure that has to compete against well-established budgetary constraints and comparisons. The subject of the cost-effectiveness of vaccination programs has been examined at multiple levels and in many settings (Miller and Hinman 1999). The overall conclusion derived from most quantitative techniques—for example, cost-benefit analysis, cost-effectiveness analysis, and cost utility and decision analysis—indicates that vaccination was one of the most effective health measures of the 20th century (CDC 1999).

DIAGNOSTICS

Evidence-based disease control strategies are now in place for most of the major infectious diseases affecting developing countries. Implementing these strategies depends on accurate diagnostic methods. Progress has been made in securing adequate drug supplies to treat or prevent diseases such as tuberculosis (TB), and in many instances, the most pressing need is for improved diagnostics to ensure wider and wiser use of effective therapies. Thus, an urgent need exists to develop diagnostic tests that are simple, cost-effective, and robust enough to be used in resource-constrained settings with endemic diseases.

Diagnostics Development Priorities for Developing Countries

The top priorities for developing new diagnostic methods pertain to HIV, TB, and malaria. In the field of HIV/AIDS, where the goal is to simplify the diagnosis of HIV, the need is for a noninvasive, inexpensive, and simple but highly sensitive and specific HIV test for saliva, sputum, urine, or other body secretions, as well as tests for monitoring highly active antiretroviral therapy.

In diagnosis of mycobacterium TB, the limited sensitivity of microscopy and the diagnostic challenges posed by smear-negative, extrapulmonary, and pediatric TB emphasize the need to find an alternative approach. In this context, the Gen-Probe Amplified Mycobacterium Tuberculosis Direct Test (Coll and others 2003; O'Sullivan and others 2002) and nucleic acid amplifications assays, as well as serological tests (Perkins 2000), have great potential. Diagnosing latent mycobacterium TB infection using tuberculin skin testing has major limitations, including the inability to differentiate latent TB from active TB. The QuantiFERON-TB test (Mazurek and Villarino 2003), which was approved by the FDA for detecting latent mycobacterium TB infection, and the MPB64 patch test (Perkins 2000), a mycobacterial antigen test (Nakamura and others 1998) specific to the mycobacterium TB complex, are promising and should undergo further evaluation.

For specific diagnosis of malaria, the most useful approach would be a rapid test to determine whether patients who present with fever have malaria. If this rapid test has the capability of estimating parasite density, it may help predict those at higher risk of progression to severe disease or treatment failure.

For the major noncommunicable diseases—for instance, cardiovascular diseases—portable imaging devices, such as radiographic or ultrasound machines, are becoming the new standard for diagnosis. Adaptation of these technologies to settings in developing countries is urgently needed.

Economics of Diagnostics R&D

R&D for new drugs and vaccines poses major challenges in developing countries because of financial constraints and lack of infrastructure. By contrast, both the timelines and the costs of developing diagnostics are significantly lower even though the process of developing diagnostics is in many respects similar to

the development of drugs or vaccines. Whereas the costs related to clinical trials and the opportunity cost of funds are lower, the process does have additional engineering requirements. For diseases with relatively large at-risk populations, large and small biotechnology companies have been sufficiently attracted to invest in diagnostic R&D and stand to generate adequate commercial returns even for inexpensive products. For less common diseases or diagnostic indications, industry investment has been minimal, and direct R&D investment by the Special Programme for Research and Training in Tropical Diseases (TDR) (http://www.who.int/tdr) and other public sector agencies or PPPs will be needed if products are to be developed.

Diagnostics activity in the TDR's Product Research and Development Unit currently focuses on two disease areas through work carried out by the TB Diagnostics Initiative (http://www.who.int/tdr/diseases/tb/tbdi.htm) and the Sexually Transmitted Diseases Diagnostic Initiative. This work is done in partnership with academic researchers, disease control experts, public health officials from disease-endemic countries, and industry. The TDR has recently invested substantially in its capacity to support the clinical development and registration of new diagnostics and will work closely with industry, regulatory agencies, and ministries of health in industrial countries and disease-endemic countries to improve the quality and standardization of diagnostic trials and to facilitate the implementation and appropriate use of proven technologies. As an example, the mission of the TB Diagnostics Initiative is to work closely with interested parties to stimulate interest; identify obstacles; and facilitate the development, evaluation, approval, and appropriate use of new diagnostics for TB in LICs (http://www.who.int./tdr/about/resources/contributions.htm). Current activities include research on new diagnostic targets and methodologies, product development programs to facilitate commercial and noncommercial R&D, and formal laboratory and field product evaluation trials. The Sexually Transmitted Diseases Diagnostic Initiative is a 10-year-old collaborative project established in recognition of the critical need for improved diagnostic tools for common sexually transmitted diseases. Its mission is to promote the development, evaluation, and application of diagnostic tests appropriate for use in primary health care settings in developing countries, with a focus on syphilis, chlamydia, and gonorrhea.

Cost Estimates of Diagnostics R&D

No systematic estimates of the costs of developing diagnostics are available that are comparable to the studies for pharmaceuticals. The costs of developing new diagnostics depend on the type of tool; the duration from discovery to approval; and the technicalities involved in technology acquisition, patent fees, market research, laboratory and field trials, marketing and product launch, and support costs. Table 6.1 summarizes costs related to the development of selected diagnostics for TB. Note that these are out-of-pocket costs and do not include the

Table 6.1 Costs of Developing Selected TB Diagnostics *(US$)*

Item		Type of test			
			Nucleic acid amplification	Screening test	Drug susceptibility testing
Location of company	Rest of world	United States and European Union	United States and European Union	United States and European Union	United States and European Union
Market research costs	10,000	100,000	50,000	500,000	500,000
Technology acquisition and patent fees		275,000	250,000	50,000	200,000
Development of prototype		3,775,000	4,000,000	4,662,000	2,825,000
Consumables used during development		1,575,000		75,000	150,000
Scale-up and validation			600,000	200,000	200,000
Total product development costs	575,000	5,625,000	4,850,000	4,987,000	3,375,000
Total costs of clinical trials (location of study sites)	180,000 (disease-endemic countries)	1,450,000 (United States and European Union)	2,000,000 (United States and European Union)	294,000 (disease-endemic countries)	
Regulatory approval costs (agencies)	100,000 (FDA, European Union)	800,000 (United States)	454,000		
Marketing and launch support costs	80,000	1,500,000	200,000		
Product support costs for one year	50,000	1,125,000	20,000		
Total	995,000	10,600,000	7,574,000	5,781,000	3,875,000

Source: http://www.who.int.tdr/about/resources/default.htm.

opportunity cost of capital (http://www.who.int./tdr/about/resources/contributions.htm).

FINANCING AND INSTITUTIONAL ARRANGEMENTS FOR NEW PRODUCT DEVELOPMENT

Research that contributes to the discovery and development of drugs, vaccines, and diagnostics occurs in public, private, and mixed settings, each with different funding mechanisms.

Public Sector

In most high-income countries (HICs), government funding from tax revenues is generally targeted to basic research—that is, research that advances understanding of underlying disease processes but is unlikely to yield commercially viable products in the near term. The research may be done in government institutions or in academic and other not-for-profit research institutions. Governments also stimulate private sector R&D through tax credits.

Private For-Profit Sector

Applied research that targets specific products is generally undertaken by the private sector using equity financing. Firms that rely on equity financing must provide a return to their investors comparable to returns on other potential investments, hereafter referred to as a competitive return. This requirement applies for multinational pharmaceutical companies, for biotechnology firms, and for firms in developing countries, unless they receive public subsidies. Start-up firms in HICs generally rely on equity capital from venture capitalists and other private investors, whereas established firms issue shares in the broadly based public equity markets but finance most of their R&D from retained earnings on existing products. The need to provide a competitive return to shareholders means that commercial firms can invest only in products that they expect will generate sufficient revenues to cover all costs, including the costs of R&D. In practice, commercial firms have focused on products with a potential market in industrial countries because of their residents' ability to pay prices sufficient to cover costs.

Differential, or "Tiered," Pricing. For global products—that is, products targeting diseases that occur in all countries, such as cardiovascular diseases—revenues generated in HICs and in the more affluent sectors of middle-income countries are sufficient to recoup the investment in R&D to the extent that, ideally, prices in LICs need to cover only the incremental or marginal costs of production for these countries.

Even with pricing at marginal cost, medicines may still be unaffordable for the poorest populations, particularly for drugs with high manufacturing costs, in which case additional subsidies may be necessary. However, the important conclusion is that for drugs for global diseases, the existence of a market in industrial countries attracts private sector investment in R&D; thus, differential (tiered) pricing provides a finance mechanism for developing new drugs that can achieve both dynamic efficiency (appropriate incentives for R&D) and static efficiency (appropriate incentives for use of existing products) (Danzon and Towse 2005).

By contrast, for drugs and vaccines that target diseases that occur predominantly in LICs, no HIC market exists in which to recoup the costs of R&D, and patents and differential pricing will not suffice to attract R&D for products that cannot expect to generate sufficient revenue to cover their development costs. In 2002, annual per capita spending on drugs alone in member states of the Organisation for Economic Co-operation and Development was US$279, while developing countries typically spent less than US$20 per capita for all health services (Sachs 2001; Troullier and others 2002). Per capita health spending on drugs by the poorest individuals, who may be the majority of patients for communicable diseases, is even lower. Thus, for products that target LIC-only diseases, even if millions of patients are in need, expected revenues are insufficient to attract private sector investment for developing new products without additional public subsidies.

For HIV/AIDS, even though the majority of the disease burden is in LICs, the markets in HICs have been sufficient to attract private sector companies to develop several drugs and to undertake considerable investment in an AIDS vaccine, albeit with little success to date. In 2001, the GATB increased the estimated size of the TB market from US$150 million to US$450 million per year, with the potential to grow to US$700 million per year (GATB 2001). This amount is within the range normally considered necessary to attract private investment. However, estimated potential revenues for antimalarials and treatments for other LIC diseases are still well below this threshold. In addition to the limited ability to pay, some developing countries still lack the health care infrastructure necessary for conducting clinical trials and for delivering medicines and vaccines effectively, which further reduces incentives for R&D investment.

Given the low potential revenues and lack of necessary infrastructure, R&D for tropical diseases and TB for the past 25 years has been far less, relative to need, than for global diseases. The number of NCEs per million disability-adjusted life years lost (a proxy for research relative to need) was 0.55 for infectious and parasitic diseases but roughly 1.25 to 1.44 for cardiovascular system diseases (Troullier and others 2002). Between 1975 and 1999, just 16 of the 1,393 NCEs registered were for tropical diseases or TB (Troullier and others 2002).[5]

Several of these products were fortuitous by-products of commercial research efforts initially intended for the oncology or veterinary market (Ridley 2003).

Multinational companies appear to be showing some signs of increasing their investment in tropical disease R&D. For example, GlaxoSmithKline, AstraZeneca, and Novartis have recently announced or established research centers devoted to tropical disease. AstraZeneca's facility in Bangalore, India, will focus on TB treatments and receive a commitment of personnel and US$40 million in investment during 2003–8. The nonprofit Novartis Institute for Tropical Diseases in Singapore is a US$122 million joint venture between Singapore and Novartis that will focus on dengue fever and TB. GlaxoSmithKline has established a research institute for TB and malaria in Spain ("Drugs for the Poor" 2003).

Orphan Drug Acts. Orphan drug acts provide additional stimulus for private sector R&D for diseases that afflict only small populations in HICs. The U.S. Orphan Drug Act grants orphan status to drugs to treat diseases that affect 200,000 or fewer patients per year in the United States. Orphan drug status provides additional R&D tax credits and seven years of market exclusivity, during which the FDA cannot approve another drug to treat the same condition unless it uses a novel mechanism of action. Such market exclusivity enhances the orphan drug's market power, enabling the developer to charge high prices that to some extent offset the low sales volumes, thereby covering the costs of R&D. The U.S. act has stimulated a sharp increase in the number of drugs developed to treat orphan conditions since its passage. The European Union recently adopted similar legislation.

The potential for orphan status in the United States and the European Union may provide some additional stimulus for commercial firms to develop drugs and vaccines for LIC diseases, but the effects are likely to be minor for several reasons. First, after one product has acquired market exclusivity, firms have few incentives to develop other products to treat the same disease. Second, the value of orphan drug status in terms of annual revenue per patient is greatest for drugs to treat chronic diseases that require daily or weekly treatment. Potential revenues for treatments for acute diseases, for which each patient needs only a short course of treatment, are likely to be smaller. Thus, though orphan drug acts may create some additional stimulus for R&D for LIC diseases, other institutional and financing mechanisms are essential. Of these, PPPs are the most promising.

"Pull" Financing Mechanisms. Since the late 1990s, organizations such as the Bill & Melinda Gates Foundation and the Rockefeller Foundation have increased their funding commitments to fight diseases in developing countries. This new funding, including funding coordinated through the Global Fund to Fight AIDS, Tuberculosis, and Malaria, is allocated primarily to paying for vaccinations and treatment. By paying for vaccines and drugs, such financing could provide additional revenues to suppliers of these products and, hence, stimulate R&D. However, for the financing of vaccines and therapeutics to serve as an effective pull mechanism for future R&D, such financing must be sustained and must pay originators enough that they can recoup the costs of R&D. Thus, purchasers such as the United Nations Children's Fund or the Global Fund face a tradeoff between paying the lowest possible prices so as to maximize their ability to supply existing medicines to current patients and paying somewhat higher prices so as to create incentives for future R&D.

Creating effective pull financing incentives for R&D is probably best done by means of explicit purchasing commitments for specific products. Some progress has been made in identifying the contractual and legal requirements of such commitments to enter into future contracts. The most promising candidates for initial implementation would be products or vaccines that are already in late stages of development or have been approved for industrial countries but for which additional purchasing commitments are needed to induce the investment necessary to undertake clinical trials and build the manufacturing capacity required to extend these products to LICs. Possible candidates are the pneumococcal vaccine and the rotavirus vaccine. For both these products, accelerated development and introduction plans have been created in the Global Alliance for Vaccines and Immunization to address the many practical issues surrounding the implementation of an advance purchase contract. When advance purchasing commitments have been successfully demonstrated on products in the late stages of development, extending this promising approach to products at earlier stages of development may be possible.

Public-Private Partnerships

In recent years, a growing number of initiatives involving partnerships between industry and government, nonprofit, and philanthropic organizations have been set up to stimulate tropical disease R&D. One of the oldest is the World Health Organization, World Bank, and United Nations Development Programme TDR, which has worked with industry, academia, and research institutions to spur R&D and has contributed to half the new drugs developed for neglected tropical diseases during the past 25 years (Ridley 2003; Troullier and others 2002) (see table 6.2 for examples of the program's initiatives). The TDR is a relatively small program, with contributions of US$30 million in 2002.

Since the late 1990s, increased government and foundation funding, particularly from the Rockefeller Foundation and the Bill & Melinda Gates Foundation, has stimulated the growth of product development PPPs, giving a "push" stimulus to R&D

Table 6.2 Selected Initiatives of the TDR

Disease	Product	Partner	Status
Uncomplicated malaria	Lapdap	GlaxoSmithKline	Dossier submitted (2002)
	Lapdap, artesunate	GlaxoSmithKline	Phase 1
	Pyronaridine, artesunate	Shin Poong	Preclinical trials
Severe malaria	Intramuscular artemether	Artecef	Registered (2000)
	Rectal artesunate	Under discussion	FDA approval letter received
Visceral leishmaniasis	Miltefosine	Zentaris	Registered (2002)
	Paromomycin	Institute for OneWorld Health	Phase 3 studies
Sleeping sickness	Intravenous eflornithine	Aventis	Registered (2001)
River blindness	Ivermectin	Merck	Registered (1989)

Source: Ridley 2003.

(Varmus and others 2004). According to the Initiative on Public-Private Partnerships for Health, about 20 PPPs were involved in product development as of 2004. Although a few focus on a specific project, most adopt a portfolio approach with multiple candidates. The latter include five targeting HIV/AIDS vaccines or microbicides; three working with malaria therapeutics or vaccines; three investigating TB therapeutics, vaccines, or diagnostics; and at least six targeting drugs for other neglected diseases (Widdus 2004).

The PPPs are heterogeneous in terms of their objectives, structure, and financing. In general, their goal is to develop products for use in developing countries with a public health rather than a commercial goal. Their sources for promising compounds include modifications of existing compounds; continued development of compounds previously abandoned because of a lack of commercial potential; and totally new initiatives coming out of academia, industry, or government laboratories. If a PPP acquires a product from another firm, the other firm typically retains patent rights in HICs and middle-income countries, and the PPP commits to noncommercial pricing in developing countries.

PPPs draw on financing from foundations and, to a lesser extent, from governments. They work closely with private industry, including large pharmaceutical and biotechnology firms, obtaining a range of in-kind contributions, including promising compounds; useful technologies; patent rights; and expertise and advice on discovery, clinical trials, manufacturing, market estimation, regulatory requirements, and so on. They operate largely as "virtual" firms, usually contracting out actual operations to other firms or to contract research or service organizations. As compounds move into human trials, PPPs must also liaise closely with disease-endemic countries regarding clinical trials, regulatory requirements, and product delivery. Thus, they face significant scientific, managerial, financing, and operational challenges.

Table 6.3 lists the leading product development PPPs and their committed funding as of early 2004. Several have received grants of US$50 million or less, with significantly larger amounts for the International AIDS Vaccine Initiative and the Malaria Vaccine Initiative. Several of the organizations rely heavily on the Bill & Melinda Gates Foundation and the Rockefeller Foundation for both their initial and continued funding (Widdus 2004). Note that the dollar funding amounts shown exclude in-kind contributions from industry and other sources, whose worth is difficult to calculate because the value to the PPPs is presumably greater than the cost to the donor.

Table 6.4 shows the product development PPPs' portfolios of products as of early 2004. The percentage of products still in preclinical development is higher for vaccines than for drugs, which may reflect the scientific challenges of developing vaccines for LIC diseases. In general, comparing funding amounts with the number of products in development across PPPs is inappropriate as an indicator of performance because the different PPPs target different problems and have received varying in-kind contributions. Also, some products are modest extensions of existing therapies, whereas others are more innovative and, hence, more risky approaches.

As table 6.3 shows, aggregate committed funding for the product development PPPs as of early 2004 was US$1.2 billion, excluding in-kind contributions. A comparison of these funding amounts to the costs per NCE suggests that current rates of investment will produce some progress, but not rapid advances. Assuming optimistically that future funding for PPPs will be US$300 million per year, that private industry will invests similar amount, and that other sources will provide US$100 million a year (all of which are probably generous estimates) would imply total investment of US$700 million per year. If this level of investment were sustained over time, it might result in two or three NCEs per year, using the conservative cost estimates of US$200 million to US$300 million per NCE. This development level would be significant progress, although it still leaves a large shortfall, given the number of diseases for which no good treatment or vaccine is available and the threat of resistance developing to existing treatments. It is

Table 6.3 Selected Endeavors by Product Development PPPs, 2004

Disease	Number of people killed annually by the disease	Number of new cases per year	PPP	Focus	Committed funds raised to date (US$ millions)
HIV/AIDS	2,800,000	5,500,000	International AIDS Vaccine Initiative	Vaccines	350
			South African AIDS Vaccine Initiative	Vaccines	45
			International Partnership for Microbicides	Microbicides	95
			Microbicides Development Programme	Microbicides	27
			Global Microbicide Project	Microbicides	64
TB	1,600,000	8,000,000	Global Alliance for TB	Drugs	42
			Aeras	Vaccines	108
			Foundation for Innovative New Diagnostics	Diagnostics	30
Malaria	1,200,000	300,000,000–500,000,000	Malaria Vaccine Initiative	Vaccines	150
			European Malaria Vaccine Initiative	Vaccines	18
			MMV	Drugs	107
Dengue fever	19,000	20,000,000	Pediatric Dengue Vaccine Initiative	Vaccines	56
Hookworm	3,000	—	Human Hookworm Vaccine Initiative	Vaccines	20
Leishmaniasis	51,000	1,000,000–1,500,000	Drugs for Neglected Diseases Initiative and Institute for OneWorld Health	Drugs	11 (Institute for OneWorld Health)
Chagas disease	14,000	16,000,000–18,000,000	Drugs for Neglected Diseases Initiative and Institute for OneWorld Health	Drugs	30 (Drugs for Neglected Diseases Initiative)
Total	5,700,000	351,000,000–353,000,000	n.a.	n.a.	1,200

Source: Sander 2004.
n.a. = not applicable; — = not available.

Table 6.4 Product Development PPPs' Portfolios, 2004

	Number of products in			
PPP	Preclinical trials	Phase 1	Phase 2	Phase 3
Aeras		2		
Drugs for Neglected Diseases Initiative[a]				3
European Malaria Vaccine Initiative				
Foundation for Innovative New Diagnostics		1	1	1
GATB[b]	10	0	1	0
Human Hookworm Vaccine Initiative	2			
International AIDS Vaccine Initiative	2	2	1	
Institute for OneWorld Health	3		1	1
International Partnership for Microbicides				
Microbicides Development Programme		1		1
MMV	14 in discovery	4	2	2
Malaria Vaccine Initiative	8	6	1	
Pediatric Dengue Vaccine Initiative				
South African AIDS Vaccine Initiative[c]	6	0		
Total	47	16	7	8
Of which drugs	26	8	5	8
Of which vaccines	19	8	2	0

Sources: Initiative on Public-Private Partnerships for Health survey, PPPs' Web sites, interviews.
a. The Drugs for Neglected Diseases Initiative has two malaria drugs in phase 3 that are partly financed by the European Union.
b. The GATB anticipates a portfolio of three phase 1 trials and expects its current phase 2 trial will enter phase 3 before 2007. Its portfolio also includes platform-related investments.
c. The South African AIDS Vaccine Initiative does not yet have any of its own products at phase 1 but is collaborating on two projects that are at this stage.

also far short of the Commission on Macroeconomics and Health's target for 2006 of US$3 billion in R&D spending for diseases in developing countries (Sachs 2001).

Industry in Developing Countries

Pharmaceutical firms in developing countries have traditionally focused on the generic sector, making use of their expertise in engineering and other skills needed for efficient drug manufacturing. More recently, the adoption of product patents has created incentives for LIC firms to invest in R&D. For example, India adopted product patents as of 2005, and several leading generic firms are already developing new products. However, assuming that these firms will focus their efforts on developing drugs for tropical diseases would be a mistake. As for-profit firms, they face similar incentives to those of commercial firms in any country, which means focusing on the global diseases that offer the greatest expected net revenues rather than diseases specific to LICs. Nonetheless, several policies might help target R&D efforts in these countries toward tropical diseases. These policies include collaboration with the product development PPPs, provision of special government funding or tax credits for products that target LIC diseases, and provision of subsidies targeting the development and scientific testing of products derived from local products and other traditional medicines.

Other Proposed Mechanisms for Increasing Affordability

In evaluating other proposals for making drugs or vaccines available in developing countries, distinguishing proposals to stimulate new product development from proposals to increase the affordability of existing drugs is critical. One proposal pertaining to affordability is that multinational companies should voluntarily license production rights to LIC producers. Experience with generic markets across countries indicates that necessary conditions for such out-licensing to reduce prices to consumers are (a) the existence of competition between multiple licensees, (b) the licensees having lower production costs than the originator firms, and (c) a mechanism that prevents middlemen and retailers from capturing any potential savings. In practice, these conditions may not be met. The more probable scenario of licensing to only one local generic manufacturer is unlikely to reduce prices to consumers.

Another proposal is that governments should purchase patent rights, paying the originator firm the estimated value of the drug (net of production costs) and then selling the product to consumers at the marginal cost of production. This proposal has several disadvantages. First, because the government would presumably have to raise taxes to pay for the patents, the tax-induced efficiency loss could offset any efficiency gain in the pharmaceutical market, so the net effect on efficiency is unclear. Second, the presumption that patents result in suboptimal drug consumption because of monopoly pricing ignores the widespread prevalence of insurance in HICs and middle-income countries, so that, in practice, consumers face out-of-pocket prices that are already close to marginal cost. Third, and most important, is the difficulty of estimating the value of a product before its use in the market, because both positive features (additional uses) and negative features (side effects) may be discovered. In addition, distortions in the amounts paid for patent rights would distort incentives for R&D. Moreover, the proposal would reduce originator firms' incentives to invest in postlaunch improvements.

INTELLECTUAL PROPERTY

The issue of intellectual property is involved in the debate about the perceived conflict between patents and access.

The Role of Patents in Drug Development

Under a patent system, an inventor is entitled to a limited monopoly for a period of time, typically 20 years. This exclusivity may permit high prices and, consequently, an increased economic return that serves as an incentive to develop new products. The system has worked quite effectively in the pharmaceutical area, where the incentives deriving from exclusivity have resulted in important new drugs. The first generation of patients pays a higher price than subsequent generations, which provides compensation for the large research costs involved in developing a new drug. When the patent expires, the price normally falls as generic competitors enter the market.

Even though this approach has been extremely successful in the developed world, it does not generally work for products for which the main market is limited to the developing world. The total magnitude of the market in the developing world for products for HIV, malaria, TB, or less widespread diseases is likely to be too small to provide an adequate incentive for the private sector. This fact, together with the fact that patents are likely to result in higher prices, has raised important concerns in the developing world.

The Drug Access Debate

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) entered into force on January 1, 1995.[6] This agreement requires the members of the World Trade Organization (WTO), which include nearly all major trading nations, to live up to defined standards of intellectual property protection. TRIPS was part of a much broader international trade package negotiated during the Uruguay Round, one of a series of international trade negotiations that have

taken place since World War II. The United States and European nations, which were the strong proponents of TRIPS, were responding to pressure from their pharmaceutical, copyright content, and trademark-based industries.

The pharmaceutical industry's concern was that a number of developing nations had made deliberate decisions to deny patent protection to pharmaceutical products and to grant protection only to processes for producing pharmaceuticals. These nations believed that inexpensive access to pharmaceutical products was so important that these products should not be patented. In its 1970 patent law, for example, India excluded pharmaceuticals from product patent protection, effectively choosing to provide low-cost pharmaceuticals for its people at the expense of eliminating incentives to create new products. This law was one of the reasons the Indian generic pharmaceutical industry was able to evolve to make and market copies of drugs that were still on patent in wealthier nations. Another concern for the pharmaceutical industry arose from the compulsory license process, a legal process available in some nations to authorize the use of a patented technology under some circumstances even over the patent holder's objection. In practice, compulsory licenses are rarely granted but are instead used as a threat to negotiate lower prices for the technology or pharmaceutical involved.

The United States was determined to change these laws and in TRIPS achieved important requirements for expanding patent protection. The most important TRIPS provision relevant to pharmaceuticals is article 27, which includes a requirement that "patents shall be available for any inventions, whether products or processes, in all fields of technology." (U.K. Commission on Intellectual Property Rights 2002). The clear intent of this language was to prohibit exclusions of pharmaceutical products as in the Indian law. Article 31 established careful procedural limitations on when a nation could grant a compulsory license. As part of the political compromise, transitional provisions gave developing nations extra time to comply with the treaty's requirements and also set up arrangements for the remaining parts of patent terms to be made available for products developed during the transition period. Because of these transitional provisions, developing nations were not generally required to provide product patents on pharmaceuticals until January 1, 2005 (a date that has since been extended to 2016 for the least developed countries).

During the years following the entry into force of TRIPS, a substantial and bitter debate over access to pharmaceutical products in developing countries focused largely on access to antiretroviral agents for HIV patients in Sub-Saharan Africa. A group of nongovernmental organizations argued that patents on these drugs in the developing world raise the prices of the products necessary to help such patients survive. The research-based pharmaceutical industry countered that many of the relevant products are not covered by patents in the nations involved and that the problem is not patents but the inadequacy of the countries' medical infrastructure.

An area of convergence has begun to emerge in relation to differential pricing: prices should be lower in developing nations than in developed nations, permitting pharmaceutical firms to recover their research expenditures in the developed world while making products available at near marginal production cost to the poor in the developing world. This differential pricing is justified because potential sales in poor nations are so small that the market provides only a minimal incentive: total sales in the poorest nations account for only about 1 percent of global pharmaceutical sales. The research-based pharmaceutical industry would prefer to achieve this differential pricing by means of a donation program or simply by charging different prices. Critics would prefer that the patent monopoly not be available to raise prices in the developing world, thereby opening up markets to local generic producers.

Movement toward agreement on differential pricing was reflected in the Doha Declaration on TRIPS agreement and public health, reached at a November 2001 WTO meeting of trade ministers. This declaration affirmed that TRIPS "should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all" (TRIPS, paragraph 4, 2001). It affirmed the right of nations to use the exceptions to TRIPS to address public health concerns, specifically stating that "public health crises, including those related to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency" and, thus, facilitate the right to use compulsory licensing (WTO 2003).

The Doha Declaration left an issue unresolved: the manufacture of drugs under compulsory license for nations that do not have the capability to manufacture the drugs themselves. The problem arises from the compulsory licensing article of TRIPS, which contains a provision, article 31(f), requiring that the manufacture of products under compulsory license be predominantly for the domestic market. Thus, a small Sub-Sahara African nation clearly has the right to grant a compulsory license but may have no local industry able to manufacture the product. If it asks a foreign firm to manufacture the product, that firm would be manufacturing the product primarily for export, a violation of TRIPS.

The Doha negotiators did not find a way to resolve this problem, and article 6 of the Doha Declaration called for members of the TRIPS Council (a group of national representatives) to find a solution by the end of 2002. By that time, all member countries except the United States had agreed to a procedure for waiving article 31(f). The new agreement covered products needed to address public health problems recognized in the Doha Declaration, but the United States feared that it would be expanded to a variety of other products and was unwilling to accept it. Finally, a compromise was reached in August 2003.

The United States accepted the 2002 document, provided that the General Council chairperson of the WTO made an appropriate parallel statement. The chair made the statement, which included language that the agreement would be used "in good faith to protect public health" and not be "an instrument to pursue industrial or commercial policy objectives," and recognized the need to respond to the industry's concern that products produced under this agreement would not be exported to major developed world markets (WTO 2003; see also UNAIDS 2003).

This agreement represents a step forward for access and will certainly place pressure on the research-based pharmaceutical industry to provide products in the developing world at low prices. It leaves several important problems only partly resolved, however. One is the need to prevent importation of the low-priced products into the developed world. Such imports would cut into the patent-protected market and affect incentives to develop new products. A second is political backlash. When the general public becomes aware that a product is available to the poor in a developing nation at a price far below that which patients in developed nations must pay, the political backlash for the pharmaceutical industry in the developed world may be severe.

Most important, resolving the legal problem of article 31(f) does not resolve the economic problem. It confirms that there will be no patent incentive for the development of drugs for diseases endemic to the developing nations and that public funds will be needed for this purpose. Such funds are currently inadequate.

The Research Tool Issue

Another important problem arises from the changing nature of medical research and of patenting practice. This is the research tool problem: many of the basic tools used in medical research are now themselves patented. For example, the research use of certain genetically modified mice is patented in the United States, as are the uses of many gene sequences and protein crystal coordinates. In the case of the malaria antigen merozoite surface protein 1, some 39 patent families cover various aspects of the protein (U.K. Commission on Intellectual Property Rights 2002).

Such patents can significantly complicate research and make it more expensive. Each one that might affect a particular research program requires legal analysis to determine whether it is valid and actually applies to the planned research program. If relevant, a license must be sought or the research program must be redesigned. The more patents are involved, the greater the likelihood that a patent holder will refuse to grant a license or will demand an exorbitant sum. Even though Walsh, Arora, and Cohen's (2003) study finds no cases of research programs being canceled midstream because of this problem, it finds

many cases of efforts to avoid the problem by, for example, modifying the research; conducting the research offshore in locations where the relevant patents are not in force; or, in some cases, simply ignoring the patent.

REGULATORY AND LIABILITY ISSUES

Developing and registering new products are generally lengthy and complicated processes (Abraham and Reed 2002; Baylor and McVittie 2003; FDA 2004) that are regulated both at the national level and, in some circumstances, at the international level. The role of the regulatory system extends beyond the launch of a new product to manufacturing and compliance standards and to postmarketing surveillance for clinical effects and potential untoward outcomes. For products that are intended to be deployed in global markets, manufacturers have to comply with regulatory requirements in the country of origin as well as the requirements of each country where the product may be marketed. One exception is the mutual recognition systems used currently by European Union countries (Pignatti, Boone, and Moulon 2004). The situation may be different for products intended for use only in developing countries; however, for legal and liability reasons, manufacturers in developed countries have refrained from working with two different sets of regulatory requirements.

The best example for illustrating this process is the FDA (2004). Over the years, FDA regulations have developed into a clear pathway. The process is initiated through an application by the manufacturer and a step-by-step approach toward licensing. The agency gets involved in every phase of the development process and approves in advance the experimental design, assays, and endpoints for clinical trials. After it has collected all the information, the agency examines the materials submitted and reaches a decision. The FDA process extends through regulating and approving marketing materials and postlicensing collection of efficacy data and information about possible side effects.

The FDA approval process differs somewhat for pharmaceutical products and vaccines. One of the main differences is the obligation of vaccine manufacturers to prepare materials for use in phase 3 trials in the final and approved production facility. This requirement means that the firm must invest in completing the manufacturing plant well ahead of launching a specific product, a process that can take three to six years. The regulatory process for vaccines also dictates batch release for every batch ready for deployment in the marketplace. This part of the regulatory process, although it ensures quality control, adds to costs and to the timeline.

In 1996, the European Union adopted a centralized procedure for applications and approvals through the European Medicines Evaluation Agency and through a mutual

recognition process (Pignatti, Boone, and Moulon 2004). In many ways, the procedure parallels the FDA process, with several differences reflecting the fact that the European Union consists of many countries, each with a country-based process that remains as an alternative or an addition to the communitywide process. The International Conference on Harmonization of Technical Requirements for Regulation of Pharmaceuticals for Human Use was established to achieve coordination of the process of drug development between industry, Japan, the United States, and the European Union (Abraham and Reed 2002; Ohno 2002). The conference's activities have improved understanding of the regulatory process and reduced duplication.

In contrast, the absence of a unified or harmonized approach to product registration and approval at the global level adds multiple layers of complexity. National systems consist of complex processes with differing thresholds and interpretations and with changing requirements in addition to differing Global Manufacturing Program standards and enforcement. A number of recent attempts have been made to resolve the issue. First among these is the World Health Organization's effort to expand its prequalification system, to develop technical standards earlier in the approval process, and to expand the availability of reference reagents for international calibration (Milstien and Belgharbi 2004). These efforts aim at injecting a higher level of quality control and transparency into the global regulatory system. The effort may have the potential to provide a global process that transcends national borders. Such a process should provide a simplified, systematic, and disciplined system that would reduce costs and speed up market access for new products.

The issue of liability in relation to harm to individuals receiving pharmaceutical products has been extremely significant in U.S. product development. It is entirely appropriate for those developing new products to be sued if they are negligent in their research or product development, but in some cases pharmaceutical firms have been sued for side effects of drugs that may have been unforeseeable or may not even have been the result of the product. This type of liability can be a barrier to product development. Although perhaps a less serious concern since the 1993 *Daubert v. Merrell Dow Pharmaceuticals* lawsuit in the United States, a case that has been interpreted to restrict the presentation to juries of evidence determined not to be "scientific," the issue is still significant. It may also be part of the reason the U.S. vaccine industry has shrunk significantly, and it has certainly affected the direction of investment, pushing it away, for example, from products such as vaccines that are used in one or a few doses in healthy people toward products used repetitively by those who already have a chronic disease (Institute of Medicine 2004). It, thus, provides pressure directly contrary to public health priorities, which emphasize prevention and, therefore, the use of vaccines.

Whether or how this trend in the United States will affect the developing world is unclear. Europe has moved toward a liability system somewhat similar to that of the United States, but many developing nations may not have such a tort liability system. Even if they do not have such a system, groups participating in pharmaceutical development might be sued in the United States for harm occurring in the developing world. Doctrines exist that restrict such suits, but firms may fear that these doctrines are insufficiently effective. Hence, recognizing the potential costs of protecting against liability and, at the same time, ensuring that products are designed and manufactured to the highest standards will be important.

NOTES

1. The phase transition probabilities in DiMasi, Hansen, and Grabowski (2003) and the overall success probability of 0.215, conditional on entering human trials, are estimated from a larger sample of 538 investigational compounds first tested in humans between 1983 and 1994.

2. The size of trial required to estimate statistical significance depends on the magnitude of the drug effect; the extent of stratification within the total sample by patient age, condition, and so on; the required statistical confidence; and other factors.

3. DiMasi, Hansen, and Grabowski's (2003) data for average cost and average number of patients are based on actual, retrospective cost data, whereas the GATB estimates are prospective estimates (best guesses) based on prior clinical trials for tuberculosis drugs in the United States and a survey of clinical trial experts to determine administrative and data management costs.

4. The MMV estimate of in-kind contributions does not include the value of basic research conducted by universities and foundations from which it obtains its lead compounds. Similarly, commercial firms also benefit from such basic research and it is omitted from the DiMasi, Hansen, and Grabowski (2003) estimates, so comparisons are not necessarily biased by this exclusion.

5. Tropical diseases include parasitic diseases (malaria, African trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, and intestinal nematode infections); leprosy; dengue fever; Japanese encephalitis; trachoma; and infectious diarrheal diseases.

6. This section is based in part on Barton (2004).

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