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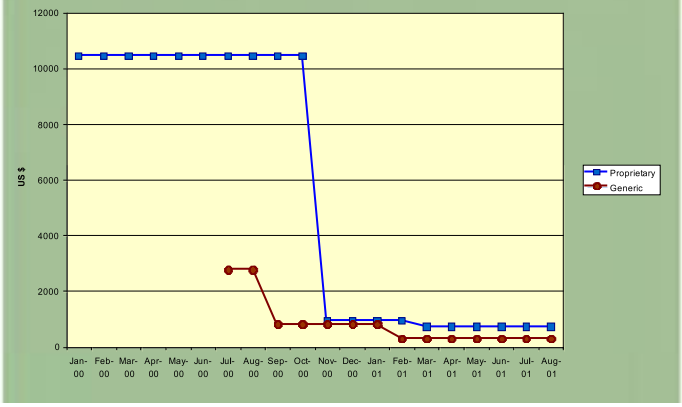

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A Global Health Innovation System (GHIS)

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Executive Summary

This paper describes a Global Health Innovation System (GHIS) based on research in innovations systems theory. This system would define how concerned countries and institutions could more effectively contribute to health care innovations, especially for the poor in developing countries. Such a system is needed because of the very rapid recent changes in global health innovation. Since the turn of the millennium, the Era of Partnerships has emerged. This era is characterized by the rise of product-development public-private partnerships and is also marked by increased networking, a trend that would benefit from greater coordination and the adoption of a range of best practices. With a comprehensive and compelling GHIS current resources could be allocated more efficiently and additional resources could be mobilized more readily.

By integrating innovation with health systems and widened perspectives, the GHIS would help overcome a set of critical health failures: failures of science, failures of the market, and failures of public health systems. It would do so by providing valuable guidance in the planning and management of innovation at the global, regional, national, institutional, and sector levels. The paper concludes by demonstrating how a GHIS could address the health failures by applying the lessons of innovation studies in a structured framework.

Introduction

There is a growing consensus about the need to develop and deliver new health technologies for diseases affecting the poor in developing countries. New funds, new organizations, and new approaches are revitalizing the public sector. Spurred by a better understanding of the market and its limitations when addressing the needs of the poor, there is a greater awareness of the public sector's essential role in promoting access to health technologies. This revitalization is relatively young, but in some areas it is moving very quickly. For example, global procurement mechanisms for vaccines, drugs, and other materials have been set up, and public-private product development partnerships (PDPs) in developed countries and some developing countries have been established.

No global model, however, has yet been put forward to plan, coordinate, conduct, and support efforts. Now is the time to construct such a global model. How do the new parts relate to each other? How do the new components relate to the old parts? And how do they relate to things occurring outside health? We must consider the big picture to determine how all of the parts can work together most effectively. Funds are limited but there is the prospect and need for more, so it is essential to find cost effective policies, strategies that can mobilize those funds. What are those policies and strategies and how do we develop them? To answer these questions, we need a global model or system. The problem has been succinctly summarized by Prof. Barry Bloom, "*There've been lots of creative ideas and lots of*

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new people, but there's one missing piece. There's no architecture of global health."[1]

Fortunately, existing research can guide our pursuit of the answers to these questions. Having carefully studied how new technologies reach markets, innovation systems theory has already contributed greatly to our understanding of the architecture of global health. Our quest to improve health care innovation should therefore include the work of scholars of innovation, and in this paper we build on innovation theory to address the health problems of the poor in developing countries. Based on widely-accepted scholarship that clearly lays out how all the players in health innovation—firms, governments, research institutes, non-governmental organizations (NGOs), citizens, and donors—can work together most effectively to assure access to urgently needed health technologies in developing countries, we argue for the creation of a Global Health Innovation System (GHIS) – the missing architecture.

The History of Health Innovation

Health innovation includes not only technologies but also better systems and policies. Since Schumpeter's analysis[2], scholars have argued that advances in human health and well-being are determined both by technological innovation and by how institutions handle new technologies. Understanding the history of health care innovation, therefore, requires us to consider both technologies and policies.

Since the 19th century, we see four major periods of health technology innovation: the Era of the Public Sector, the Era of the Private Sector, the Era of Public Sector Reawakening, and the Era of Partnerships. Our analysis is based in part on the work of Stokes [3], which we have adapted to the field of health technology innovation. The Era of the Public Sector is the period from the mid-19th century to World War I. The Era of the Private Sector is the period from World War I to the fall of the Berlin Wall. The years from the fall of the Berlin Wall to the dawn of the 21st century, we refer to as the Era of Public Sector Reawakening. The birth of the 21st century marks the beginning of the Era of Partnerships. The transitions from era to era take place in response to broader world changes, particularly the struggle between capitalism and socialism and the emergence of globalization.

The Era of the Public Sector is epitomized by the work of Pasteur. Working within the university, he was able to develop a number of human and animal health technologies that were widely adopted and greatly improved medical practice. His initial discoveries and technological innovations, such as disproving spontaneous generation and developing the rabies vaccine, were made possible largely by public sector institutions, such as l'Ecole Normale in Paris. The explosive demand for rabies vaccination led Pasteur in 1888 to create the Pasteur Institute in Paris, a private, state-approved institute recognized by the President of France. In 1891, Pasteur dispatched Albert Calmette to Saigon, (today Ho Chi Minh City), Vietnam, where he founded the first Institute outside France. Other disciples set up establishments modeled on the Paris Institute in several developing countries. Invariably, these were public institutions closely associated with national governments. Of course, Pasteur had no choice: no private sector pharmaceutical or vaccine industry existed in the second half of the 19th century, so he had to create production facilities and structures himself.[4]

The Era of the Private Sector emerged in Germany when chemical companies applied their manufacturing skills to medicines[5]. They soon recognized the high investment returns of these technologies and established research capabilities to create new and even more profitable products. During this Era, the public sector became less involved in activities that brought new medicines and vaccines into wide use. To some degree, this was due to less support for science in the Socialist east and to the shift to funding "basic" research in the capitalist West, which left it to industry to translate such research into products. This was the established "linear paradigm" described in Vanevar Bush's report to the President of the United States at the end of World War II: "*Science the Endless Frontier*"[6].

The Era of Public Sector Reawakening began in the 1970s, when several development organizations (foundations and governments) established after World War II became concerned about health in developing countries, especially the absence of health

technologies. Around this time, the World Health Organization (WHO) established its Special Programmes: the Human Reproduction Programme (HRP), the Tropical Disease Research and Training Programme (TDR), and the Diarrheal Disease Control Program (CDD). Each of these programs sought to develop or apply new technologies and strategies for the pressing health needs of people in developing countries. With support from the Ford and Rockefeller Foundations, The Population Council in New York and the Program for Appropriate Technology in Health (PATH) in Seattle also created programs to begin product research and development to address health needs in developing countries. The United States government dramatically increased funding for the NIH, which led to the unprecedented growth of biomedical research there and in collaborating centers around the world. But in the health field, collaboration between the public and private sectors during this period was uncommon and viewed with suspicion. In other fields, particularly in engineering schools and land grant colleges, a tradition of public-private collaboration went back to the late 19th century, especially in the United States [7]. In health research and development, however, neither sector understood the other, and collaboration was difficult, at best. For example, private-sector representatives were excluded from almost all WHO meetings, and universities and companies rarely interacted, in part because no clear legal framework allowed public institutions to manage IP rights.

The passage of such legislation as the Bayh-Dole Act in the U.S. in 1980 [8], the fall of the Berlin Wall on 9 November 1989, and the collapse of the Soviet Union on Christmas Day, 1991, made it possible to view the relationship between the public and private sectors more objectively. It became more acceptable for academics in the West to work closely with pharmaceutical companies; conversely, pharmaceutical companies saw the benefits of closer collaboration with universities and nonprofit research centers. Beginning in the 1990s and flowering in the early part of the 21st century, a number of new initiatives were launched that have since become known as product development public-private partnerships (PDPs) [9, 10]. They seek to accelerate the development of health products for use in developing countries. Examples include the founding of the International AIDS Vaccine Initiative (IAVI) in 1996, the Aeras Foundation in 1997 to develop TB vaccines, and the Medicines for Malaria Venture in 1999 (MMV) [10].

These developments led to the current *Era of Partnerships*. It began to be understood that for-profit pharmaceutical companies in wealthy industrialized countries would not address the needs of the poor in developing countries without incentives from government or other public sector agencies. On the other hand, the private sector had certain skills and abilities that the public sector lacked, including the ability to manufacture large numbers of products to very high standards.

The Era of Partnerships

We are in the very first years of the new Era of Partnerships, and, among many issues, we need to understand better how the public and private sectors can partner most effectively. Ignorance is mutual. While the public sector faces such challenges as managing IP rights for the public's benefit, IP management practices are well-established in the private sector[11]. The private sector, on the other hand, is eager to learn how to handle the special needs of poor populations in both developed and developing countries[12]. The ground is moving under everyone's feet: a number of developing countries are beginning to reap the fruits of substantial investments in biotechnology over the last 25 years. These countries, such as Brazil, China, India, South Africa and others, are now known as Innovative Developing Countries (IDCs)[13, 14]. India is becoming a global center for both vaccine and drug production and is also rapidly increasing its capability to undertake research and development. It already has extensive capabilities in clinical assessment[15]. China is also very rapidly expanding its research capabilities[16].

Early evidence collected and analyzed by Mary Moran and other investigators shows that PDPs have the promise to develop and introduce new health technologies for developing countries[12]. Numerous questions, however, still need answers. To be sure, the new Era of Partnerships has seen a

range of proposals to encourage or create initiatives promoting health technology innovation for the poor. These include double-bottom-line venture capital funds (where both profits and social benefit are measured); France's airline solidarity contribution [17]; humanitarian licensing practices at research universities[18]; fast-track regulatory approval vouchers[12]; global procurement funds such as GAVI and the Global Fund to Fight AIDS, TB, and Malaria; advance market commitments[19]; and others. We do not know, however, which of these are most cost-effective, which are synergistic, and which may cross-react to produce unwanted side-effects[20].

The Era of Partnerships is structured by technological innovation, the legacy of the geopolitical struggle between capitalism and socialism, and globalization. This last factor has affected many aspects of health worldwide. Jet travel can transmit diseases from one part of the world to another in a matter of hours. Pharmaceutical firms are now global companies, marketing their products to over 100 countries. Because of the very large profits they have made off of critically needed health products—especially by the poor—these companies have been admired and criticized. Globalization has led university investigators to collaborate through worldwide research systems, which has made science a global undertaking. All of these aspects of globalization are profoundly affecting how knowledge is produced and how health technology innovation occurs [21] [22].

We do not yet know how this new Era of Partnerships can operate most effectively in the field of health innovation. Insistent questions have arisen about how to best regulate new drugs and vaccines, how to manage patents and other forms of IP for new health applications, and how to fund research in academia and industry. Many more such questions will continue to arise as we learn more about the new structure, limitations, and possibilities of the new Era of Partnerships.

We do know, however, one thing for certain: this new era requires a global perspective. The WHO Commission on Intellectual Property Rights and Innovation has recently called for a global plan to make the most of this new era[23]:

> *"It is important that all the contributions of all stakeholders are taken into account so that their respective energies can be mobilized towards the achievement of a common goal… For this purpose, the need is to develop a Global Plan of Action which would provide a medium term framework for action by these partners, including the setting of clear objectives and priorities and a realistic estimation of funding needs if these are to be achieved. … Viewed across the field, there are few or no available mechanisms at present to advise on appropriate priorities for resource allocation between R&D on different diseases, the balance between resources needed for R&D and delivery for each disease or the means to monitor and evaluate the impact of resources devoted to treatment and delivery. Such a Plan would also provide an important basis for measuring progress towards the achievement of these goals."*

If health technology innovation is to contribute to alleviating death and disease among the poor worldwide, its operations must be global. It must be able to identify the nature and causes of so-called "health failures" and to propose strategies to cope with them. And these strategies must involve all countries—from industrialized to least developed countries. In short, the Global Plan of Action called for by the WHO Commission should be a part of a Global Health Innovation System (GHIS).

The GHIS as a Response to "Health Failures"

A Global Health Innovation System is warranted because of a number of "health failures." We identify three kinds of these: science failures, market failures, and public health failures.

Science failures occur when we lack the knowledge to make tools or mechanisms to address health problems. For example, we do not know how to make safe and effective drugs or vaccines against such important diseases as dengue, avian flu, tuberculosis, and all parasitic diseases (malaria, leishmaniases, and trypanosomiases, etc.). To address this failure globally, we need more basic and applied research, which requires not only increased funding but also enhanced strategies for developing new products that will be accessible to the poor in developing countries. Some of the most promising strategies involve PDPs

and funding agencies in industrialized countries to address scientific issues of interest to developing countries (e.g., the genome projects for tropical pathogens and their vectors [24], [25]).

Market failures occur when the costs of vaccines, drugs, or other health interventions bar the poor from access, when the cost of developing or producing new drugs is very high, or when their delivery requires costly structures, such as sophisticated tertiary health care units. Examples of these kinds of products are antiretrovirals, combination therapies against malaria, and regimens for fighting drug-resistant tuberculosis. To address these failures, we must either provide much greater funding for such mechanisms as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, or we need to find more efficient ways to produce these products and lower their cost to consumers. We can address such market failures by a number of means, including procurement funds and funding PDPs. Other options include increasing the health budgets of national governments or stretching health expenditures through government negotiations with drug suppliers to reduce the costs of pharmaceuticals. One example of an innovative financing system is the Provisional Contribution on Financial Movement (CPMF) that Brazil established in the 1990s to finance health care, which generated revenue of 1.5% GDP for several years and helped deliver antiretrovirals to millions [26] [27].

Public health failures occur when good governance or sound priorities are lacking. Corruption, crises, war, or cultural and religious factors can block access to cheap and readily available interventions. Resistance to immunization by religious or cultural factors, for example, has made polio eradication more difficult. Obesity and tobacco consumption are other examples. To address these public health failures, we need more education, better leadership within civil society, and the strengthening of human rights. Recent innovations that are helping to address these public health failures include National Immunization Days[28], the WHO Tobacco Convention, educational TV campaigns, and better management and budgeting practices, as in the Tanzania Essential Health Interventions Project, TEHIP [29].

These failures point to a broad based "failure of policy": the global, national, and institutional policies needed to effectively address these failures are lacking. A sound GHIS would fill this need, and we believe that innovation systems studies can provide valuable guidance about how to make it work most effectively.

What We Can Learn from Innovation Systems Studies

Over the last three decades, innovation studies have taught us much about the essential elements of effective innovation systems. We highlight four: the role of the firm, the role of governments, the value of networks, and the need for adequate and sustained financing.

1. **The role of the firm.** Private firms are the key actors in innovation. While historically some innovation, such as the development and production of early vaccines, took place through state-owned or parastatal organizations, they are of much less importance today [30]. A new technology has very little chance to reach the market without the sponsorship or partnership of a firm. This insight helps us to understand from another point of view why public-private partnerships are necessary. Lall has examined this issue with respect to developing countries and shows that firms are also essential there [31].
2. **The role of government and the public sector.** After the fall of the Soviet Union, some argued that the government should not be involved in directing or stimulating innovation (this was a component of the "Washington Consensus"[32]). A number of economists, however, have demonstrated that the government is in fact a necessary and essential partner in innovation. Korea is often cited as the prime example[33]. We believe that while the government cannot determine innovation, it does have an essential role to play in setting ground rules and providing funding and other incentives.
3. **The value of networks.** Innovation studies show that the most effective firms and organizations are those with the most dynamic networks. Whether in the public or private sector, these organizations reach out to actors in the key areas in which they work. They build collaborative part-

nerships or exchange information. Conversely, organizations operating within limited networks are less innovative and successful[34].

4. **Adequate and sustained financing.** Acquiring innovation capabilities is a long- term process of 10-30 years that requires long-term funding at high levels. By contrast, the pace of technological innovation is very rapid[35], imposing extra challenges to developing countries.

While most innovation studies focus on developed countries, innovation in developing countries has also received some attention. One focus has been on whether or not developing countries can innovate. Viotti argues that developing countries do not innovate but learn, and he divides them into two categories: active learning and passive learning[36]. Defining innovation as the development and commercialization of truly new technologies, he argues, by that definition, developing countries are not currently capable of innovation. But it seems that some developing countries—the IDCs—may be poised to make truly innovative contributions. India, for example, has already moved into the first frontier of innovation in information technology. Nevertheless, the vast majority of the world's innovators are in developed countries. Developing countries must therefore devote a larger proportion of their innovation activities to learning from others. And given the four major lessons described above, developing countries should also work to stimulate innovative firms, provide long-term sustained funding to develop innovation capabilities, and promote the establishment of networks not only among themselves but also with leading centers in developed countries[37].

In sum, a GHIS should help to involve firms and government, create and sustain networks, and mobilize and maintain adequate financing. It must also facilitate networks with nodes in both developed and developing countries.

Promising Developments

As documented by the work of DiMasi[38] and Towse[39], the resources necessary to develop new drugs and vaccines are substantial: between $400-$1,285 million (in year 2000 dollars). As Towse and Glickman[40] point out, the funds available to current PDPs are insufficient to develop a range of new technologies successfully. Every effort must therefore be made to achieve the highest level of cost effectiveness when allocating resources to develop new and improved health technologies. But where can guidance for such efforts be found? The GHIS would help to meet this need.

Certain types of health innovation systems are already emerging. For example, PDPs are setting up global systems to promote the development of new drugs or vaccines. With both public and private sector collaborators in developed and developing countries, they are addressing all of the issues associated with developing and introducing new technologies. This includes research and development, market development in individual developing countries, international trade issues, manufacturing issues, intellectual property rights, and regulatory matters[41].

In addition, several developing countries are beginning to build collaboration networks. For example, Brazil, China, Cuba, India, Nigeria, Russia, South Africa, Thailand, and Ukraine have formed a network to boost production of antiretrovirals and other health products[13]. These networks must address all the issues related to the development and introduction of new technologies, including the critical area of intellectual property rights. It is not clear whether these networks will succeed: they are in very early stages of development.

Within some developing countries, such as Brazil, India, and South Africa, networks have been created to facilitate the development and introduction of new health technologies that meet their citizen's needs. All of these countries strongly emphasize forming and promoting public private partnerships. In Brazil, for example, it used to be very difficult to partner with private companies. Due to the Law on Innovation enacted in December 2004, a new, enabling environment strongly encourages such partnerships [42].

Other efforts to develop focused global health innovation systems include the Bill and Melinda Gates foundation's promotion of an HIV Enterprise, which will provide a worldwide coordinated strategy to address the need for new HIV vaccines[43],

and Dr. Gerald Keusch has proposed the formation of a network to link medical research councils and universities around the world in concerted strategies to develop new health technologies[44].

Each of these initiatives (PDPs, developing country health innovation programs, and international networks) are either relatively new or have yet to be fully launched. Unfortunately, there is little if any cross learning among these various initiatives, and there is a lot of repetition and duplication. One initiative addressing the need for cross links is the Centre for the Management of IP in Health R&D in Oxford England (MIHR). MIHR is attempting to identify and disseminate best practices for IP management in order to insure access to new health technologies by the poor in developing countries (www.mihr.org). WHO is promoting another cross-linking initiative, the WHO Developing Countries' Vaccine Regulators Network, created in September 2004. Including Brazil, China, Cuba, India, Indonesia, Russia, South Africa, South Korea, and Thailand, it brings together national regulatory authorities to prepare standard approaches for the review and approval of vaccines and drugs needed in developing countries[45]. Brazil and Kenya have proposed to the World Health Assembly a treaty concerning health R&D. The proposed treaty would result in the establishment of a global mechanism for priority setting in health R&D. It would also set non-enforceable targets based on GNP for support of health R&D in priority areas for the poor. The treaty would allow member states to modify laws and policies concerning intellectual property in ways that would enhance access by the poor. Finally, the treaty would establish various operating institutions (possibly within WHO) for the management of priority setting, oversight of financial contributions, monitoring of activities under the treaty, and other matters. This treaty and a resolution concerning it will be considered at the World Health Assembly in May 2006. If the resolution is approved, the treaty might go into effect in 2009 following preparatory work[46]. Representing potentially important contributions to the creation of a GHIS, these valuable efforts should be promoted.

A Framework for a GHIS

We propose a framework for the GHIS based largely on the work of Lall[47]. The Framework identifies six components of health technology innovation[48]:

- Development and expansion of national health delivery systems, including an attractive, domestic, private-sector market for health products;
- Development of manufacturing capability for health products;
- The drug and vaccine regulatory system;
- The IP regulatory system;
- Development of R&D capability by the public and private sectors;
- Development of international trade systems for health products, including global procurement funds.

Because these innovation components are dynamically linked, successfully developing and introducing new technologies requires concerted attention to each of the six components [49]. Progress in one requires progress in all, and failure in one may impede progress in all. National innovation policies and the crafting of global policy interventions and norms must be considered. And to create strategies for product development and introduction, we must also attend to the roles of the public and private sectors in each of the six components. These roles of the public and private sectors for any given technology development will necessarily be inadequate if they are considered independently of one another. For national policies, moreover, the relative emphasis given to the components will differ according to the kind of country: developed, IDC, or low-income.

The framework can be used to develop not only strategies for particular technology innovation initiatives but also strategies for national health innovation. Indeed, the value of such a framework is readily apparent. When a country wishes to accelerate progress in science and technology, its strategy must encompass all six components. Likewise, if it wants to develop comprehensive financing strategies or capacity building strategies, it must address all six components. The ministry of science and technology, for example,

cannot develop a comprehensive innovation strategy on its own. It must work with the ministry of health, the ministry of industry, and the ministry of trade.

The Framework applies equally to the operation of international networks, such as the HIV Enterprise. Such enterprises will have to address issues with respect to each of the six components, as will PDPs.

Using the Innovation Components to Address the Health Failures

By focusing on the six components of innovation, effective innovation policies can be developed. But different actors and different countries have different roles to play in accelerating health innovations and addressing health failures. We have therefore mapped the six components of health innovation against the three kinds of health failure (i.e., science failures, market failures, and public health failures). *Science failures* can be addressed primarily through considering drug regulation, IP, and research and development issues. *Market failures* are primarily addressed by working on the components of innovation for domestic markets and international markets. *Public health failures* can also be addressed by looking at why domestic markets, which include national health service delivery systems and the private sector's delivery of health services, do not work efficiently. Understanding how international markets work, such as those for tobacco (an example where we want to innovate by reducing the use of the technology and tobacco consumption), will also move us towards solutions. We argue, however, that addressing science failures, market failures, and public health failures requires addressing all six components of innovation.

This health innovation assessment and the identification of the three areas of health failure lead us to propose a comprehensive matrix to illustrate how various countries and institutions within those countries can contribute to addressing health failures through innovation. There are roles for industrialized countries, for IDCs, and for the least developing countries. Table 1 provides this matrix and illustrates how different agencies and organizations in both the public and private sectors in different kinds of countries can be brought together to help address health failures.

The matrix of Table 1 articulates two dimensions:

(i) The vertical (column) "diagnostics/therapeutics" axis:
- *Diagnostics*: Lists the three kinds of **failures** (interventions do not exist, interventions exist but are too expensive, cost-effective interventions are available but do not reach the poor)
- *Therapeutics*: Lists the appropriate type of **innovation** required to cope with each kind of failure (new products, new processes, new strategies/policies)

(ii) The horizontal (row) player axis:
- *Players*: Displays the three categories of **countries** whose national innovation systems are responsible for the development & implementation of the innovations and interventions (industrialized, IDCs, Least-Developed Countries).

The cells of the matrix display examples of health actions, where each country category intervenes appropriately to cope with each kind of health failure. For these actions to take place, the countries and institutions will need to address the four elements of an effective innovation system: the role of the firm, the role of the public sector, the value of networks, and sustained funding.

Developing the GHIS

The new millennium continues to bring major changes to the world. In health these changes—new funds, new organizations, and new opportunities to develop the health technologies needed in developing countries—have helped give birth to the Era of Partnerships for health innovation.

Most of the partnerships, however, have focused missions and concentrate their activities on develop-

Table 1: Coping with health failures: An example of a Health Innovation -- Country Category matrix

		Health Failures		
		Science failure (knowledge/learning gap)	**Market failure (resources gap)**	**Public Health failure (best practices gap)**
Actions by National Innovation Systems	**Industrialized Countries**	Public funding of R&D of interest to developing countries (e.g. NIH genome projects of tropical pathogens)	Drug procurement mechanisms (e.g. Stop TB Partnership Global Drug Facility, GDF)	Drug donation programs (e.g. Merck Mectizan); Donor support to health systems (e.g. Rotary International & poliomyelitis vaccination)
		Private sector participation at PDPs; Big Pharma institutes dedicated to neglected diseases (e.g. Novartis Institute for Tropical Diseases, Singapore; GSK drug discovery unit in Tres Cantos, Spain)	Differential drug pricing (e.g. Novartis' antimalarial Coartem® in endemic countries sells as Riamet® in industrialized countries)	Actions through Global Conventions (e.g. Tobacco Convention against smoking; UN Framework Convention on Climate Change to monitor impact of climate changes on insect-borne diseases)
	Innovative Developing Countries	Health innovation networks (e.g. South/South: WHO Developing Countries Vaccine Regulators Network; e.g. North-South: genomics/bioinformatics networks for the study of tropical pathogens)	Innovative financing systems (e.g. Provisional Contribution on Financial Movement, or CPMF taxation, imposed by Brazil to buy antiretrovirals)	Pressure from health sector and civil society (e.g. Brazil Constitution's "Health is the citizen's right and the State's obligation and responsibility")
		"Bayh-Dole"-like laws to foster academia-industry partnerships (e.g. Innovation Law, Brazil)	Negotiating price reductions (e.g. Brazil/Abbott deal to lower price on antiretroviral drug Kaletra)	National Immunization Days; cash transfer programs to reduce poverty and inequality (e.g. The Bolsa Familia Project in Brazil)
	Least Developed Countries	South-South networking with IDCs (e.g. collaboration between Brazil and lusophone Africa in the strengthening of public health schools and R&D institutes)	Funding mechanisms (e.g. The Global Fund to Fight AIDS, Tuberculosis and Malaria; The Global Alliance for Vaccines and Immunization)	Better priority setting (e.g. The Tanzania Essential Health Interventions Project, TEHIP)
		Participation at clinical trial platforms (e.g. European & Developing Countries Clinical Trials Partnership, EDCTP)	Regional production of generic drugs; Popular Pharmacies ("Boticas Populares") that sell generic and essential drugs at a reduced price to poor people	Innovative approaches in relation to educational campaigns, empowerment of women, fighting corruption
		New products, methods	**New processes**	**New strategies or policies**
		Health Innovations needed		

ing specific interventions or products. Although an important component of a future GHIS, their compartmentalized mandates are no substitute for the global architecture called for by Professor Bloom.

We believe that a new architecture for health innovation is possible, necessary, and urgently required. It should be based on the lessons provided by innovation studies, effectively addressing each of the six innovation components and the three different health failures by identifying appropriate roles for each country and public- or private-sector organization.

A GHIS does not exist today and so we do not know what exact form it would assume. But without changes from the status quo, it is likely that 10 or 20 years from now we will have only a few new products on the market: most will be stuck in the pipeline. To open the floodgates to new innovation, we need a widely accepted, understood, and cost effective GHIS. We propose that its architecture should be integrated to become more than the mere sum of its parts: the innovation systems of PDPs, developing countries, developed countries, and international networks. One may think of it as an overarching system that discusses, shapes, and provides a long-term strategic vision, a system that offers best practices and policies adapted to the particular needs and environments of all the participating organizations.

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Living with TRIPS: Innovation of New Health Technologies for the Poor

Meeting Report, New Delhi, December 2005

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Background

One year has passed since the accession of India and other middle-income nations into the World Trade Organization's (WTO) Agreement on Trade Related Aspects of Intellectual Property (TRIPS). Mandating a minimum set of intellectual property (IP) protections for patented pharmaceutical products, TRIPS has raised questions about how its new global standards for patent protection will affect R&D investment, innovation, and product availability, especially for developing economies with significant innovative capacities in health R&D. To explore these issues the Indian Council for Medical Research (ICMR) and the UK-based Centre for Management of IP in Health R&D (MIHR) convened an international meeting in New Delhi on "Living with TRIPS: Innovation of New Health Technologies for the Poor."

Attention has focused on India because of its established strengths in generic drug production, potential cost-advantages as an R&D base for multinational firms, and large prospective market for low-cost medicines. These factors make India a bellwether for gauging the impact of TRIPS on health product innovation and access. Vigorous debates in India and elsewhere preceded the implementation of TRIPS, and it is now possible to begin to pursue some of the questions raised in that debate. Will TRIPS lead to monopolies on new drugs where previously imitation was possible? Will TRIPS encourage foreign investment for the health industry or create external constraints? Will TRIPS lessen interest by developing country firms in diseases of the poor, where markets are uncertain, or motivate the development of innovative drugs against diseases of poverty? Will the international product development partnerships (PDPs) that are now generating a pipeline of drugs for poverty-related diseases find it easier to form partnerships with institutions and emerging suppliers in developing countries?

Conference participants were predominantly practitioners: research managers, licensing specialists, and technology managers from the public sector, academe, and PDPs. As Dr. Pramilla Senanayake, Chair of the MIHR Board of Trustees, noted when opening the conference, "We face the collective challenge under a *globalized* IP regime of *globalizing* efforts to address diseases of poverty, promoting local innovation for national need, and improving the transfer of information and access to technology from the North to the South."

Early Perspectives: TRIPS in Context

Perhaps the meeting's most important outcome was the consensus that conclusively documenting the benefits or costs of TRIPS for developing countries may not be possible. Innovation is a dynamic process influenced by many external variables. These include the level of government support for

Eiss, R, RT Mahoney and K Satyanarayana. 2006. Living with TRIPS: Innovation of New Health Technologies for the Poor. *Innovation Strategy Today* 2(1):13-16. www.biodevelopments.org/innovation/index.htm

science and technology, government programs to promote trade, the capabilities of national drug regulatory agencies, and government efforts to enhance competencies in these and other areas. Historical precedent suggests that strengthening IP will increase foreign direct investment and flows of technology transfer, as long as essential preconditions exist. These include supportive R&D environments, effective judicial systems to enforce patent law, and viable domestic and export markets. Professor Sandy Thomas of the Nuffield Council on Bioethics reinforced the point that IP is just one factor affecting innovation: "when markets are present, innovation and TRIPS can be potentially complementary because of the IP incentives TRIPS provides."

Perhaps the most controversial issue surrounding TRIPS is its impact on the price and availability of new medicines. By enforcing product patents, TRIPS will reduce the availability of generic versions of patented medicines, thus eliminating a de facto price control on medicines in developing countries. Medecins Sans Frontieres noted, for example, the key role generic competition played in determining prices for HIV anti-retrovirals in India, Brazil, South Africa, and other countries.

All agreed that the price effects of implementing TRIPS should be monitored closely, both in countries with strong generic industries and in countries relying on imports of generic substitutes, but participants also emphasized the need to address underlying structural impediments to access besides price. These include the equity and efficiency of health financing and distribution systems, evidence-based analysis to improve current practice, and local community involvement. An instructive and oft-cited case example of delivery failure is the uneven access to medicines on WHO's list of essential drugs, of which less than five percent are on-patent.

Apart from the potential effects of patents on price and availability post-TRIPS, the comparative therapeutic benefits of new chemical entities over available generics will also have health implications. So, in assessing TRIPS over time, the rate of pharmaceutical innovation will be a key variable in measuring the health impact of strengthened patent regimes.

A second significant outcome of the meeting was strong consensus of the need to build skills in IP management so that TRIPS can be adapted to a nation's advantage. Developing countries that choose to invest in science and technology must, of necessity, address IP issues to participate in the international marketplace. IP competencies will enable them to gain access to emerging tools, technologies, and resources to develop products. All agreed on the acute need to establish policies and procedures and train staff to effectively manage IP. Priorities include training in contract negotiation, statutory protection, patent searching and filing, technology valuation and business strategy development, as well as the development and implementation of IP policies and strategies at the institutional level, especially within public research institutions and universities.

Emerging Strategies to Reach the Poor

While the conference's central theme related to the health needs of poor populations, the implications of TRIPS for developing products to treat diseases of poverty proved difficult to assess. Technology transfer and innovation in general are strongly viewed as ways to grow an economy. Yet it is clear that emerging pharmaceutical industries can not only generate new knowledge, skilled labor, and markets, but also address social objectives. Health-related products can be developed to meet local needs. But will the emerging pharmaceutical industries in India, China, Brazil, and elsewhere become a source of new medicines for diseases that disproportionately affect low- and middle-income nations? Early evidence suggests that pharmaceutical firms in India are taking a global focus, exploiting their strengths to develop or improve therapeutic drugs for well-characterized medical conditions that exist in robust global markets. For example, based on projected sales growth, Ranbaxy Laboratories aspires to increase its percentage of revenue from OECD sales from 20% in 2000 to 70% in 2007 (presentation at investors conference in Mumbai, September 2004).

Dr. R. N. Mashelkar, Director General of the Indian Council for Industrial and Scientific Research, observed that the public sector remains responsible for promoting the development of new technologies to meet local needs. The Government of India is addressing this task by promoting investment in drug development through several innovative schemes, such as increased R&D tax benefits and subsidies to support industry-university partnerships. The New Millennium Indian Technology Leadership Initiative, for example, supports local technology partnerships between publicly supported R&D institutes and industrial companies. Among health related activities,

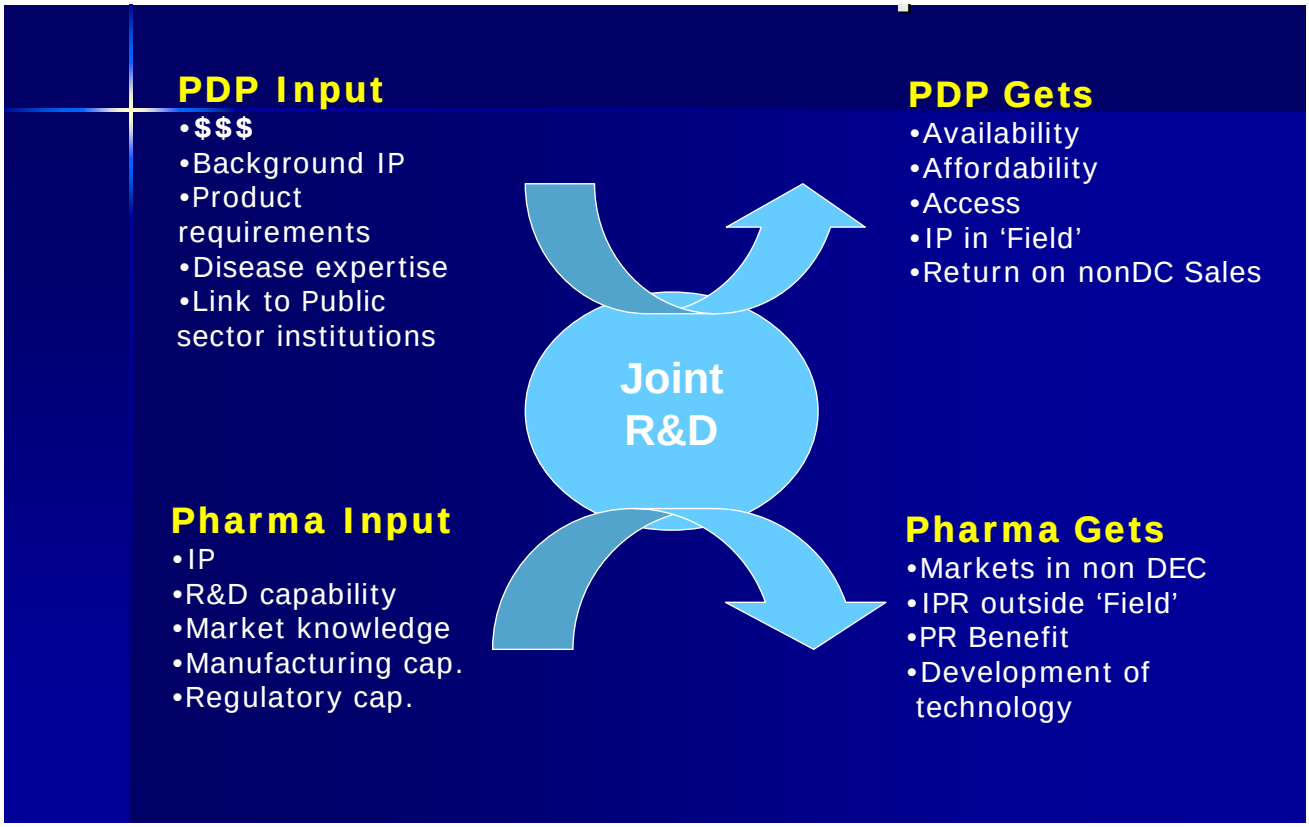
the program supports the development of new targets, drug delivery systems, bio-enhancers, and therapeutics for latent M tuberculosis in efforts to better manage the high disease burden of tuberculosis in India. Researchers are also working to identify gene-based drug targets for prevalent cancers in India. The program may serve as a model for supporting local public-private partnerships in other regions, especially as firms seek academic ties to enhance their R&D base in drug discovery. Importantly, when the public sector invests in product development, it can control the IP to help benefit the poor (e.g., by setting conditions for how the covered technology is to be distributed or marketed).

New global IP standards have emerged just as PDPs are pioneering creative forms of IP management. PDPs offer a new way to look at IP: as a negotiating tool for developing quality, affordable therapeutics and vaccines for diseases of the poor. The conference featured examples of public interest management of IP by PDPs working in India. Dr. V. N. Venugopal of the Medicines for Malaria Venture (MMV) described technology partnerships to develop an artemisinin-derived lead compound for malaria. He expressed a pragmatic, representative view in explaining their success in terms of collaboration with the private sector, an achievement made possible by identifying and managing IP effectively. Indeed, although each PDP adapts its IP strategies to the respective contributions of its public-sector and industrial partners, PDPs share common working tenets. They are constructing deals that both present private-sector incentives and meet public-sector social objectives through , negotiated agreement on territorial markets; pricing structures for public and private markets; or field of use, among other areas. Dr. Venugopal illustrated this synergistic relationship in Figure 1.

TRIPS and Public Health Safeguards

The conference also focused on compulsory licensing and parallel importation. These public health safeguards are provided under the TRIPS agreement and were reinforced by the DOHA Ministerial Conference. The timely discussion coincided with the WTO

Figure 1: How the PDPs and Pharma address the needs of the poor



Council's decision to permanently adopt a key policy on compulsory licenses adopted as a waiver in 2003. As the WTO's Ms. Jayashree Watal noted, the waiver has significantly improved the ability of developing countries without manufacturing capabilities to import patented drugs from sources other than the originator company. The waiver will become a formal part of the agreement after WTO members ratify it.

Production under compulsory licenses presents several operational challenges. Firms need to secure adequate know-how from the patent holder in order to re-create products. The products must also reach markets that are large enough to enable compulsory licensees to recoup development and production costs. While compulsory licenses are potentially beneficial tools, participants noted that there are also other ways developing countries can help ensure that IP does not create barriers to access. These include conventional licensing arrangements and,, notably, the ability of countries to enact laws permitting and regulating the government's use of patented inventions. Other avenues include the actions of patent courts to protect the public interest, the thoughtful management of genetic resources and traditional knowledge, and the judicious framing of competition law and policy.

In sum, the international IP standards mandated by the TRIPS agreement allow member nations considerable discretion to enact laws and provisions that meet treaty obligations and support national innovation policies and development priorities.

Summary Conclusions

The conference raised important considerations for countries adapting to TRIPS:

- IP is one of several innovation determinants in health R&D; when assessing impact, IP must be considered in the context of other competencies;
- Creatively managed, IP under a globalized regime can be used in the public interest to improve access to new medicines and public health interventions by poor populations;
- Countries aspiring to adapt TRIPS to national advantage must build institutional capabilities and policies in IP in order to benefit from emerging technologies and to participate in the global marketplace;
- TRIPS, importantly, enables countries to establish national patent policies and practices that both meet treaty obligations and address national economic needs and social values.

As an outcome of the conference, ICMR and MIHR will negotiate a Memorandum of Understanding to enhance technology transfer skills in the Indian public sector and develop partnerships with technology management offices at research universities in other countries. This MOU will also help build professional networks in best practice.

Dedication

This conference was dedicated to the memory of Sanjaya Lall, a professor of Development Economics at Oxford University, who passed away unexpectedly last year in June. Professor Lall was one of the world's leading commentators on trade, competitiveness, and globalisation, and his writings on IP and developing countries are acutely sensitive and penetrating. He was a humble and warm person who simply had to be admired—and loved. His powerful intellect, illuminating insights, and humor made us respect and esteem him greatly.

India, TRIPS and HIV/AIDS:

*Exploring the effects of TRIPS compliance on the availability of Indian antiretrovirals**

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Executive Summary

Context: The developing world today is home to over 38 million of the 40 million people living with HIV. A frighteningly large number of these people are unable to obtain the basic antiretrovirals that they so desperately need. A large majority, moreover, do not receive the most effective form of HIV treatment, triple therapy, which is readily available to people living in the developed world. Of the numerous obstacles that may block access to antiretrovirals in poor countries, one of the most daunting is cost. Until recently, a year's worth of triple therapy ranged in price from US$10,000 to 15,000 --hardly affordable for a teacher in Uganda earning less than $2,000 annually or the typical Indian household garnering less than $3,000 a year. Fortunately, this situation has recently changed. With the introduction of generic drugs in the 1990's, the price of HIV and AIDS treatment has dropped dramatically. Several Indian pharmaceutical companies have emerged as world leaders in the production of relatively inexpensive, generic antiretrovirals. However, the competitive advantage that permitted these Indian companies to flourish over the past three decades is presently vanishing.

Prior to 1 January 2005, India did not extend patent protection to pharmaceutical products. This allowed Indian pharmaceutical companies to freely copy and manufacture virtually any drug of their choosing. On 1 January 2005, however, India officially transitioned into an era of extending patent protection to pharmaceutical products. To effect this transition, the Indian Patent Office began examining the first of the more than 9,000 applications deposited in a repository known as "the Indian mailbox" over the past ten years by pharmaceutical companies eager to earn Indian patents on their drugs. Though the pharmaceutical transition is now officially underway, it will be sometime before its true effects are fully appreciated. The vast majority of the mailbox applications are yet to be examined, and it is unknown at this time which applications will lead to patents and, of those that do, what each will ultimately claim. In the interim, heated debate has arisen over the potential influence that India's pharmaceutical transition may exert on drug prices. Some fear that the less expensive generic drugs, including those used to treat HIV and AIDS, will suddenly skyrocket in price or simply disappear from the market. In an attempt to better inform this debate, this paper takes a look at antiretrovirals, the Indian mailbox, and the surrounding legal framework.

Summary of Findings: To better understand the applications related to antiretrovirals that are likely pending examination in the Indian mailbox, a fairly comprehensive list was compiled of US patents claiming currently marketed single antiretrovirals

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and fixed antiretroviral combination pills. The priority date on each of these US patents was established via the USPTO to determine whether the underlying application (or an application related thereto) was eligible for deposit in the Indian mailbox. In particular, if the priority date of an application underlying a surveyed US patent fell between 1 January 1994 (one year before the first day on which an application may have been deposited in the Indian mailbox to account for the one year foreign filing grace period), and 31 December 2004, it was concluded that a similar application may have been deposited in the Indian mailbox.[1] Since the survey shows that any application pending in the Indian mailbox is sister to a successful US application for a US patent, and further that the requirements for patentability in India are very similar to those in the United States, any such application pending in the mailbox may very well result in an Indian patent.

Of the ninety (90) US patents surveyed, fifty four (54) had priority dates that permitted their underlying applications to be deposited in the Indian mailbox; however, the majority of these (44) were for improvement patents. The vast majority (i.e., 85%) of the surveyed US patents that claimed the basic formula of currently marketed antiretrovirals had underlying applications that excluded them from possible mailbox deposit. Because India may not issue patents on these drugs, the pharmaceutical transition should not have a strong effect on the price of basic antiretrovirals within India. Consequently, the fears that the transition will cause a substantial increase in the cost of basic HIV/AIDS drugs seem largely unfounded.[2]

Yet all concern should not be extinguished. The survey also found that the vast majority of the US patents claiming fixed combination pills (FCPs) do have priority dates that permitted submission. If these applications were submitted, and if their issuance as US patents indicates that they will issue as Indian patents, up to five of the six FCPs currently marketed could potentially come under Indian patent protection in the near future. In this event, the generic manufacturers wishing to continue production in India of patented FCPs will be legally required to obtain licenses. These licenses may be the product of voluntary negotiations between the generic manufacturers and the patent holder or may instead be compelled by § 11A of the Indian Patent Act. In either case, generic manufacturers able to obtain a license will find themselves newly saddled with royalty payments, the cost of which may be passed on to the consumer by way of an FCP price increase. It should be added, however, that numerous internal factors and external pressures influence the price that drug companies set for their life-sustaining drugs. It is thus difficult to predict with any certainty whether a price increase in FCPs will ultimately materialize. In addition, industry royalty rates (even those negotiated under adverse conditions) rarely exceed 10% of net profit. Given these two factors, it seems fairly certain that any FCP price increase caused by India's pharmaceutical transition will be relatively modest.

Conclusions: On a final and broader note, a number of actions can be taken to help moderate the cost of medicines patented in India after 2005. For example, interest groups may be able to use pre-grant opposition to help minimize the number of questionable patents granted and thus deter patent evergreening. Additionally, after a three-year period, compulsory licenses may be sought within India to help exploit the profound anchoring effect of generic competition on proprietary drug prices. Similarly, developing countries lacking pharmaceutical manufacturing capabilities may also secure Indian generics under compulsory licensing schemes. Generic producers may utilize India's Bolar provision to help rush generic drugs to the market post-patent expiration. Lastly, India's upper and lower house may be petitioned to correct the flawed language that persists in the Indian Patent Act (e.g., the definition of pharmaceutical substance). It is true that several of these precautionary measures are relatively new or have yet to be used, but WHO members repeatedly assure that these legal mechanisms were intended to be and should be fully exploited to help ensure that life-saving medicines do not become prohibitively expensive for the citizens of low-income nations. Whether India and other WHO members will actively bear out these assurances will only be determined by the passage of time and the persistent efforts to exploit the precautionary measures offered by the TRIPS agreement and adopted into law by member nations.

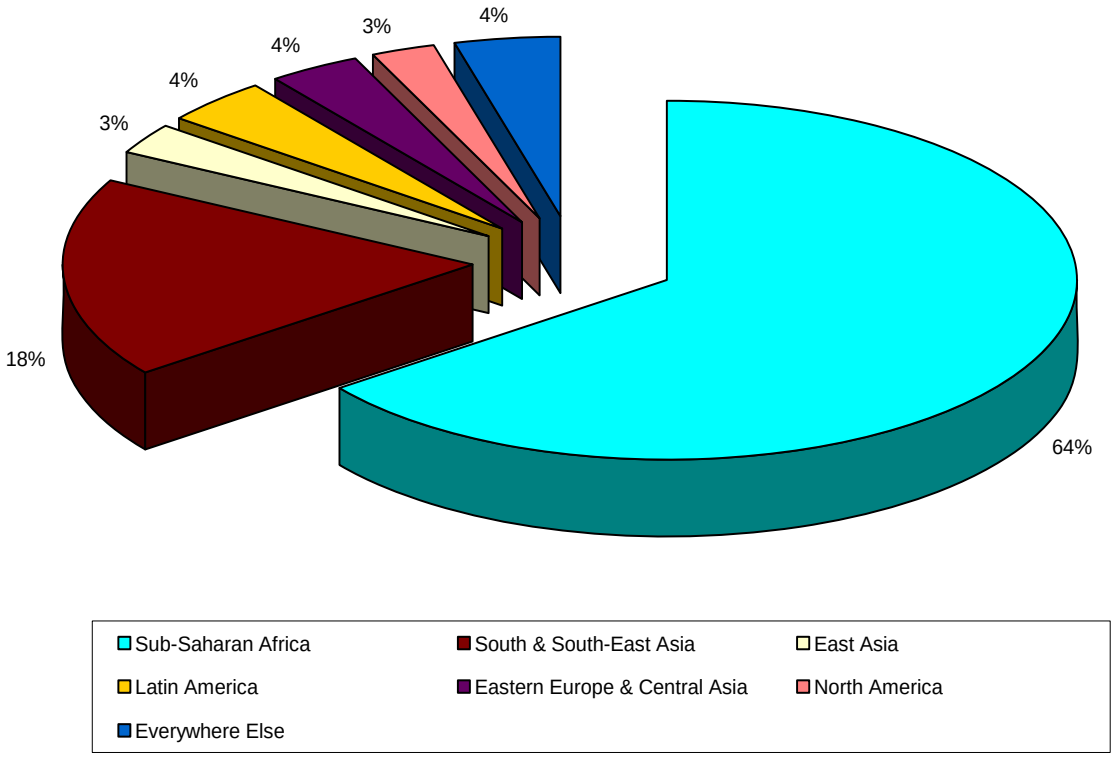
HIV, AIDS, and the Developing World

It will probably never be known when the human immodeficiency virus (HIV) infected its first human host. Many speculate that the first infection occurred prior to 1970. But it was not until 1981, after the virus had spread to at least five continents, that US health workers first became aware of what we now know as acquired immunodeficiency syndrome (AIDS).[3] As reports slowly emerged, what initially appeared to be a few isolated cases revealed itself as an epidemic—one that did not discriminate by sexual preference or nationality. In 1985, just four years after the first case of AIDS was recognized in the United States, the director of the World Health Organization (WHO) estimated that as many as ten million people might be infected worldwide.[4] Twenty years later, that estimate has now quadrupled and continues to grow. More than three million people with AIDS died last year, while five million more were infected.[5] However, unlike the infections and deaths experienced in the 1980's, these infections and deaths occurred almost entirely in developing world, in regions such as Africa and India (Figure 2).

The Current Impact of HIV on the Developing World

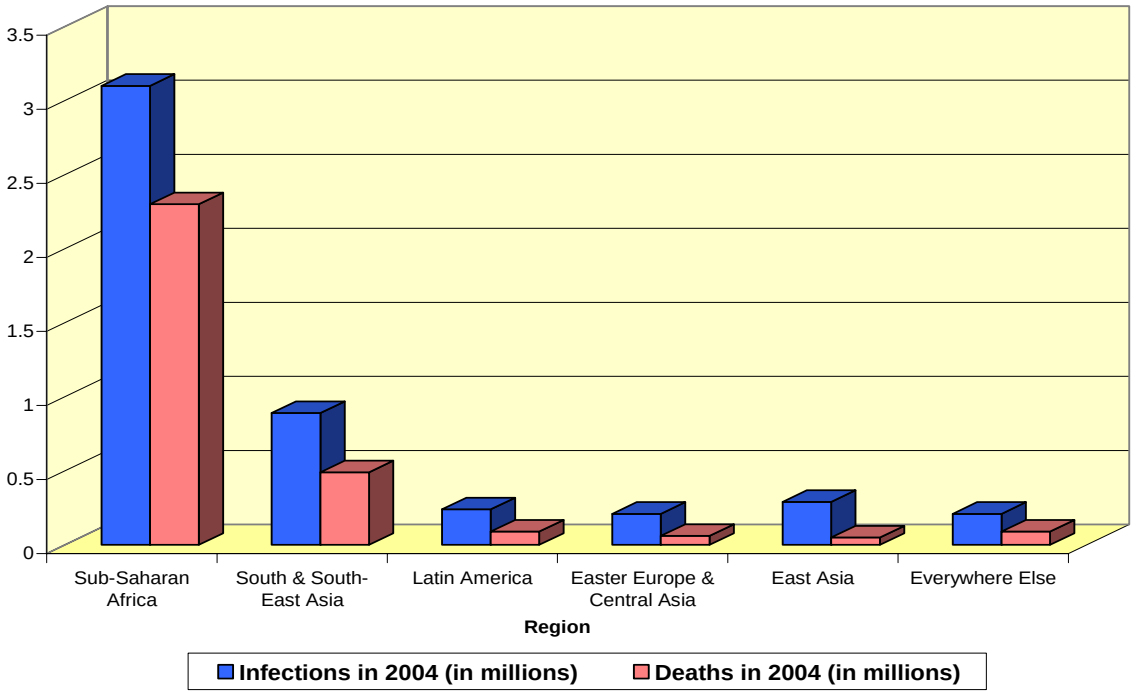
Of the 40 million people currently living with HIV, more than 95% reside in the developing world (Figure 1).[6] It is not surprising that AIDS will soon be the number one killer in many developing countries.[7] Today, Africa is hardest hit by the AIDS epidemic, particularly the sub-Saharan region, which nearly 65% of adults and children infected with HIV called home in 2004.[8] The overall rate of infection among adults in sub-Saharan Africa is more than seven times the global average, and in the African region of Botswana the infection rate has soared to 38.8%.[9] As of 2001, an estimated 21.5 million Africans with AIDS have died.[10] This has detrimentally affected Africa's social fabric and economy. It is estimated that African gross domestic product will be capped by roughly 17% in 2010 due to the influence of HIV.[11]

Figure 1: Number of people living with HIV (end of 2004)



Source: World Health Organization, *Regional HIV/AIDS Statistics and Features, end of 2004.*

Figure 2: Infections vs. Deaths in 2004 (million people)



Source: World Health Organization, *Regional HIV/AIDS Statistics and Features, end of 2004.*

A person residing in the developing world with HIV or AIDS will likely have a very different experience than someone who resides in the developed-world. Often, HIV/AIDS patients living in the developing world are unable to obtain even basic health care. This is especially troubling for AIDS patients because almost any infection could prove fatal. Without treatment, many AIDS patients living in the developing world become too debilitated to perform ordinary tasks. Typically, such people cannot work, although they desperately need money because of the lack of a social services safety net. If they can work, they may have difficulty finding employment due to the intense social stigma that accompanies their disease. Understanding is usually abhorrently low in rural areas, and AIDS sufferers may be considered cursed or unclean. Even people infected with the virus often do not understand their condition. They may act upon misconception or superstition. For example, in Africa, it is not uncommon for a man infected with HIV to rape and infect young female children in accordance with the superstitious belief that AIDS may be cured by having sexual intercourse with a virgin.

The Current Impact of HIV on India

The first documented case of HIV infection in India occurred in 1986.[12] Despite efforts by India's National AIDS Control Organization (NARCO), India's HIV population has since grown to be the second largest in the world.[13] At the end of 2003, nearly one percent of the Indian population—over five million adults and children—were living with HIV or AIDS.[14] From a geographic perspective, HIV infections are fairly concentrated; six of the thirty-five Indian states account for 80% of the cases.[15] From a demographic perspective, however, the infections are more evenly distributed. Mainly confined previously to urban areas and at-risk groups (e.g., sex workers, IV drug users, and truck drivers), HIV is quickly spreading into the general Indian population. The epidemic is growing progressively younger too; more than a third of new infections occur in people under 30 years of age.[16] An increasing number of women are being infected, and consequently the rate of mother-to-child HIV transmission is escalating.[17] In two Indian states, Manipur and Nagaland, more than one percent of all pregnant women are now infected.[18]

Sadly, India's future does not look much brighter. In its current condition, the health care system is ill equipped to adequately treat even a modest fraction of the infected population: on average there is only one trained Indian doctor for every 5,000 HIV patients.[19] The United Nations Population Division projects that adult HIV prevalence will escalate in India to 1.9% by 2019 and that nearly 50 million Indians will die from AIDS between 2015 and 2020.[20] According to another report produced by the National Intelligence Council, India will experience 20 to 25 million AIDS cases by 2010.[21] This may make India the country with the highest number of HIV infections in the world.[22]

The Virus, the Disease, and the Drugs

The Virus

The Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the human immune system. As a retrovirus, HIV utilizes the enzyme reverse transcriptase to transcribe its genetic make-up from RNA into DNA, which may then integrate into the genome of a human host cell. After integration has occurred, the virus may utilize a host cell's reproductive machinery to generate its own offspring. Each infected host cell may then produce a small swarm of daughter viruses that exit the cell, sometimes destroying it, in search of new cells to infect and destroy. When docking with a human host cell, HIV binds to a particular protein (i.e., CD4) that is particularly abundant on the surface of T4-lymphocites. T4-lymphocites, or T-helper cells, are a type of white blood cell that warns the immune system when pathogens are present in the body. As HIV destroys an increasing number of T-helper cells, the body's immune response is slowly debilitated. Over the course of several years, HIV causes the immune system to enter into a chronically compromised state generally known as Acquired Immunodeficiency Syndrome (AIDS), wherein the body is particularly susceptible to opportunistic infections. [23] AIDS is described in greater detail in the next section.

The process of reverse transcription (i.e., the production of DNA from viral RNA) is prone to error.[24] While this may seem like a reproductive disadvantage, it is truly a great advantage. The occurrence of genetic errors during transcription, specifically those errors occurring in the regions that encode for the molecular targets of therapy (i.e., HIV protease and reverse transcriptase enzymes), enables future generations of HIV to become drug resistant.[25] As the Stanford HIV Drug Resistance Database explains:

> *Because of this high mutation rate, HIV exists within an individual as a complex mixture of genetically related but distinguishable variants often referred to as a "swarm" or "quasispecies"… When a prescribed anti-HIV treatment does not succeed in completely suppressing viral replication, the replicating HIV quasispecies is given the opportunity to develop new mutations. During drug therapy, those viruses that carry or develop mutations that confer drug resistance are selected for and eventually predominate… The duration of virus suppression experienced by patients receiving drug therapy depends on the time it takes for the virus population within a patient to acquire a sufficient number of drug-resistance mutations to render the therapy ineffective.*[26]

To decrease the likelihood that drug resistance will develop, it is important for HIV patients to be provided with a comprehensive treatment regimen that they must adhere to strictly. Triple therapy regimens, in particular, help decrease the occurrence of drug resistant viral swarms by combining three or more ARVs that attack multiple elements of the virus' reproductive machinery. In this way, triple therapy may repress the replication of viral strains that have developed drug resistance to some but not all of the administered ARVs. Triple therapy is discussed in more detail below.

The Disease

As stated above, as HIV destroys more T4-lymphocites, the immune system is slowly compromised and eventually enters into a state of failure generally known as AIDS. Most people do not have any symptoms when they are first infected with HIV, though many experience a temporary flu-like illness within a couple months. After this flu-like illness passes, most people enter into an asymptomatic period. It may take up to ten years for full-blown AIDS to develop, if it develops at all. However, even before the development of full-blown

AIDS, a person may experience weight loss, depletion of energy, rashes, flaky skin, and short-term memory loss. A few experience shingles or develop herpes infections.

When AIDS does fully develop, the body is particularly susceptible to opportunistic infections caused by bacteria, viruses, fungi, parasites, and other such microbes. It is these opportunistic infections, not the virus itself, that lead to AIDS related deaths. If a person with AIDS contracts such an opportunistic infection, he or she may experience a variety of symptoms including shortness of breath, seizure, diarrhea, fever, vision loss, headache, weight loss, coma, and death. Fortunately, with the recent advent of triple therapy described below, modern treatment programs have been able to successfully impede viral replication and decrease the likelihood of opportunistic infection and thereby significantly increase the quality and duration of the lives of AIDS patients.

The Drugs

Drugs that combat the retrovirus HIV and hinder opportunistic infections are generally referred to as antiretrovirals (ARVs). ARVs help reduce, or more accurately suppress, a patient's viral load by interfering with biological mechanisms that the virus utilizes to replicate. There are four classes of ARVs, distinguished by the biological mechanism with which they interfere. They are: (1) nucleoside reverse transcriptase inhibitors (NRTIs), (2) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (3) protease inhibitors (PIs), and (4) fusion inhibitors (FIs). Table 1 briefly outlines the four antiretroviral classes and how each operates to suppress the HIV replication.

The first of two milestones in HIV/AIDS treatment of occurred in 1987 when the FDA approved NRTI zidovudine as the first antiretroviral.[27] Prior to that time, no drug existed to combat the HIV virus and few existed that could decrease the likelihood of opportunistic infections. The second milestone came eight years later with the approval of the first PI, Saquinavir. It was at this time that powerful "drug cocktails" were developed that combined Saquinavir with two or more other ARVs in a daily treatment regimen commonly known as Highly Active Antiviral Therapy (HAART) or optimal triple therapy.

With the introduction of triple therapy in Europe and the US, the number of opportunistic infections, hospitalizations, and deaths dropped dramatically.[28] Not only did triple therapy regimens help HIV and AIDS patients stave off death, they also produced marked improvement in patients' quality of life.[29] Some AIDS patients improved so dramatically that the healing powers of triple therapy regimens were boldly compared to those demonstrated by Christ when He reclaimed Lazarus from death. Given these considerable therapeutic powers, the significant repercussions of triple therapy treatment seemed trivial. As one observer explains:

> *These combination therapies are not perfect: they do not eradicate the virus, they needed to be taken for life, and they have serious side–effects. In addition, some have to be taken according to rigorous schedules and/or have dietary conditions. However for the vast majority of people, these medicines reduce or eliminate opportunistic infections, improve quality of life and significantly extend life. With access to care including antiretroviral treatment, HIV can become a chronic disease like any other, allowing most people to resume normal activities, including work.*[30]

As mentioned above, triple therapy treatment is so effective because it attacks multiple aspects of the viruses' reproductive machinery, thereby decreasing the likelihood that drug resistance will develop. This is vitally important both for the person receiving the triple therapy and for its incidental benefit to the public: the decreased likelihood that drug resistant HIV strains will develop and spread. It is thus in everyone's best interest that people with HIV—including those that live in developing countries—receive optimal treatment.

For patients receiving triple therapy, the number of pills that must be taken can be quite large (usually around twelve per day and potentially exceeding thirty per day). This not only increases the burden on the patient, but also increases the likelihood of non-adherence with the regimen and therefore the probability that a drug-resistant HIV strain will develop. Fixed combination pills (FCPs) have helped ease this burden by combining two or more ARVs into single dosages that may be taken as few as two times per day. FCPs may also decrease production costs, which may consequently decrease the overall cost of triple therapy treatment. Of the FCPs cur-

rently marketed, Kaletra® is the only one that contains an antiretroviral that is unavailable individually (i.e., Lopinavir). As shown on the next page in Table 2, there are currently five brand name FCPs available on the US market. Most of these have only recently been approved by the FDA.

Table 1: Overview of Antiretroviral Classes

Antiretroviral Class	Operation	Examples
Fusion Inhibitors (FIs)	FIs prevent the entry of the virus into a human cell by inhibiting fusion of HIV with the cell's membrane.	Enfuvirtide
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	NNRTIs bind to the enzyme reverse transcriptase and disable it, preventing the virus from converting its RNA into DNA.	Delavirdine, Efavirenz, and Nevirapine
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	NRTIs interrupt early stages of viral reproduction by providing HIV with faulty building blocks, which, when used in lieu of a normal building block, slows the rate of viral reproduction.	Abacavir, Adefovir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zalcitabine, and Zidovudine
Protease Inhibitors (PIs)	PIs interrupt the later stages of virus reproduction. In particular, PIs disable protease, a protein that HIV uses for viral building blocks.	Amprenavir, Atazanavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, and Tipranavir

Table 2: Fixed Combinations with Formula and FDA Approval Date

Fixed Combination (TM)	Formula	FDA Approval Date
Combivir®	Lamivudine + Zidovudine	1997
Epzicom®	Abacavir + Zidovudine + Lamivudine	2004
Kaletra®	Lopinavir + Ritonavir	2000
Trizivir®	Lamivudine + Abacavir	2000
Truvada®	Emtricitabine + Tenofovir Disoproxil Fumarate	2004

Source: Approved Medications to Treat HIV Infection.

The Cost of Treating AIDS in the Developing World

For some time now, the World Health Organization (WHO) has released a list of what it considers to be essential drugs (i.e., drugs that will satisfy the "minimum medicine needs for a basic health care system.")[31] Accordingly to WHO estimates, "currently one third of the world's population lacks access to essential drugs and… over 50 per cent of people in poor countries in Africa and Asia do not have access to even the most basic essential drugs."[32] Many factors limit the availability of life-saving medicines, including ARVs, within developing countries. These include distributional problems, poor diagnostics, questionable drug quality, and sub-par research.[33] Notwithstanding this, one of the most daunting obstacles to obtaining essential medicines in poor areas has historically been, and continues to be, the cost of treatment. Cost is especially significant in developing countries partly because per capita spending on health is a fraction of that spent in developed countries.[34] Furthermore, public subsidies for medicine are lower, and so the burden falls more heavily on household resources to pay for medical needs. It is estimated that in low-income countries roughly 50% to 90% of the cost for treatment falls on the personal pocket book at the time of illness.[35]

Cost may pose an especially great obstacle for obtaining ARVs, most of which remain protected by patents in most of the world. Indeed, cost may often pose an insurmountable barrier for triple therapy treatment consisting of three or more ARVs consumed daily. It is thus not surprising that only a

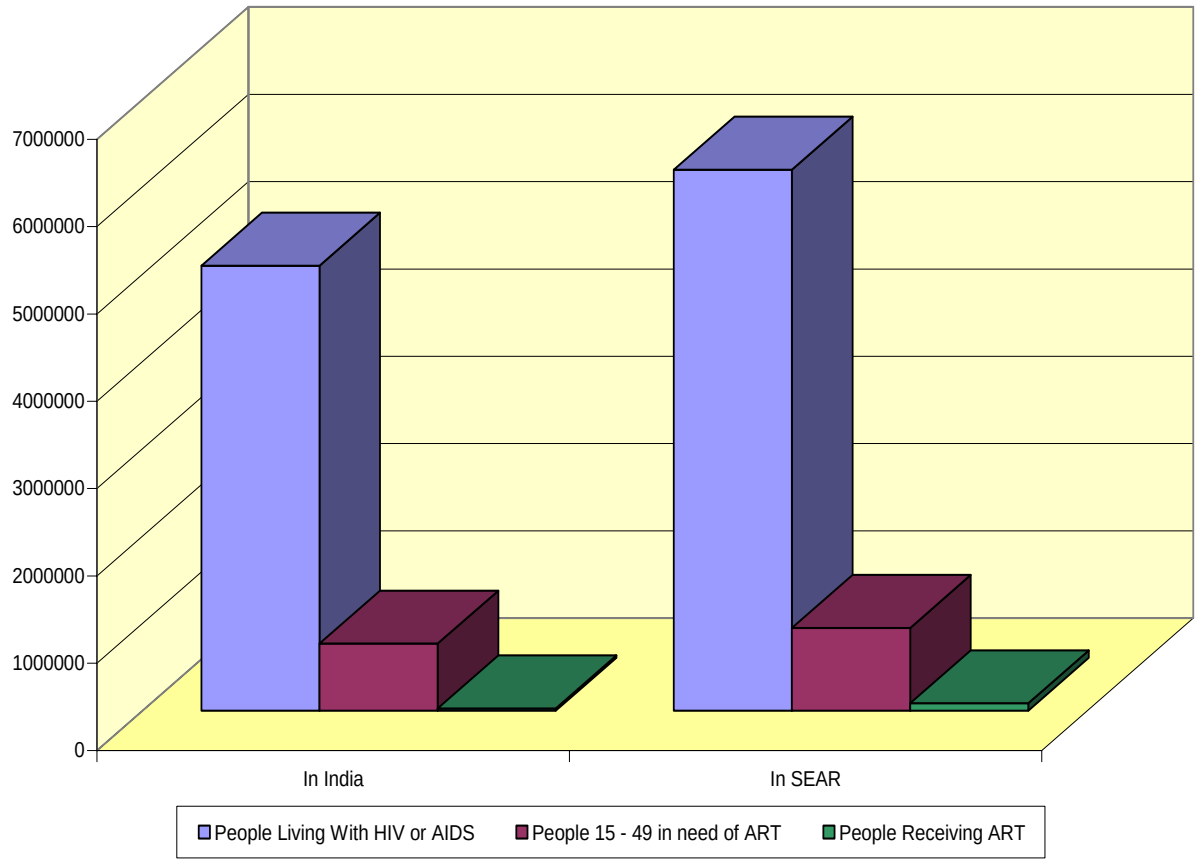
small percentage of people living in developing countries are being treated with ARVs, and even fewer are receiving triple therapy.[36] In India, for example, of the 600,000 AIDS patients in need of triple therapy treatment, only 30,000, or 2%, are getting it (see attached Figure 3).[37] Even when triple therapy treatment regimens are administered in developing countries, they are typically NRTI based regimens, which are less expensive than PI based regimens. This is unfortunate because studies suggest that regimens based on PIs are more effective than those based on NRTIs.[38]

The next two sections briefly explore how patents and generic competition may affect drug prices. The final section then briefly presents an emerging scheme that seeks to regulate the cost of life-saving drugs at affordable levels: equity pricing.

How Patents Affect Cost

Though many factors may affect the price that a company sets for a proprietary drug, one of the most influential factors is market power. In fact, market power by definition directly correlates to the degree of control a company may exercise over the price of its drugs. And an important way that a company can gain power in the pharmaceutical market is by patenting a drug. However, it should be understood that a patent only bestows upon its holder a legal monopoly: the right to exclude others from making, using, selling, offering to sell, and importing the claimed subject matter. A patent does not promise that the patent holder will make or sell the claimed subject matter, nor does it usually confer a true economic monopoly. The market power of a patent is created by the demand for the product it claims, demand that is counterbalanced by the

Figure 3: Antiretroviral therapy needs in Southeast Asia



Source: World Health Organization, Regional Office for South-East Asia, *HIV/AIDS Fact and Figures*

number and closeness of available non-infringing substitutes. The more alternatives, and the more indistinguishable they are from the patented product, the more competitive the market and the less separation between marginal revenue and marginal cost. Accordingly, one would predict that when a proprietary drug is subjected to competition in the form of less expensive generic alternatives, its price will gravitate toward that of the generics.[39] As the next section below explains, this has indeed proven to be the case.

The Effect of Generic Competition on Drug Price

It is has been well documented that the introduction of generic competition correlates to a drastic reduction in proprietary drug price. One group noted that "generic competition is one of the most powerful tools that policymakers have to lower drug prices in a sustainable way."[40] The price anchoring effect associated with generic competition has been observed within the ARV market, specifically with the recent introduction of generic ARVs produced by firms in Brazil and India. A recent study performed by the WHO compared the prices of six ARVs from 1996 through 2000, only four of which were exposed to generic competition. Of those exposed to generic competition, three had their prices reduced by over 60% in this five-year period, and the fourth had its price slashed by over 90%. In contrast, the two ARVs that were not exposed to generic competition during this period experienced only relatively moderate price reductions (i.e., under 20%).[41]

Expensive triple therapy regimens have also recently decreased in price with the introduction of generic competition. Prior to 2000, a year's worth of triple therapy treatment cost roughly $10,000 to 15,000.[42] However, in 2000, generic competition was introduced and the price for proprietary triple therapy regimens soon dropped dramatically. In 2000, the popular triple therapy regimen combining stavudine, lamivudine, and nevirapine was offered in its proprietary form for over $10,000 per annum. With the introduction of less expensive generic drugs from Brazil and India, the price of this triple therapy treatment plummeted by more than 90%.[43] Indeed, as can be seen in Figure 4, the proprietary version of this triple therapy combination experienced multiple price drops that closely shadowed those of the generic alternative.[44] The recent antiretroviral cost decrease also correlated to a direct increase in the number of HIV/AIDS patients taking ARVs. Uganda's Joint Clinical Research Centre, for example, reported that patient access to ARVs increased threefold during this time period, from 962 in 2000 to 3,000 in 2001.[45]

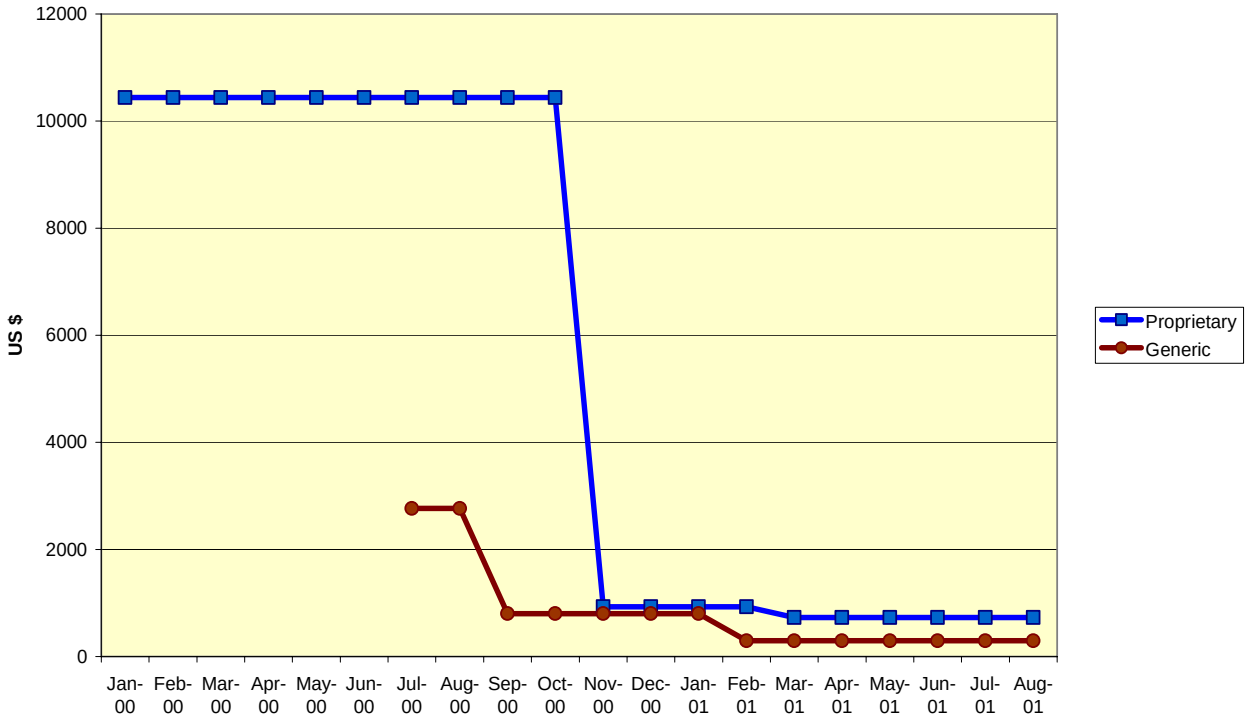
A Potential Solution: Equity Pricing

Several groups have advocated different approaches for lowering essential drug prices and ensuring that "the price of a drug is fair, equitable and affordable, even for a poor population and/or the health system."[46] One of the more popular approaches, equity pricing, employs combinations of various vehicles in an attempt to accomplish this goal. These include:

1. encouraging companies to engage in differential pricing;
2. taking advantage of TRIPS precautionary measures, such as compulsory licensing, parallel importation, and generic acceleration;
3. global bulk buying via a body such as the United Nations or UNICEF; and
4. stimulating local drug production through voluntary licensing and technology transfer.

Though TRIPS precautionary measures will be discussed below (see Section entitled *The TRIPS Agreement and India*), equity pricing and other systems aimed at maintaining low drug prices are outside the scope of this paper. For more about equity pricing, see *Pills and Pocketbooks: Equity Pricing of Essential Medicines in Developing Countries* by Ellen 't Hoen of Médecins Sans Frontières (Doctors without Borders).

Figure 4: Price effect of generic competition



Source: Reproduced from Pierre Chirac, *Increasing the Access to Antiretroviral Drugs to Moderate the Impact of AIDS: an Exploration of Alternative Options*, Chapter 14 of overall UNICEF study *AIDS, Public Policy and Child Well-Being*, June 2002, at 3.

India: The Generics Giant

The Indian pharmaceutical industry has grown impressively during the past thirty years largely due to fertile grounds provided by the Indian Patent Act of 1970. This act did not extend patent protection to pharmaceuticals products (or foods, insecticides, and chemicals) despite doing so for the processes used to make such products. In this environment, Indian firms became particularly adept at reverse engineering foreign drugs developed by multinational pharmaceutical giants. With minimal R&D costs and an inexpensive labor pool, Indian firms flourished; during the past decade, for example, the Indian pharmaceutical industry has averaged roughly 15% growth *each year*.[47] By recent estimates (2002 – 2004), the Indian drug market is now worth over $7.5 billion.[48] Even with TRIPS compliance, many expect the Indian market to continue growing. The Economist Intelligence Unit predicts that India's pharmaceutical sales, which were roughly $4.6 billion in 2004, will grow to $6.9 billion by the end of 2007 and to $8.3 billion by the end of 2009.[49]

As India's pharmaceutical industry expanded, so too did its exports. Between the fiscal years 1995/96 and 2002/03, Indian pharmaceutical exports grew over 20% each year.[50] By recent estimates, India exports nearly 1/3 of the drugs it produces, which amounts to over $3.1 billion worth of pharmaceuticals.[51] As pharmaceutical imports were recently valued around $645 million, this resulted in a trade surplus of $2.5 billion.[52] Although there are over 22,000 registered pharmaceutical manufacturers in India that are diverse in size and capacity, the lion's share of the market (roughly 70%) is controlled by India's top twenty companies.[53] Many of these derive more than half of their total revenue from international sales.[54] India's top pharmaceutical firm, Ranbaxy Laboratories, derived 78% of its $1.18 billion of net

sales from exports in 2004.[55] Similarly, India's second largest firm, Dr. Reddy's Laboratories, derived 64% of its $444 million of net sales from exports in the 2003/04 fiscal year.[56]

One of India's main exports is generic drugs.[57] In fact, India is now among the world leaders in generic distribution, and Ranbaxy Laboratories is one of the world's largest generic manufacturers.[58] In view of India's substantial generic output, it is understandable that many countries and groups have come to rely on generic Indian ARVs as "a lifeline of medicines for poor countries."[59] For example, Médecins Sans Frontières (Doctors without Borders), which has treatment facilities in a large variety of developing areas throughout the world, estimates that 70% of its 25,000 AIDS patients are currently taking Indian generics.[60]

The Indian Mailbox

Although the Indian mailbox was opened at the beginning of 2005 and the majority of the applications contained therein have been purportedly published (those claiming priority on or before July 30, 2003), it remains excessively difficult to look inside the mailbox. The pending mailbox applications have yet to be loaded onto a digital database, and so they are still not electronically searchable. For now, any search of the Indian mailbox must necessarily be a physical search. To pursue such a search would require hiring an Indian patent firm to dispatch an agent to the Indian patent office that houses the mailbox applications. That agent would then have to read through a large group of applications and determine if any claim the subject matter of interest. As might be imagined, this is time consuming and expensive. [61] Fortunately, this situation will change in the next few years: the Indian patent office is reportedly in the process of loading information from these patent applications into an electronic database. Additionally, the examination of mailbox applications is now underway; the large number of pending applications should slowly dwindle and a smaller number of patents should emerge. In the interim, however, some insight may be gained by conducting a survey of US patents pertaining to currently marketed antiretrovirals in order to determine which, if any, have underlying applications that were eligible for deposit in the Indian mailbox.

Opening the Mailbox

Although the Indian mailbox was opened this January, it will be sometime before the true effects of pharmaceutical transition are known. The vast majority of the applications are yet to be examined, and it is unclear which applications will lead to patents and the breadth of subject matter that each will ultimately claim. To gain a better understanding of the applications that may be pending in the Indian mailbox and that may lead to patents concerning antiretrovirals, a survey was conducted to determine which US patents claimed for antiretrovirals have underlying applications eligible for deposit in the Indian mailbox. This survey was performed in the following steps:

1. The antiretrovirals and fixed combination pills currently marketed were identified;
2. A fairly comprehensive list of US patents underlying each of these drugs was compiled;
3. The priority date for each of the underlying US patents was determined via the USPTO; and
4. The priority date of each of these patents was compared to the mailbox window to determine eligibility for mailbox deposit.

The results of the survey are summarized in Figures 5 and 6 and Tables A to E in the Appendix. Fifty-four (54) of the ninety (90) US patents considered had priority dates that allowed their underlying applications to be deposited in the Indian mailbox. However, the majority of these (44) were for improvement patents. The vast majority (85%) of the US patents that claimed the basic formula of the marketed antiretrovirals had underlying applications that excluded them from possible mailbox deposit. This includes twelve of the thirteen ARVs labeled by the WHO as essential, as well as the three ARVs that form the popular triple therapy regimen discussed above (i.e., stavudine, lamivudine, and nevirapine). Patents cannot be retroactively issued on these drugs, so generic manufacturers will remain free to continue producing their generic versions of these ARVs. In view of this, the Indian transition to protecting pharmaceutical products should

Figure 5: Basic ARV patents with possible mailbox deposit

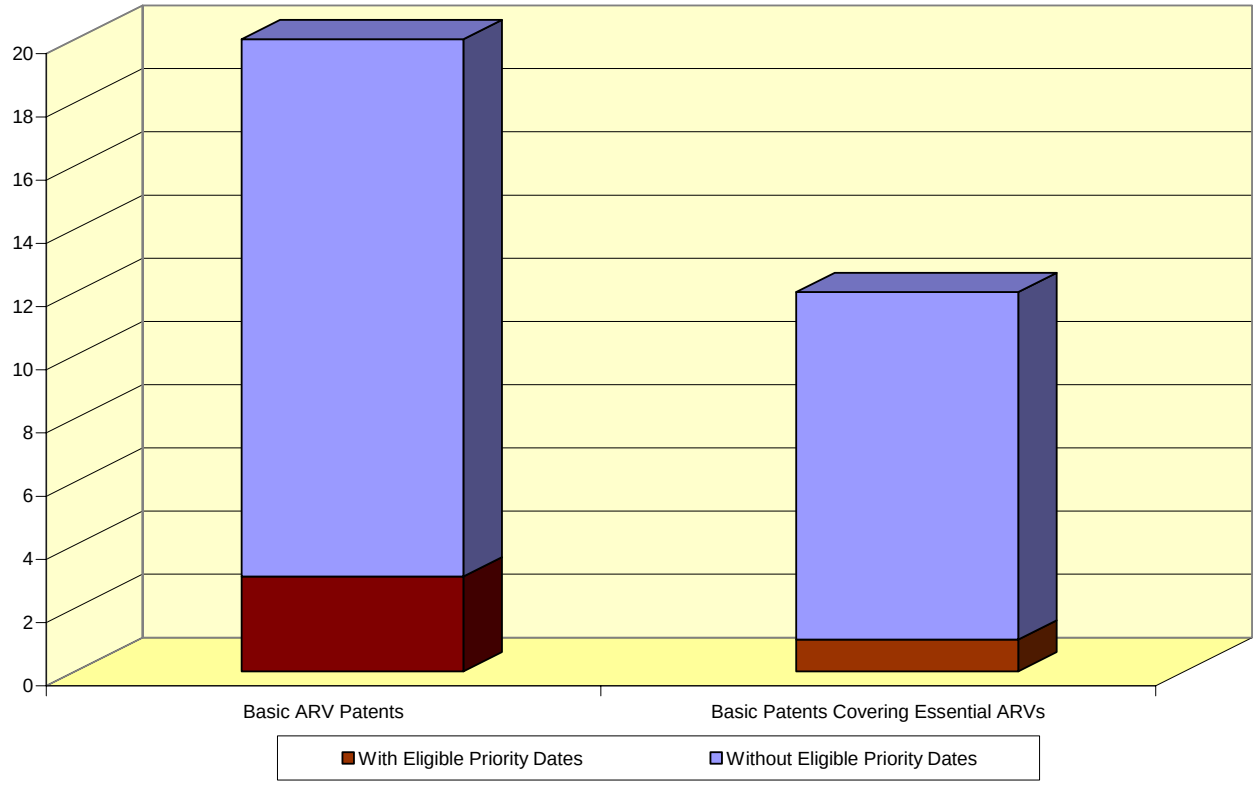
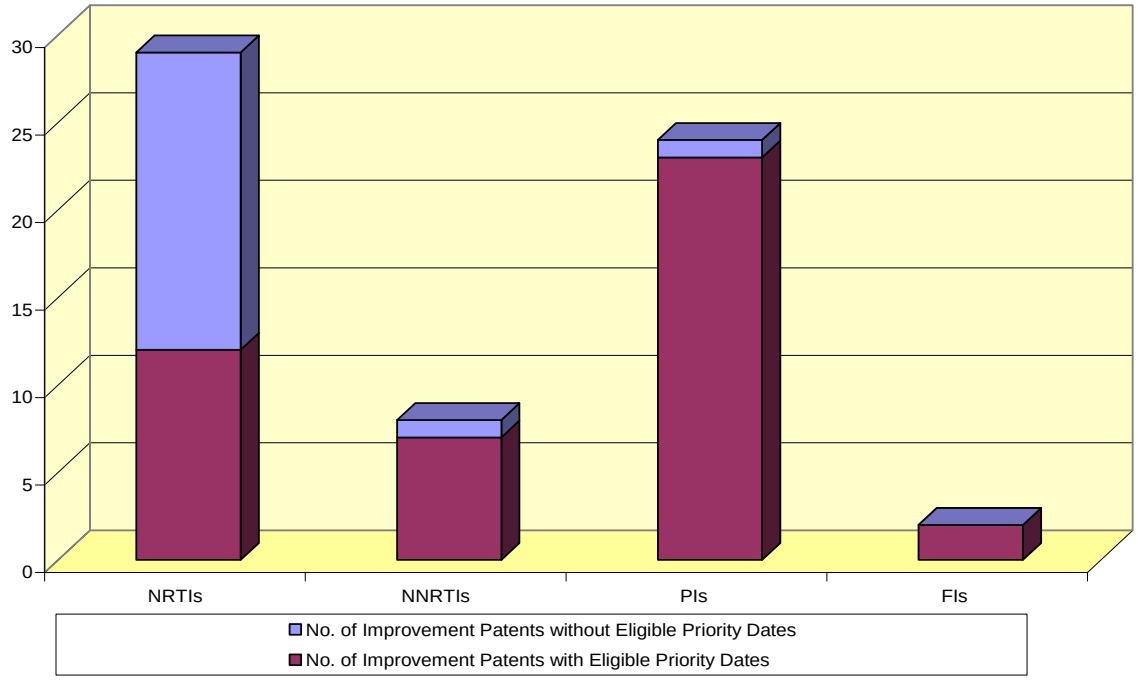


Figure 6: Basic ARV patents with possible mailbox deposit



Source for both Figures: See endnote 64.

not strongly affect the price of basic antiretrovirals.[63] Even if a small group of patents does issue claiming a minority of basic ARV formulae, this should not substantially increase the ARV price: many suitable generic alternatives to these newly patented drugs will remain unpatented and in the public domain, thus preserving the competitiveness of the basic ARV market.

Fixed combination pills are, however, another matter. At least five out of the six combination pills (FCPs) are subject to patents having underlying applications with priority dates that permitted mailbox deposit. For this reason, a large majority of the FCPs currently produced could potentially come under Indian patent protection in the near future. This includes the popular Combivir® and Kaletra,® the only fixed combination pill labeled as a WHO essential drug.[64] If one or more FCP patents do in fact issue from the mailbox, the non-patent holding manufacturers will be legally required to obtain a license to continue production of generic FCPs within India. These licenses may be voluntarily granted by the patent holder to one or more generic producers by way of negotiations. Alternatively, one or more non-exclusive licenses may be compelled under § 11A of the Indian Patent Act, discussed below. In either case, those generic producers able to obtain licenses will face royalty payments. These royalty payments will likely tend to be greater if the licensing agreement is negotiated rather than compelled: an FCP patent holder will be in a superior bargaining position relative to a generic manufacturer who has already invested in tooling up, developing distributional channels, and the like. Such a patent holder may well be able to demand a royalty rate greater than the "reasonable royalty" rate promised by § 11A of the Indian Patent Act. Regardless of the licensing scheme employed, the fundamental result will be increased production costs for generic manufacturers producing FCPs. This could potentially cause a modest price increase at the consumer level. However, given the numerous factors and external pressures that influence drug prices, it is difficult to predict with much certainty whether FCP prices will even modestly increase.

The TRIPS Agreement and India

As permitted by the TRIPS agreement, India has incorporated several precautionary measures into its patent act to prevent life-saving drugs from becoming prohibitively expensive. These include a generic grandfather clause, a general compulsory licensing provision, pre-grant opposition procedures, and a generic acceleration provision (i.e., a Bolar provision). These precautionary measures are each discussed below and briefly review some of the minimum intellectual property standards required by India's adoption of TRIPS.

TRIPS Minima & India's Compliance

Under the authority of the World Trade Organization (WTO), the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was established as the most comprehensive IP treaty to date. Among other things, TRIPS provided an effective dispute resolution forum, required members to enforce protective measures both criminal and civil, and established a substantive set of minimum standards regarding the scope and use of intellectual property.[65] By establishing these minima (some of which are included in Table 3), TRIPS endeavors to harmonize the IP laws of its members in order to promote cooperative relations and facilitate trade.

Through three amendments to the Indian Patent Act of 1970, including the recent passage of the 2005 Amendment, India has come into full compliance with TRIPS, at least ostensibly. India now provides twenty years worth of patent protection to inventions in all fields of technology, including products in the pharmaceutical field, providing that the technology is 1) novel, 2) the product of an inventive step, and 3) capable of industrial application. [66] The Indian Patent Act, as amended, further confers patent rights in accordance with TRIPS Article 28. It allows for compulsory licenses to be granted in certain sets of circumstances discussed in more detail below.

TRIPS Precautionary Measures & Doha

The TRIPS agreement permits the adoption of several legal precautionary measures designed to deter important drugs from becoming excessively costly

(some of these safeguards are highlighted in Table 4). To further emphasize that these precautionary measures are intended to be used freely to protect public health, WTO members involved in the Doha Ministerial Conference of November, 2001, issued a declaration stressing that TRIPS should be interpreted "to support public health – by promoting both access to existing medicines and the creation of new medicines."[67] The following sections briefly discuss some of the precautionary measures permitted by TRIPS and adopted through Indian legislation.

India's Adoption of TRIPS Precautionary Measures

Grandfather License for Certain Generic Producers

Perhaps the Indian legislation's most generous concession for generic producers is in the 2005 Amendment to the Indian Patent Act. This Amendment changed Section 11A to bestow compulsory licenses upon generic producers that have "made significant investment and were producing and marketing [a generic drug for which an India mailbox patent issues] prior to 1 January 2005," providing that the generic producers pay the patent holder a reasonable royalty.[68] Exactly how this amendment to Section 11 will play out is unclear. But generic producers that fall within the scope of this language should be able to breathe a slight sigh of relief: prior to this amendment, those producers that had invested in generic production means and established trade relations would have been in a fairly weak bargaining position when negotiating licensing agreements to permit continued production. Still, despite its relative newness, this amendment has already garnered criticism that asserts that the phrases "reasonable royalty" and "significant investment" are unclear and will therefore lead to excessive litigation (or at least threats thereof) that smaller firms can ill afford. These critics press for more definite guidelines and suggest that, in lieu of determining a reasonable royalty on a case-by-case basis, a fixed royalty rate should be set (e.g., 4%).[69] These critics should note, however, that the phrase "reasonable royalty" was borrowed directly from the TRIPS compulsory

Table 3: Highlighted TRIPS Minima

TRIPS Article	Concerning	Brief Summary
27	Patentable Subject Matter	With limited exceptions (e.g., to protect public order), patents shall be available in *all* fields of technology provided that they are (1) new, (2) involve an inventive step, and (3) are capable of industrial application.
28	Rights Conferred	For a product, the patent must bestow the holder to prevent unauthorized making, using, offering for sale, selling, and importing. Note that these are the same rights granted under the US Patent Act (§ 271).
33	Patent Life	Term must be at least 20 years from the filing date.

Table 4: Highlighted TRIPS Precautionary Measures

TRIPS Article(s)	Concerning	Brief Summary
30	Generic Acceleration (i.e., Bolar Provision)	Generic drug manufacturers may obtain marketing approval for a patented drug without the patent holder's permission and before the drug is off patent.
6	Exhaustion and Parallel Imports	A product that is sold with the patent owner's consent in one country may be imported into another country freely.
30 & 31	Compulsory License	If a number of conditions are met, someone may practice the patent without the holder's consent in a limited number of events, including a national emergency. The compulsory license must be non-exclusive and non-assignable, and the licensee must pay the patent holder adequate remuneration.
8 & 40	Anti-Competitive Practice	Governments may act to prevent patent holders from abusing monopoly rights (e.g., unreasonably restraining trade).

license provision. Moreover, courts routinely determine what should constitute a reasonable royalty in a variety of situations (e.g., when determining damage awards in cases where lost profits cannot be shown or no competition existed between the patent holder and the infringer). The concept of "significant investment," on the other hand, will likely prove more difficult to apply. If "significant investment" is determined independently of firm size (i.e., by sheer dollar amount), smaller generic producers will be unfairly disadvantaged; however, if "significant investment" considers firm size (e.g., by comparing the amount of investment to total firm assets), larger generic producers may be unfairly disadvantaged.

Compulsory License

Articles 30 and 31 of TRIPS offer WTO members the ability to grant compulsory licenses in certain circumstances (e.g., in the event of a national emergency). Such compulsory licenses are required to be non-exclusive and non-assignable, and the recipient of such a license must pay the patent holder adequate remuneration. The Indian version of the compulsory license is set-forth in § 84 of the Indian Patent Act. This provision allows the government to grant a compulsory license if "the reasonable requirements of the public" are not being met or if "the patented invention is not available to the public at a reasonable price." However, § 84 also states that a compulsory license can only be granted three years after patent issuance unless a national emergency is declared. Considering that such a declaration has not been made in the history of the Indian Patent Act, it is unlikely that a national emergency will be declared if prices increase for basic ARVs or (even more unlikely) for fixed combination pills. The absence of such a declaration means that any compulsory license granted under § 84 will come, at the soonest, three years after the patent grant. Thus, § 84 will almost certainly not prove helpful in addressing price issues related to mailbox patents in the near future.

A quick note should be made here of the relatively recent developments concerning the compulsory license provision of TRIPS. Currently, TRIPS Article 31(f) states that "products made under a compulsory licensing scheme must be predominantly for the supply of the domestic market." The apparent restrictiveness of this language caused concern among WTO members who lack sufficient domestic production facilities to take advantage of the compulsory license provision. Reacting to these concerns, the WTO General Council issued a decision in August of 2003 that allowed "the obligations of an exporting member [under Article 31 to] be waived" if the importing member is a least developed country (lack of manufacturing capabilities is presumed) or confirms that "it has insufficient or no manufacturing capacities in the pharmaceutical sector for the product(s) in question."[70] To help allay fears that this waiver might be abused, the 2003 Decision limits Article 31 in several ways: by ensuring that the quantity of drugs produced is equivalent to the quantity needed and is entirely exported (see § 2(b)(i)), by establishing labeling standards and online publication requirements (see §§ 2(b)(ii) and (iii)), and by requiring adequate remuneration in view of the economic value *to the importing member* (see § 3). Furthermore, the Decision takes steps to deter the creation of gray markets: Sections 4 and 5 require members to take "reasonable measures" to discourage the re-exportation of imported drugs after they have been delivered to an importing member, unless the re-exported drugs are distributed to a qualified member country (i.e., a member that shares the health problem in question and is party to a regional trade agreement in accordance with § 6 of the Decision). The waiver will remain in effect until TRIPS Article 31 is officially amended in accordance with the 2003 Decision.

To take advantage of the flexibility that the 2003 Decision imparted to TRIPS Article 31, the Indian Patent Act was recently amended to add the following text:

> *Compulsory licence shall be available for manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity in the pharmaceutical sector for the concerned product to address public health problems, provided compulsory licence has been granted by such country or such country has, by notification or otherwise, allowed importation of the patented pharmaceutical products from India.*[71]

This amendment to the Indian Patent Act will undoubtedly be welcomed by India's generic manu-

facturers and underdeveloped nations alike. Generic manufacturers will appreciate the amendment's potential to bolster the ultra-valuable generic export market during this transitional period, and underdeveloped nations will appreciate the amendment's attempt to protect the lifeline of relatively inexpensive Indian generics that their citizens living with HIV/AIDS have come to rely upon.

Pre-Grant Opposition

In a pre-grant opposition, a published application may be contested by an outside party that brings prior art to an examiner's attention in an attempt to negate one or more patentability requirement (e.g., novelty, inventive step, etc.). Until recently, the Indian Patent Act allowed pre-grant oppositions only at the discretion of the Indian Controller. The 2005 Amendment changed Sections 25 and 26, however, so that pre-grant opposition may be exercised at the discretion of "any person." Interest groups or a concerned government agency might use this power to help deter patent evergreening However, the current difficulty in searching and viewing the mailbox renders the pre-grant opposition virtually meaningless for pending mailbox applications.

Generic Acceleration (i.e., Bolar Provisions)

Provisions based on TRIPS Article 30, commonly known as Bolar provisions, allow generic drug manufacturers to practice making a patented drug before patent expiration in an effort to gain governmental approval. The goal of such provision is to help speed generic drugs to market after patent expiration. The Indian government has provided for such generic acceleration; however, the Indian Bolar Provision will not apply to any patents issuing from the Indian mailbox for at least ten years (when the first of the patents issuing from mailbox applications expire) and thus in this context is of little help.

India's Attempt to Limit Patentable Pharmaceutical Inventions and Patent Evergreening

Though not precautionary measures per se, it is appropriate to discuss here some changes made by the 2005 Amendment to India's Patent Act that are intended to limit the scope of patentable pharmaceutical inventions. The 2005 Amendment attempts to limit the pharmaceuticals patentable under Indian law in two ways: 1) by changing the definition of the term "pharmaceutical substance," and 2) by broadening the scope of Section 3(d), which describes certain subject matter excluded from patentability. After the first of these changes, pharmaceutical substances are now defined as "any new entity involving one or more inventive step." As one might imagine, this definition is receiving an onslaught of criticism for being overly broad. The criticism is well justified. The only substantive components of the definition are redundant of two of the requirements for patentability: the requisites for novelty and an inventive step. If these two parts are removed, the definition reads an inconsequential "any… entity."

Section 3(d) of the Indian Patent Act describes subject matter that may not be patented. The 2005 Amendment changed the wording of Section 3(d) so that the following subject matter is not patentable:

> *The mere discovery of a… known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*[72]

Only time will reveal if the language in Section 3(d) truly narrows the field of patentability—despite its excessive use of the qualifier "mere." However, it is interesting to note that the intent of the amendment—to distinguish more incidental advances from true pharmaceutical inventions that generally would not be developed and disclosed but for the inducement of a patent—indicates a concern, expressed by many throughout the world, that pharmaceutical companies may push questionable improvement patents through overworked governmental patent offices in an attempt to unfairly extend the duration of their drug monopolies.[73] An in-depth discussion of whether patent evergreening, as it is commonly called, is an effective tool utilized by pharmaceutical conglomerates is a separate and extensive topic that cannot be discussed here. It is, however, appropriate to mention that the results of the survey described above in Section 6 did implicate patent evergreening in at least two ways. First, as may be recalled, over two-thirds of the ARV patents surveyed pertained to improvements on existing ARVs, not on basic ARV formu-

lae. It appears that, at least in the area of AIDS/HIV drugs, the bulk of intellectual property relates more to variations and refinements than to foundational medicines. Secondly, at least five out of the six currently marketed fixed combination pills are under patent protection in the US and all of the US patents had underlying applications permitting mailbox submission. Some critics feel that this is a form of patent evergreening. They argue that combining three ARVs into a single medicine should not rise to the level of an inventive step. Whether the Indian Patent Office agrees with these critics remains to be seen. However, given that United Sates patents have been granted for claims for all but one of the fixed combination pills based on similar or identical applications, it is arguably likely that any such mailbox applications claiming FCP combinations will ultimately issue as Indian patents.

Conclusions

In view of the above, it is extremely unlikely that India's transition into an era of patented pharmaceutical products will substantially affect the price of basic antiretrovirals. However, it is quite possible that several fixed combination pills that are currently produced and marketed by generic firms in India will soon come under Indian patent protection. In this event, non-patent holding manufacturers will be legally required to obtain licenses to continue producing the generic versions of these pills in India, which could potentially translate into a modest price increase in fixed combination pill prices. Concerned parties should stay aware of the issuance of any patents from mailbox applications claiming fixed combination pills and any subsequent license agreements. The brunt of efforts, however, is probably better spent addressing other areas (e.g., distribution systems) that will likely have a greater effect on the cost and availability of HIV/AIDS treatment in India and elsewhere.

On a final and broader note, a number of actions can be taken to help moderate the cost of medicines patented in India after 2005. For example, interest groups may be able to use pre-grant opposition to help minimize the number of questionable patents granted and thus deter patent evergreening. Additionally, after a three-year period, compulsory licenses may be sought within India to help exploit the profound anchoring effect of generic competition on proprietary drug prices. Similarly, developing countries lacking pharmaceutical manufacturing capabilities may also secure Indian generics under compulsory licensing schemes. Generic producers may utilize India's Bolar provision to help rush generic drugs to the market post-patent expiration. Lastly, India's upper and lower house may be petitioned to correct the flawed language that persists in the Indian Patent Act (e.g., the definition of pharmaceutical substance). It is true that several of these precautionary measures are relatively new or have yet to be used, but WHO members repeatedly assure that these legal mechanisms were intended to be and should be fully exploited to help ensure that life-saving medicines do not become prohibitively expensive for the citizens of low-income nations. Whether India and other WHO members will actively bear out these assurances will only be determined by the passage of time and the persistent efforts to exploit the precautionary measures offered by the TRIPS agreement and adopted into law by member nations.

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Appendix

For the sources of all tables, please refer to endnote 64.

Table A: Non-Nucleoside Reverse Transcriptase Inhibitors

Generic Name	Main Trade Name	A WHO Essential Drug?	Patents Issued (all US utility)	Priority Date	Eligible for Deposit?
Delavirdine	Rescriptor®	No	5,563,142	2/22/1994	YES
			6,177,101	6/7/1999	YES
Efavirenz	Sustiva® and Stocrin®	Yes	Unknown*	8/7/1992	No
			5,519,021	6/2/1995	YES
			5,663,169	6/2/1995	YES
			5,811,423	3/12/1997	YES
			6,238,695	4/6/1999	YES
			6,555,133	4/2/2001	YES
			6,639,071	10/19/2001	YES
Nevirapine	Viramune®	Yes	Unknown*	11/17/1989	No
			5,366,972	7/13/1993	No

Table B: Fusion Inhibitors

Generic Name	Main Trade Name	A WHO Essential Drug?	Patents Issued (all US utility)	Priority Date	Eligible for Deposit?
Enfurvirtide	Fuzeon®	No	5,464,933	6/7/1993	No
			6,133,418	11/6/1995	YES
			6,475,491	6/6/1998	YES

Table C: Protease Inhibitors

Generic Name	Main Trade Name	A WHO Essential Drug?	Patents Issued (all US utility)	Priority Date	Eligible for Deposit?
Amprenavir	Agenerase®	No	5,585,397	9/7/1993	No
			5,646,180	12/5/1995	YES
			5,723,490	4/19/1995	YES
			6,730,679	3/20/1997	YES
Atazanavir	Reyataz®	No	5,849,911	4/22/1996 (CH)	YES
			6,087,383	12/21/1998	YES
Fosamprenavir	Lexiva®	No	6,436,989	12/24/1997	YES
			6,514,953	7/18/1998 (GB)	YES
Indinavir	Crixivan®	Yes	Unknown*	11/8/1991	No
			5,413,999	5/7/1993	No
			6,645,961	3/4/1998	YES
			6,689,761	2/1/1995	YES
Lopinavir	N/A	Yes	N/A	N/A	N/A
Nelfinavir	Viracept®	Yes	Unknown*	10/7/1993	No
			5,484,926	2/2/1994	YES
			5,952,343	6/7/1995	YES
			6,162,812	4/1/1999	YES
Ritonavir	Norvir®	Yes	Unknown*	12/29/1992	No
			5,541,206	4/25/1995	YES
			5,484,801	5/12/1995	YES
			5,635,523	4/6/1995	YES
			5,648,497	3/24/1995	YES
			5,674,882	3/29/1995	YES
			5,846,987	3/20/1997	YES
			5,886,036	3/20/1997	YES
			5,948,436	3/13/1995	YES
			6,037,157	6/26/1996	YES
			6,232,333	11/7/1997	YES
			6,703,403	11/20/2001	YES
Saquinavir	Fortovase ® and Invirase®	Yes	5,196,438	12/11/1989 (GB)	No
			6,008,228	5/7/1996	YES
			6,352,717	11/17/1998 (EP)	YES

Table D: Nucleoside Reverse Transcriptase Inhibitors

Generic Name	Main Trade Name	A WHO Essential Drug?	Patents Issued (all US utility)	Priority Date	Eligible for Deposit?
Abacavir	Ziagen®	Yes	5,034,394	12/22/1989	No
			5,089,500	6/27/1988 (GB)	No
			6,294,540	5/17/1997 (GB)	YES
Adefovir	Preveon® and Hepsera®	No	4,724,233	4/25/1985 (CS)	No
			4,808,716	4/25/1985 (CS)	No
			5,663,159	10/11/1994	YES
			6,451,340	9/10/2001	YES
			6,635,278	12/15/1998	YES
Didanosine	Videx®	Yes	Unknown *	5/15/1985	No
			4,861,759	8/11/1987	No
			5,254,539	2/28/1991	No
			5,616,566	4/30/1993	No
			5,880,106	10/2/1997	YES
Emtricitabine	Emtriva®	No	5,210,085	2/22/1991	No
			5,814,639	2/16/1993	No
			5,914,331	6/7/1995	YES
			6,642,245	6/7/1995	YES
			6,703,396	3/6/1991 (GB)	No
Lamivudine	Epivir®	Yes	5,047,407	2/8/1989	No
			5,532,246	1/3/1991	No
			5,905,082	6/3/1991 (GB)	No
			6,004,968	3/26/1997 (GB)	YES
			6,180,639	5/2/1990 (GB)	No
Stavudine	Zerit®	Yes	4,978,655	12/17/1986	No
Tenofovir	Viread®	No	4,808,716	4/25/1985 (CS)	No
			5,922,695	7/25/1997	YES
			5,935,946	7/25/1997	YES
			5,977,089	11/6/1998	YES
			6,043,230	5/19/1999	YES
			6,057,305	8/5/1992	No
Zalcitabine	Hivid®	No	Unknown*	8/26/1985	No
			4,879,277	8/11/1987	No
			5,028,595	8/21/1989	No
Zidovudine	Retrovir®	Yes	4,724,232	3/16/1985 (GB)	No
			4,818,538	3/16/1985 (GB)	No
			4,828,838	3/16/1985 (GB)	No
			4,833,130	3/16/1985 (GB)	No
			4,837,208	3/16/1985 (GB)	No

Table E: Fixed Combinations

Trade Name	Formula	A WHO Essential Drug?	Relating To:	Patents Issued (all US utility)	Priority Date	Eligible for Deposit?
Combivir®	Lamivudine + Zidovudine	No	Zidovudine	4,724,232	3/16/1985 (GB)	No
				4,818,538	3/16/1985 (GB)	No
				4,828,838	3/16/1985 (GB)	No
				4,833,130	3/16/1985 (GB)	No
				4,837,208	3/16/1985 (GB)	No
			Lamivudine	5,047,407	2/8/1989	No
				5,905,082	6/3/1991 (GB)	No
				6,180,639	5/2/1990 (GB)	No
			Combination	5,859,021	5/16/1991	No
				6,113,920	10/31/1996	YES
Epzicom®	Lamivudine + Abacavir	No	Abacavir	5,034,394	6/27/1988 (GB)	No
				5,089,500	6/27/1988 (GB)	No
				6,294,540	5/17/1997 (GB)	YES
			Lamivudine	5,047,407	2/8/1989	No
				5,905,082	6/3/1991 (GB)	No
				6,180,639	5/2/1990 (GB)	No
			Combination	6,417,191	3/30/1995 (GB)	YES
Kaletra®	Lopinavir + Ritonavir	Yes	Ritonavir	5,541,206	4/25/1995	YES
				5,635,523	4/6/1995	YES
				5,648,497	3/24/1995	YES
				5,674,882	3/29/1995	YES
				5,846,987	3/20/1997	YES
				5,886,036	3/20/1997	YES
				6,037,157	6/26/1996	YES
				6,232,333	11/7/1997	YES
				6,703,403	11/20/2001	YES
			Combination	5,914,332	11/26/1996	YES
				6,284,767	12/8/1998	YES
				6,458,818	7/2/1999	YES
				6,521,651	11/10/1999	YES
Trizivir®	Abacavir + Zidovudine + Lamivudine	No	Zidovudine	4,724,232	3/16/1985 (GB)	No
				4,818,538	3/16/1985 (GB)	No
				4,828,838	3/16/1985 (GB)	No
				4,833,130	3/16/1985 (GB)	No
				4,837,208	3/16/1985 (GB)	No
			Abacavir	5,034,394	6/27/1988	No
				5,089,500	6/27/1988 (GB)	No
				6,294,540	5/17/1997 (GB)	YES
			Lamivudine	5,047,407	2/8/1989	No
				5,905,082	6/3/1991 (GB)	No
				6,180,639	5/2/1990 (GB)	No
			Combination	6,417,191	3/30/1995	YES
Truvada®	Emtricitabine + Tenofovir Disoproxil Fumarate	No	Emtricitabine	5,210,085	2/22/1991	No
				5,814,639	2/16/1993	No
				5,914,331	6/7/1995	YES
				6,642,245	6/7/1995	YES
				6,703,396	3/6/1991 (GB)	No
			Tenofovir	5,922,695	7/25/1997	YES
				5,935,946	7/25/1997	YES
				5,977,089	11/6/1998	YES
				6,043,230	5/19/1999	YES

Notes ***(all web pages have last been accessed on 19 March 2006)***

1. Indeed, considering the generally small prosecution cost in relation to the large potential profit margin associated with ARVs, it is arguably likely that such applications have been filed in the Indian mailbox.
2. Other forces, however, may contribute to an increase in the price of basic ARVs, including the removal of Indian governmental price control.
3. AVERT, *The History of AIDS*.
4. *Id.*
5. 800,000 of the infected were children. Pierre Chirac, *Increasing the Access to Antiretroviral Drugs to Moderate the Impact of AIDS: an Exploration of Alternative Options*; Chapter 14 of overall UNICEF study *AIDS, Public Policy and Child Well-Being;* June 2002; at 3.
6. Boulet et al., *Patent Situation of HIV/AIDS-Related Drugs in 80 Countries*, UNAIDS, January 2000, at 2.
7. Pierre Chirac, at 3.
8. World Health Organization, Regional Office for South-East Asia, *HIV/AIDS Fact and Figures*.
9. Copson, *AIDS in Africa*, CRS Issue Brief for Congress, May 2003, at 3.
10. *Id.*
11. Raquel Pontes de Campos, *Dispute over generic AIDS drugs pits the world's haves against have-nots*, Seattle Times Article, June 2001, at 2.
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14. *Id*.
15. *Id*.
16. AVERT, *The History of AIDS*.
17. *Id*.
18. *India: Epidemiological Fact Sheet on HIV/AIDS and other Sexually Transmitted Disease*, UNICEF, UNAIDS and WHO, 2004, at 2.
19. *India may become highest HIV infected nation by 2006,* The Economic Times, July 2004, at 1.
20. AVERT, *The History of AIDS*.
21. *Id.*
22. *Id.*
23. The CDC definition of AIDS encompasses all HIV-infected people who have fewer than 200 CD4+ T cells per cubic millimeter of blood. As a comparison, healthy adults usually have CD4+ T-cell counts exceeding 1,000. National Institute of Health, *HIV Infection and AIDS: An Overview*.
24. According to the Stanford HIV Drug Resistance Database, "nearly one viral mutation occurs during each cycle of replication." Stanford HIV Drug Resistance Database, *The Biology of HIV Drug Resistance*.
25. *Id*.
26. *Id.*
27. For completeness—The first NNRTI and the first PI was FDA approved in 1996 and 1995, respectively. The first and only FI to gain FDA approval to date, tenofovir, did so in 2001.
28. In fact, AIDS-related mortality in Europe and the US dropped by more than 70% with the introduction of triple therapy. Pierre Chirac, at 4.
29. Gossel, *AIDS: A Primer for Pharmacists on Therapeutic Control and Patient Counseling*, August 2003.
30. Pierre Chirac, at 4.
31. The list's 13th and most recent version published in 2003 contains 316 individual medicines, including 12 antiretrovirals from three of the four classes.
32. World Health Organization, Review of Patent Legislation of India, Indonesia, Sri Lanka and Thailand, September 2004, at 1
33. Médecins Sans Frontières (Doctors without Borders), *Will the lifeline of affordable medicines for poor countries be cut?,* February 2005, at 2.
34. World Health Organization, *The World Medicines Situation*, 2004, at 2.
35. World Health Organization, *What are Essential Medicines?*
36. Pierre Chirac, at 5.
37. World Health Organization, Regional Office for South-East Asia, *HIV/AIDS Fact and Figures*.
38. See Carter, *Meta-analysis finds PI-based HAART better than NNRTI regimens in NRTI experienced*, January 2004; see also Yazdanpanah, *Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials,* 2004.
39. Of course, the proprietary drug producer may create an artificial market differential by promoting its brand name.
40. Hoen et al. *Pills and pocketbooks: Equity pricing of essential medicines in developing countries,* April 2001, at 2.
41. World Health Organization, *HIV/AIDS Antiretroviral Newsletter*, Issue No. 8, December 2002, at 3.
42. Pierre Chirac at 3.
43. Pierre Chirac at 8.
44. As Graph 4 shows, after the introduction of generic competitors, starting with a Brazilian generic in July at $2767 and then the Indian generic Cipla in September at $800, the price of the proprietary drugs dropped to under $1,000 by mid-October. Similarly, when generic prices dropped to $350 the next year, proprietary prices tracked the drop by decreasing to $727.
45. Martinez-Jones et al., *Access to Antiretroviral Therapy in Uganda*, June 2002, at 11.
46. Hoen et al. at 1.
47. Economist Intelligence Unit, *Indian Market Profile*, February 2005.
48. *Id*.
49. Id at Industry Forecasts.
50. *Id*.
51. *Id*.
52. *Id*.
53. *Id*.
54. *Id*.
55. *Id*.
56. *Id*.
57. *Id*.
58. Pierre Chirac, at 9.
59. Médecins Sans Frontières (Doctors without Borders), *Will the lifeline of affordable medicines for poor countries be cut?,* February 2005, at 2.
60. *Id* at 3.
61. A representative example: one Indian patent firm estimated that such a search would take roughly 500 hours. At an hourly rate of $300, a complete search would cost approximately $15,000.
62. It should be noted, however, that other factors may contribute to a price increase amongst basic ARVs. One of these factors is potentially the loosening of governmental price control, which began in India in 1995. The most recent pharmaceutical policy, passed in 2002, is expected to cut the number of drugs subject to price regulation by over half. Economist Intelligence Unit, Indian Market Profile, February 2005.
63. Kaletra® is also the only currently available source of the ARV lopinavir.
64. The information contained in the tables in the Appendix was compiled mainly from three sources: the www.Thinkpharama.com database, the United States Patent and Trademark Office website (www.USPTO.gov) and the following source: Boulet et al., *Patent Situation of HIV/AIDS-Related Drugs in 80 Countries*, UNAIDS, January 2000 ("the Boulet reference"). The list of US patents covering each antiretroviral may not be,

and most likely is not, exhaustive. Some patents are listed as unknown; these are taken from the Boulet reference, which listed priority dates for several antiretroviral patents but did not provide corresponding patent numbers. Despite attempts, the patents marked as "unknown" could not be verified. It was felt that these references were still reliable enough to be included with the data because of the reputable organizations associated with the Boulet reference (i.e., UNAIDS and the WHO).

[65] McManis, *Intellectual Property and International Mergers and Acquisitions*, 1998.

[66] The Indian Patent Act defines "inventive step" as follows: "'inventive step' means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art." *The Patents (Amended) Act, 2005*, April 2005, at 2.

[67] World Trade Organization, *Fact Sheet: TRIPS and Pharmaceutical Patents*.

[68] *The Patent (Amendment) Act of 2005*, April 2005, note 10 at p. 14.

[69] Amin and Gopakumar, *A Critical View of the New Indian Patent (Amended) Act 2005, 2005*, at 3.

[70] Interestingly, the 2003 Decision leaves the decision of whether manufacturing capabilities are sufficiently lacking to qualify for Article 31(f) importation to the discretion of the importing member. See generally, World Trade Organization, *Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health: Decision of the General Council of 30 August 2003*.

[71] *The Patent (Amendment) Act of 2005*, April 2005, at 14.

[72] Of course, after subject matter has passed into the public domain, it may never be reclaimed by any subsequent patent. *Id.* at 2.

[73] A related concern, albeit one that concerns mainly developed nations, is that patents are being granted (and/or FDA approval is being given) for drugs (often called "me too" drugs) that are chemically similar and therapeutically equivalent or inferior to existing drugs, which pharmaceutical conglomerates then heavily promote thus creating a false impression of therapeutic superiority. For example, Pfizer's Lipitor®, which was the number one selling drug in the United States last year, is widely considered to be chemically and therapeutically equivalent to multiple other non-proprietary drugs that have been on the market for years.

A Critique of Innovation Systems Perspectives on Agricultural Research in Developing Countries

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Executive Summary

Innovation systems perspectives on agricultural research and technological change in developing countries are increasingly popular for the study of how society generates, disseminates, and utilizes knowledge.

The innovation systems perspective is a significant change from the conventional, linear approach to research and development. It provides an analytical framework that explores complex relationships among diverse actors, social and economic institutions, and technological and institutional opportunities. The perspective also challenges claims that technological change drives social and economic development, suggesting instead that development is driven by the institutional context in which technological change occurs.

Recent empirical work has extended the innovation systems approach. It is now being used to study not only national innovation systems in industrialized-country manufacturing but also developing-country agriculture, shifting the emphasis from a unidirectional technology transfer approach to a more complex, process-based systems approach. This shift in perspective is appropriate for the study of developing-country agriculture because it can help policymakers, researchers, research managers, donors, entrepreneurs, and others identify and analyze new ways to encourage innovation. It offers greater insight into the complex relationships between state and non-state actors, processes of institutional learning and change, market and non-market institutions, public policy, poverty reduction, and socio-economic development.

This framework, however, has yet to be fully applied to understanding how innovation occurs in developing countries, and its application to the design of mechanisms that would strengthen agricultural innovation systems has not even begun. The perspective of much of the emerging literature is limited to the conventional role of the public research organization. The few methodologies deployed do not extend beyond ungeneralizable, context-specific descriptive analysis, which is of only limited relevance to policy analysis and poverty reduction.

There is ample scope for empirical studies to employ more diverse methodologies, both qualitative and quantitative. Furthermore, empirical studies could provide more relevant analyses of public policies in support of not only science, technology, and innovation but also of poverty reduction and economic growth.

Much can be done with this new framework. More effort is required to identify measures and accumulate data on national and sectoral innovation systems. We must also develop taxonomies to classify agents, institutions, and systems. And we must focus more on identifying policy options that can steer the innovative process toward more welfare-improving outcomes.

With more, better-quality information, innovation systems researchers will be able to more accurately understand the strategic behavior of diverse actors in the context of different social and economic institutions. They will also be able to make meaningful comparisons over both time and space, all of which will allow them to suggest new policy options for strengthening innovation systems. These approaches can work even with the data limitations in developing countries. More importantly, they can go a long way in fostering development and reducing poverty in developing-country agriculture.

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Introduction

Innovation systems perspectives on agricultural research and technological change are quickly becoming popular for studying how society generates, disseminates, and utilizes knowledge. They are also being deployed to better understand how to strengthen such systems to support growth, development, and poverty reduction in developing countries. The more theoretical innovation systems literature represents a significant change from the conventional, linear perspectives on agricultural research and development (R&D). It provides a framework for the analysis of complex relationships and innovative processes that occur among multiple agents, social and economic institutions, and endogenously determined technological and institutional opportunities. The emerging body of empirical literature is equally significant because it provides analysis of different forms of cooperation (e.g., research consortia, corporate joint ventures, virtual knowledge networks, and industry clusters) among state and non-state actors (e.g., public research organizations, private companies, rural entrepreneurs, and farmers' organizations) in various sectoral, spatial, and temporal contexts. Taken together, the innovation systems framework demonstrates the importance of studying innovation as a process: knowledge is accumulated and applied by heterogeneous agents in complex interactions that are conditioned by social and economic institutions.

Such analyses of developing-country agriculture are acutely needed. International and national agricultural research systems face significant institutional and organizational challenges that have led to insufficient funding, difficulties in training and maintaining good scientists, obstacles to accessing new scientific knowledge and technology, and other significant constraints (Pardey and Beintema, 2001; Byerlee and Fischer, 2001). Because innovation systems approaches offer greater insight into the complex relationships between diverse actors, processes of institutional learning and change, market and non-market institutions, public policy, poverty reduction, and socio-economic development, an innovation systems approach should be able to help policymakers, researchers, donors, entrepreneurs, and others identify and analyze new ways to encourage innovation.

Yet there is little evidence to suggest that an innovation systems framework approach to developing-country agriculture is, in fact, providing real solutions to today's challenges. While the framework is helping to change the mind-set of researchers and policymakers by encouraging them to consider new and unconventional actors and relationships, several methodological and analytical shortcomings are limiting its relevance to policy and policymaking processes. Its effect on social welfare improvement in developing countries is therefore limited.

This paper attempts to address three questions in the context of an innovation systems perspective on developing-country agriculture:

- How do we accurately describe research and innovation activity as part of a system, society, or economy that changes over time?
- How does policy affect the processes that determine the range and scope of innovations generated and disseminated within a system, society, or economy?
- How does policy affect the processes that determine the distribution of the social and economic gains of innovation?

Section 2 reviews innovation systems literature on developing-country agriculture. Section 3 provides an overview of the conventional terminology used in innovation systems literature, and Section 4 presents the strengths and weaknesses of the innovation systems framework, as well as recommendations for improving the framework in its application to developing-country agriculture. Section 5 offers concluding remarks.

Innovations Systems Literature and Developing Country Agriculture

While the foundations of the innovation systems perspective lie in Schumpeter's (1939; [1934] 1961) works on technological change, the literature has expanded considerably with more modern contributions from the fields of evolutionary economics and systems theory (Nelson and Winter, 1982; Dosi et al., 1988; Freeman, 1987; Metcalfe, 1988; Lundvall, 1992; Edquist 1997). Yet this literature has had little influence on the study of agricultural research and technological change in developing countries. Theories of technological change in agriculture that developed in the latter half of the 20th century have tended toward the Hicksian notion of innovation induced by relative factor scarcities rather than the Schumpeterian system, in which market structures and socioeconomic institutions affected (and responded to) technological innovation. By introducing relative factor scarcities and prices as the key determinants of innovation, Hicks ([1939] 1946) married the notion of innovation to the larger neoclassical framework. His work informed the modern theories of agricultural development and economic development posited most notably by Hayami and Ruttan (1971). Their work, in turn, gave rise to dense literature on the role of public research systems in generating technological change in agriculture (Echeverría, 1990; Huffman and Evenson, 1993; Anderson, Pardey, and Roseboom, 1994; Alston, Norton, and Pardey, 1995; and Alston, Pardey, and Smith, 1999, among others), bolstered by studies on the successes of the Green Revolution (Lipton, 1989; Hazell and Ramasamy, 1991; and Hazell and Haddad, 2001, among others).

The primary focus of this literature has been the public sector agricultural research organization. In effect, this research has transformed into the study of how national agricultural research systems (NARS) effect technological change through a linear model of research, development, and extension. The NARS perspective highlights the public-goods nature of agricultural research and the absence of market access or purchasing power among many agrarian agents, thus appropriately emphasizing the state's role in fostering technological change. Yet the NARS approach tends toward linearity insofar as the movement of knowledge is described as originating from some known source (the scientific researcher) and flowing to some end user (the farmer), assuming that the social and economic institutions in which this process occurs are largely exogenous and unchanging.

A slightly more sophisticated approach is found in the agricultural knowledge and information systems (AKIS) perspective, which incorporates important concepts from the study of information and knowledge economics. The AKIS perspective highlights the links between research, education, and extension in generating knowledge and fostering technological change (Nagel, 1979; Röling, 1986, 1988).[1] More importantly, by focusing on the dynamics of dissemination through extension, the approach rectifies some of the conceptual gaps that had impeded analyses of how knowledge moves between researchers and end users.

Embedded in the study of how knowledge flows between and among agents, the AKIS perspective is less linear than the NARS approach. Yet it may be argued that the perspective is limited in its ability to conduct analysis beyond the nexus of public sector research, university research, and extension services, or to consider heterogeneity among agents, the institutional and historical context that conditions their behaviors, and the learning processes that determine their capacity to change and innovate. The innovation systems approach broadens the NARS and AKIS perspectives by focusing on the processes by which diverse agents engage in generating, disseminating, and utilizing knowledge; the organizational and individual competencies of such agents; the nature and character of their interactions; and the market and non-market institutions that affect the innovation process.

The innovation systems approach is, however, still nascent in the study of developing-country agriculture. Biggs and Clay (1981) and Biggs (1989) offer an early foray into the field by introducing several key concepts—institutional learning and change, and the relationship between innovation and the institutional milieu in which innovation occurs—that become central to later innovation systems studies on developing-country agriculture. For example, Hall and Clark (1995), Hall et al. (1998), Johnson and Segura-Bonilla (2001), Clark (2002), Arocena and Sutz (2002), and Hall et al. (2002, 2003) introduce the innovation systems approach to the study of developing-country agriculture and agricultural research

systems. Regional and national applications of the innovation systems approach are considered by Roseboom (2004), Chema et al. (2003), Peterson et al. (2003), and Hall and Yoganand (2004) in Sub-Saharan Africa; by Vieira and Hartwich (2002) in Latin America; and by Hall et al. (1998) in India. Several studies focus on the institutional arrangements in research and innovation, e.g., Hall et al. (2002) on public-private interactions in agricultural research; Porter and Phillips-Howard (1997) on contract farming; Hall et al. (1998), Allegri (2002), and Kangasniemi (2002) on producers' associations. Other studies focus on specific technologies such as Chataway (2005) and Hall (2005) on agricultural biotechnology.

These studies distinguish themselves from other works on agricultural R&D because they embed analyses of research and technology within the wider context of institutional change and innovation processes. Furthermore, they offer some answers to research questions that the conventional R&D literature is often unable to address. For example, Ekboir and Parellada (2002) detail the social and economic changes that encouraged the diffusion of zero-tillage cultivation in Argentina, a process that resulted from a complex series of events and interactions among farmers, farmers' organizations, public researchers, and private firms. Smith (2005) studies the institutional and organizational learning processes that went into forming and operating a public-private partnership to develop a livestock vaccine for cattle in Kenya. Clark et al. (2003) unlock the mysteries of a successful donor-funded project in post-harvest packaging for small-scale farmers in India by studying the institutional learning and change processes that were incorporated into the project design. These studies are linked by their emphasis on the role of diverse actors and interactions within complex systems of innovation and the institutional context within which these processes occurred.

Key Terms and Definitions

To better understand the conceptual framework offered by the innovation systems approach, we provide here a summary of conventional terms and definitions. First, an *innovation* is defined here as any new knowledge introduced into and utilized in an economic or social process (OECD, 1999). Second, *agents* are defined as those individuals and companies that constitute the principle actors in processes of innovation. Agents typically enter not as rational maximizers responding to price signals, but as strategists, responding to other agents' behaviors and their institutional context.[2] Secondary agents include state and non-state actors also engaged in processes of innovation whose activities relate directly and are dependent on individuals and companies. Third, an *innovation system* is defined as a set of interrelated agents, their interactions, and the institutions that condition their behavior with respect to the common objective of generating, diffusing, and utilizing knowledge and/or technology.

In an innovation system, the company often constitutes the focal agent of inquiry and represents the primary agent. In agriculture, this includes multinational and national agribusiness companies, small/medium agro-enterprises, individual entrepreneurs, farmer/producer associations, rural cooperatives, or other community-based groups. These agents engage in the production, processing, marketing, and distribution of agricultural commodities, as well as in the purchase of agricultural and agro-industrial inputs. In each of these activities, they also engage in processes of knowledge creation, dissemination, and application through both market and non-market relationships.

An innovation system is also host to individuals who, in the agricultural sector, include farmers, farm households, agricultural laborers, and rural communities. Their functions are often the same as the company insofar as they produce agricultural commodities; consume agricultural inputs; and produce, exchange, and utilize knowledge in market and non-market relationships. The individual agrarian producer is also the smallest economic unit through which innovation flows, inextricably tied to the company within an innovation system.

Secondary to this relationship is the public research system, including national research organizations, extension systems, state marketing agencies, institutes of higher learning, international research centers, and (though sometimes categorized sepa-

rately) non-governmental organizations. The public research system traditionally engages in non-market relationships with farmers and companies to generate and disseminate knowledge or technology, although some relationships (e.g., contracting research to companies, or contracting seed multiplication to farmers) are based on market exchanges.

Next, consider the role of *knowledge* in an innovation system. Knowledge can be categorized in many different ways. Knowledge may be classified according to form—for example, as scientific/technical knowledge or organizational/managerial knowledge, as well as codified/explicit and tacit/implicit knowledge (Hall et al., 2002). Knowledge may also be embodied in some good, service, or technology; or it may be distinct, disembodied, and complementary. Knowledge may be further characterized by its degree of accessibility and accumulation over time or among agents, depending on an agent's capacity to exchange, learn, and absorb. Since there is no limit to the taxonomy of knowledge, we assume that these classifications suffice for the present purposes.

Next, consider the *sources of knowledge* in an innovation system. Knowledge sources may be external to a given agent within an innovation system—for example, a scientific journal article documenting a laboratory breakthrough, or a neighbor who introduces one to a new way of achieving something. Alternatively, the knowledge source may be some internal process—for example, the reorganization of human and scientific resources within a company to improve efficiency (Malerba, 2002). Knowledge may derive from the conventional providers of advanced research: public research organizations, private laboratories, and universities. Yet it may also emerge from the practices and behaviors of individuals, households, and civil society organizations (Clark, 2002). In sum, knowledge sources are not simply those entities producing cutting-edge science; rather, they are any entities that introduce knowledge into a social or economic process.

Next, consider the different *interactions* or relationships between and among agents in an innovation system. Interactions are numerous and varied, and include such relationships as spot market exchanges of goods and services that embody new knowledge or technology; costless exchanges of non-rival, non-excludable knowledge made available in the public domain; long-term, durable exchanges that incorporate complex commitment mechanisms and related transaction costs; collusive arrangements among oligopolistic companies; and hierarchical/command structures that govern the exchange process. Equally important are those interactions among individuals and organizations that are characterized by learning and feedback processes. The study of how individual agents structure their strategic interactions is what gives the approach its definitive *systems* perspective.

It is worth noting here the centrality of *cooperation*—incompletely-specified, non-market exchange relationships that allow for opportunistic behavior by agents involved in the exchange—in the context of an innovation systems framework (Fritsch, 2004). Cooperation, though only one of several forms of interaction, is one of the key behavioral aspects of agents in an innovation system and is conditioned by the institutions that promote or impede it. This concept is particularly relevant when studying learning processes or relationships that blur the traditional roles of distinct actors—for example, partnerships between public and private research entities (Pray, 2001; Hall et al., 2002; Spielman and Von Grebmer, 2004).

Next, an innovation system includes those *institutions* that affect the process by which innovations are developed and delivered: the laws, regulations, conventions, traditions, routines, and norms of society that determine how different agents interact with and learn from each other, and how they produce, disseminate, and utilize knowledge. These factors determine the efficiency and stability of cooperation and competition, and whether agents in an innovation system are able to interact so as to generate, diffuse, and utilize knowledge. An institution may be no more explicit than a traditional tendency toward (or away from) informal entrepreneurial behavior in agrarian society, such as farmer exchanges of seed and other planting materials; or it may be more codified in the laws that govern how private, knowledge-based companies are established, licensed, and taxed, and the extent to which such companies can appropriate the rents from innovation.

Finally, an innovation system requires some unit of study or *dimensions of analysis* to delineate its boundaries (Metcalfe, 1997; Carlsson et al., 2002). Analysis may focus on the spatial (local, national, and regional economic or geopolitical units); the sectoral (manufacturing, agriculture, or any sub-sector thereof); or the technological (for

example, information and communications technology, agricultural biotechnology, or other distinct technology sets). Further, analysis may focus on the material, such as a particular good or service that forms the focal point of a given commodity value chain. Analysis may also focus on a temporal dimension by studying how relationships among agents change over time as a result of knowledge transfers, feedback mechanisms, institutional learning, decision rules, adaptive behavior, and organizational transformation (Nelson and Winter, 1982). In short, an innovation systems framework offers a diversity and wealth of analytical dimensions.

Innovations Systems and Developing Country Agriculture

An innovation system is thus defined as a network of agents, along with the institutions, organizations, and policies that condition their behavior and performance with respect to generating, exchanging, and utilizing knowledge. Returning to the three questions posed earlier, this section reviews several areas where an innovation systems approach can contribute to the improvement of pro-poor agricultural research and innovation in developing countries. It also considers where this approach and its applications are still under development. How applied innovation systems research proceeds in light of these recommendations may determine its relevance to improving the impact of agricultural innovation on poverty reduction, food security, agricultural development, and economy-wide growth in developing countries.

The Role of Farmers, Companies, and Institutions

The most apparent value of the innovation systems framework lies in its ability to widen otherwise narrow or conventional analytical perspectives on developing-country agricultural research and innovation. Emphasizing the study of interactions and processes among diverse agents and institutions involved in the innovation process, the framework offers a more comprehensive analytical approach than either the NARS or AKIS perspectives.

But beyond this contribution, there is limited evidence to suggest that the full value of the framework is being applied to understand how innovation occurs or to design mechanisms that strengthen agricultural innovation systems in developing countries. Some of the emerging literature on agricultural innovation systems remains tied to a conventional focus on the structure and reform of brick-and-mortar public sector "institutions" rather than on the "rules of the games" that describe the wider characteristics of an innovation system (see, for example, Chema, Gilbert, and Roseboom, 2003). And while several agricultural research initiatives use the language of the innovation systems approach to suggest a new analytical perspective, they still appear closely wedded to the conventional priority of strengthening national, public sector partners without fully recognizing the complexity of the processes and systems within which these partners operate (see, for example, FARA, 2004; Roseboom, 2004; Sumberg, 2005).

Indeed, Sumberg (2005) applies and extends this criticism to agricultural research and innovation systems in Sub-Saharan Africa. He reasons that because an innovation system comprises a complex, diverse, and diffuse set of processes, it is well adapted to address the agro-ecological and socio-economic needs of a region as vast and heterogeneous as Sub-Saharan Africa. He argues, however, that efforts to create a formal system based on coordinated hierarchies among national and supra-national organizations—highlighted by public research organizations such as the Consultative Group for International Agricultural Research (CGIAR), the Forum for Agricultural Research in Africa (FARA), and the New Partnership for Africa's Development (NEPAD), and other international bodies—is an unresponsive, supply-driven system that overlooks the region's demands for innovation. In other words, the use of an innovation systems framework to create a system that is arguably antithetical to the diffuse nature of innovation will do little to encourage technological change in Sub-Saharan Africa.

In short, early applications to developing-country agriculture suggest a far narrower—and, arguably, less informative—approach that revolves around the trials and tribulations of a single, typically public sector, agent. This overlooks the analytical strength of the innovation systems framework and its unique

approach to understanding complex and diverse agents, institutions, and interactions.

Admittedly, this narrow approach reflects certain realities in developing-country agriculture. Agricultural research and innovation in many developing countries are focused on attaining food security and alleviating poverty by enhancing crop yields for farmers and improving food availability for consumers with limited market access or purchasing power. This strategy has traditionally required that research outputs be generated as non-excludable, non-rival (public) goods that require public sector investment in research and innovation. This is most acute in Sub-Saharan Africa, where more than 97% of agricultural research is undertaken by the public sector (Beintema and Stads, 2004). But it is no less relevant in Asia and Latin America.

These narrow approaches, however, overlook the importance of understanding the wider system and process of social and technological change in agriculture. They also neglect the institutional factors that underlie these processes. More importantly, these narrow approaches do little to change the nature of how innovation occurs in developing-country agriculture, leaving many urgent puzzles unanswered.

More study of the dynamics of innovation is clearly needed. This includes the study of non-state actors in relation to, separate from, or even in spite of public-sector research organizations. Several studies (e.g., Hall et al., 2002, 2004) attempt to do this, but more analysis is required on the heterogeneity among non-state actors, changes in the institutional contexts in which heterogeneous actors operate, and alternative forms of interaction among such actors.

Tools and Methods of Analysis

Applied to the study of innovation policy in OECD countries, the innovation systems approach relies on diverse and rigorous qualitative and quantitative methods. The choice of method has been driven by two separate strains in the literature (Balzat and Hanusch, 2004). The first strain derives from academic efforts to improve the understanding of how innovation occurs. It relies on tools such as country case studies and descriptive models of national innovation systems, which, until recently, have lacked a formal method of analysis. The second strain derives from more policy-driven efforts to improve the performance of national innovation systems. It relies on tools for conducting cross-country comparisons, such as innovation benchmarking and ranking and comparative case studies of best practices.

The literature is increasingly characterized by the use of a wide variety of systematic, replicable, and consistent tools of analysis, including in-depth social and economic histories; policy benchmarking, cross-country comparisons, and best practices; statistical and econometric analysis; systems and network analysis; and empirical applications of game theory, to name but a few (Balzat and Hanusch, 2004). This methodological diversity and rigor bring credibility and strength to the study of innovation systems.

However, in its current application to developing-country agriculture, the innovation systems approach is making limited use of these powerful tools and methods. Currently, the favored methodology in the study of agricultural research in developing countries is the descriptive case study, often drawn from an action research or stakeholder analysis exercise (Hall et al., 2004). Several recent studies have become more diagnostic in their approach by identifying institutional constraints and recommending alternative policies, incentive structures, or organizational reforms that might remove such constraints (Kangasniemi, 2002; Hall et al., 2002; Hall et al., 2004). But more often than not, studies are simply *ex post* descriptions of the dynamics and complexities of some technological or institutional innovation. And there the analysis ends.

This is not to say that action research lacks rigor; rather, action research has been a fundamental tool in identifying agricultural innovation systems in developing countries and establishing "proof of concept" for further study. However, reliance on action research should not preclude the use of other equally rigorous qualitative and quantitative methods. In fact, greater diversity in the choice of methods can only strengthen the literature by improving the robustness of hypotheses testing based on the innovation systems framework.

There are several possible methodological approaches that could strengthen the study of innovation systems in developing-country agriculture. One might be to analyze the costs and benefits of knowledge production or dissemination given the complexity of interactions among diverse agents. Such an approach could include standard measurements of costs and benefits combined with measures of the transaction and risk management costs that are so fundamental to many different types of non-market

interactions. An alternative approach might be to employ well-developed methodologies used to study social learning processes among agrarian agents (Foster and Rosenzweig, 1995; Conley and Udry, 2001).

Yet another approach might be to consider the dynamic effects of market structure on the innovation process by using empirical applications of cooperative game theory and other tools of industrial economics. This is illustrated by Naseem and Oehmke (2004), who model R&D races under various oligopoly scenarios in which both public and private researchers conduct work on advanced genomics research. They suggest that under a certain set of market conditions, public organizations can play a role in increasing the level of genomics research despite the nature of the R&D race.

Another useful method, already employed by the OECD in its studies of innovation systems in industrialized countries, is benchmarking, or best practice (OECD, 2002, 2001). Through comparative studies of innovation systems, this method allows researchers and policymakers to compare the dynamics of innovation—the policies, institutions, organizations, and processes that influence innovation outcomes—in one country or region against another. This approach requires identifying appropriate indicators of innovation, including not only R&D investment statistics but also indicators of absorptive capacity among companies; the quality and quantity of investments in human capital; labor, input, and commodity market conditions; infrastructure; and so on.[3]

Another useful tool is the empirical application of non-cooperative game theoretic models to break down interactions into key decision points and payoffs. Methodologies in this vein include descriptive modeling of the relations and networks through which information moves between and among agents. This is a particularly powerful set of tools for analyzing knowledge-intensive sectors such as agricultural research. For example, Binenbaum, Pardey, and Wright (2001) dissect the relations between organizations, the incentives that motivate their behavior, and the problems associated with those incentives. By reconstructing the relations and incentives under alternative scenarios, the analytical output, typically embedded in game theory, develops an enhanced perspective on the process by which information flows between organizations. Key elements include analysis of players and their objectives, incentives, and relations; the structure and flow of information and the mechanisms that make information flows possible; the choice variables and sequence of moves among players; and the relation and incentive problems that impede players' moves and the flow of information. Similarly, De Bruijn and Van der Voort (2002) study interactions (e.g., public-private partnerships) by identifying the dilemmas and tensions that characterize their interaction through a combined product and process analysis (i.e., input-throughput-output) approach.

The novelty and context-specificity of a given innovation, however, often necessitate less intricate methods that rely on the descriptive or comparative analysis of agents and their mechanisms of interaction. However, if the action research approach falls short in this context, another method developed by Elliott et al. (1985) and Elliott (1990) might prove useful. This approach, referred to as *agricultural technology management system (ATMS) analysis*, attempts to analyze relationships not only within and among organizations but also between organizations and their external environments. Designed to improve organizational design and managerial functions, the approach emphasizes separate analyses for systems, organizations, and technologies. It offers a variety of analytical tools, such as responsibility charting, events analysis, priority setting, and so on.

The ATMS approach alludes to the possible use of other, more conventional tools common to the study of business management and organizational behavior—tools that could improve our understanding of the inner workings of public research organizations, private research companies, and nongovernmental organizations. These might include such exercises as the analysis of innovation processes within value chains (Kaplinsky and Morris, 2000; Humphrey and Schmitz, 2001). The value chain approach examines how producers, buyers, and sellers separated by time and space progressively add and accumulate value as commodities are transformed and passed from one member of the chain to the next. It focuses on how product and process innovations can improve the efficiency of the value chain.

In sum, when the innovation systems framework is applied to developing-country agricultural research it makes limited use of the diverse analytical tools available in the existing literature on innovation systems and in other areas of empirical inquiry.

More effort is required to identify measures, accumulate data on national and sectoral innovation systems, and develop taxonomies with which to classify agents, institutions, and systems. With more, better quality information, innovation systems researchers will be able to more accurately model the calculus of agents' behavior with respect to the strategic behavior of others and the context of social and economic institutions. They will also be able to make meaningful comparisons over both time and space and to suggest alternative policy options to strengthen innovation systems. Even with data limitations in developing countries, these approaches can work.

Relevance to Policy Analysis

Methodological issues aside, the value of the innovation systems approach is its use in informing policymakers about options that may enhance the potential for innovation and improve the distribution of gains from innovation. Recommendations in this vein come from studies such as Kangasniemi (2002) on policies to strengthen the research role of agricultural producer associations in East and southern Africa; Hall et al. (2002) on enhancing opportunities for public-private partnerships in Indian agriculture; and in several studies presented in Hall et al. (2004) on partnerships, institutions, and learning in South Asia and Sub-Saharan Africa.

Yet beyond these (and several other) examples, the link between empirical analysis and policy recommendation remains either nascent or weak when in an innovation systems framework is applied to developing-country agriculture. With so many case studies conducted and so many lessons learned, researchers should be well positioned to advise governments on policy options and incentive structures that generate greater levels of innovation and improve the distribution of these gains.

It may be argued that advising governments with research-based policy recommendations is an old-fashioned, top-down approach to promoting change, and that institutional learning through action research and capacity-strengthening efforts is more effective. Indeed, there is a growing consensus behind the need for strategies that combine policy research with effective capacity-strengthening and communication approaches (Young, 2005; Court and Maxwell, 2005; Von Grebmer, 2005; Court and Young, 2004; Pannell, 2004). What remains to be seen, however, is whether institutional learning approaches offer better and more cost-effective access to the leverage points needed to change institutional design and public policy than, say, conventional policy recommendations and advising. At present, the esoteric nature of the innovation systems literature as applied to developing-country agriculture provides insufficient evidence to conclude that this is the case.

The general absence of policy analysis in the emerging literature may result from the complexity of a "systems" approach and the weakness of its associated methodologies, a point not lost on Clark (2002). Case studies and action research may help illustrate complex relationships and assemble seemingly unrelated bits of knowledge, but they are insufficient tools with which to persuade policymakers and effect policy change. The absence of policy analysis may also result from the depth, breadth, and complexity of innovation policy—a topic covering policies in industry, agriculture, trade, finance and investment, education, science and technology, labor, and so on. To effect real change, however, analyses of innovation policy should extend from case studies to more comprehensive analyses of national and sectoral policies at a level that is relevant for crafting and coordinating policy options or for making constructive cross-country benchmarks and recommendations for best practice. By combining well-grounded empirical analysis with a solid understanding of the institutional context in which innovation occurs, the innovation systems approach can be a powerful tool in designing public policy and incentive structuring.

This concept ties closely to Omamo (2003), who argues that policy analysts must pay closer attention to processes of institutional innovation and their historical, socioeconomic contexts, and rely less on formula-based prescriptions for agriculture in Africa. Here, the innovation systems framework offers the right focus on institutional innovation, institutional context, and historic path-dependency, but it needs to extend itself into the realm of policy analysis by asking the right questions. It must ask *how* alternative policy options can be designed, implemented, and operationalized, rather than *why* innovation systems look the way they do in developing countries.

Relevance to Poverty Reduction

Finally, the innovation systems framework offers a new perspective on innovation processes that are fundamental to reducing poverty and improving food security. This is highly relevant for the study of agriculture in developing countries, where 75% of the world's poor reside (IFAD, 2001).

Yet few studies in the emerging literature on innovation systems in developing-country agriculture ask the fundamental economic question: whether a given innovation increases welfare. This means asking whether i) an innovation increases efficiency in the production or utilization of knowledge directly relevant to those goods and services used by the poor in consumption or production, or ii) whether an innovation improves the distribution of social surplus in a manner beneficial to the poor. Few studies make that leap from descriptive *ex post* analysis of an innovation system to an *ex ante* analysis of how an innovation system promotes institutional and technological changes that are explicitly pro-poor. Although some authors (e.g., Kangasniemi, 2002) reference smallholder African farmers as a key target group for innovation-relevant policy improvement, there are few other examples of distributional or poverty analysis in the innovation systems framework.

Ultimately, by putting innovation (rather than poverty) at the center of their study of developing-country agriculture, most studies limit the relevance and value of an innovation systems framework to developing-country agriculture. This means that more work needs to be done within the innovation systems framework on the relationship between innovation—both technological and institutional—and poverty. This implies studying both (a) the economic growth prospects associated with innovation and (b) the distributional consequences of innovation.

The former opens up a whole new field of macroeconomic inquiry that combines innovation systems perspectives with endogenous growth theory (e.g., Romer, 1990; Barro and Sala-i-Martin, 1995). This type of marriage enhances the study of economic growth by providing new perspectives and indicators that better capture and measure innovative capacities (Balzat and Hanusch, 2004).
The latter offers possibilities for analyzing key technological changes in agriculture. This includes analyses of how innovations affect wages for landless laborers, incomes for smallholders, or bargaining power for vulnerable social groups, which implies more analysis of distributional and political economy issues (e.g., the distribution of income, knowledge, and power and their relationships to innovation processes). This also includes the analysis and valuation of tacit, non-traditional, and non-industrial knowledge sources often held by those with the least ability to realize the benefits of innovation: small-scale farmers, food-insecure households, landless agricultural laborers, women and children, and other marginalized or vulnerable groups. And finally, making use of the tools and methods suggested above could lead to less focus on *ex post* descriptions of innovation systems and more focus on *ex ante* analyses of how innovation policy affects poverty reduction.

Conclusions

The organizing principles of the innovation systems approach—studying interactions and institutions that affect heterogeneous agents' strategic efforts to innovate, adapt, and complement—are an important break from the neoclassical principles of optimizing agents and equilibrium outcomes. In agriculture, these perspectives are critical to shifting socioeconomic research beyond technological change "induced" by the relative prices of land, labor, or other production factors in agriculture. It should also move research beyond the concept of linear technology transfers—such as from industrialized to developing countries or from advanced, international research centers to national systems—as an engine of change.

The innovation systems perspective argues against the perception that technological change drives social and economic development, suggesting instead that development is driven by the institutional context in which technological change occurs. With an improved understanding of the institutional context, we can better understand the impacts of technological change on vulnerable groups in rural society. The innovation systems perspective usefully widens otherwise narrow horizons in the agricultural

research community. The framework can be used to fill knowledge gaps and frame socioeconomic research within a wider context of diverse actors, knowledge sources, institutions, and interactions.

To be relevant in the context of developing-country agriculture, however, the literature requires further development and application. Much of the emerging literature in this area is limited by a lack of perspective beyond the conventional role of the public research organization; few methodologies beyond ungeneralizable, context-specific descriptive analysis; limited relevance to policy analysis and policymakers; and limited relevance to poverty reduction and food security.

New applications of the innovation systems framework to developing-country agriculture should include more analysis of agents and agent behavior, the institutions that condition their behavior, and the diverse interactions that characterize their behavior. Furthermore, such applications should study in more depth the policy options that may affect the innovative process and steer it toward more welfare-improving outcomes. With this approach in mind, and with a set of diverse tools at hand, the innovation systems framework has great potential to improve the study of developing-country agriculture.

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Notes

1. For a useful comparison of the NARS, AKIS, and the innovation systems approach, see Chema, Gilbert, and Roseboom (2003).
2. Carlsson et al. (2002) vest agents with four different types of capabilities: selective, organizational, functional, and learning. From a strict economic perspective, these capabilities are difficult to distinguish since each is reduced to the simple question of whether the agent is making rational decisions in his or her effort to efficiently allocate scarce resources for innovation. Having said that, the subtle differences between different types of capabilities are meant to capture the robustness, flexibility, and responsiveness of agents in a dynamic innovation system, and therefore may merit further examination.
3. By way of example, the Consultative Group on International Agricultural Research (CGIAR) could consider updating its Agricultural Science and Technology Indicators (ASTI) initiative to reflect the more comprehensive approach taken by the OECD (1999).

Systems of Innovation: Models, Methods, and Future Directions

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Executive Summary

The literature on innovation systems offers a broad analytical framework for examining processes of technological and institutional change. From its earliest roots in the literature on technological change and economy, to its adoption of modern concepts from evolutionary economics and systems theory, the innovation systems framework is highly relevant for studying the complex interactions among diverse agents engaged in the generation, exchange, and use of knowledge.

The innovation systems approach focuses on complex relationships among diverse actors, social and economic institutions, and technological and institutional opportunities. It represents an important break from the neoclassical principles of optimizing agents and equilibrium outcomes, providing us with new tools to better understand some of the more elusive elements of economic development.

Of particular analytical usefulness are game theoretic and population game models. These describe how heterogeneous actors interact and evolve over time through strategic patterns of behavior. The models illustrate the importance of institutional design: given a set of agents in a particular game, any change in the payoff structures may change the outcomes of the game. Whether the result of spontaneous emergence or of choices made by system actors, institutions influence the nature and character of the system.

The models suggest the importance of change over time. For instance, an innovation system operating in a society that prioritizes the welfare of small farmers may, in the early years of agricultural modernization, choose to limit the payoffs of being a private-sector innovator. In the long run, however, society may choose to change its priorities. Changes in institutional design over the long-term necessarily influence the nature and character of the system.

The models also imply that optimality is not a necessary outcome of evolutionary processes. Rather, such processes tend towards a trajectory that may or may not be stable over the long-term. Thus, where policies can be designed to affect the evolutionary process of innovation, the trajectory of a system can potentially be guided toward greater innovative output and more favorable distributions of innovative rents and social welfare. Public policy should enable an innovation system to remain flexible, generate incentives for innovative activity, and create institutions that respond to and learn from the innovative process.

In the study of agricultural and economic development, the innovation systems perspective is an important move. It goes beyond the study of technological change "induced" by the relative prices of land, labor, or other production factors in agriculture. It also moves us beyond the concept of linear technology transfers—from industrialized to developing countries, from advanced and international research centers to national systems—as an engine of change. The perspective thus applies not only to the study of innovation in industrialized country manufacturing but also to other areas of economic inquiry, including innovation in developing economies.

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Introduction

Innovation systems perspectives offer a broad analytical framework to examine processes of technological change. By shifting the emphasis of study from linear models of technology production and transfer to complex interactions among diverse agents engaged in generating, exchanging, and using knowledge, innovation systems perspectives have opened up a whole new field of social and economic inquiry. There are enormous opportunities to extend the application of these perspectives from manufacturing and industry in industrialized countries to various sectors in developing countries.

This paper begins by tracing the literature on innovation systems from its roots in early work on technological change to more modern studies of evolutionary economics and systems theory. Section 3 presents a series of game theoretic and population game models to describe how heterogeneous actors within an innovation system interact and evolve over time through strategic patterns of behavior. Section 4 discusses new opportunities to expand innovation systems analyses from the study of innovation in industrialized-country manufacturing to other areas of economic inquiry, including developing economies.

The Innovations Systems Framework: A Literature Review

Adam Smith ([1776] 1993) first noted the influence of innovation—new production techniques and new divisions of labor—on output and society. But it is the work of Ricardo (1821) that provides a useful starting point for discussions of both orthodox (neoclassical) and heterodox economic perspectives on innovation and technological change. Ricardo's analysis captured the fundamental challenges of economic—specifically agricultural—production: the diminishing marginal returns from land and the importance of technology in shifting production possibilities. More importantly, his analysis introduced factor bias as a determinant of the impact of technological change on productivity, income, and welfare. Ricardo did this by distinguishing between two types of technology: that which "increases the productivity powers of the land" and that which "obtains its produce with less labor" (p. 54). The former described the land-saving techniques of production undertaken in early 19th-century England—crop rotation, water management, and intensive use of livestock manure to preserve soil fertility—that combined several inputs to increase output per unit of land. The latter described the use of improved agricultural tools and machines that substituted capital for labor, but, in the Ricardian schema, had no effect on land productivity. Here, Ricardo provided an early analytical framework for studying the form and nature of innovation and its impact on social and economic well-being.

Ricardo's analysis gave rise to further interest in the social and economic effects of technological change by such classical political economists as List (1841), Mill ([1848] 1965), and Marx ([1894] 1990). In fact, it is List who is credited with the earliest description of a "national system of political economy"—a precursor to the innovation system concept—in which production results not only from the activities of the firm but also from those social and economic institutions (e.g., education, infrastructure) that make production possible (Lundvall et al., 2002; Freeman, 1995). Leontieff (1941) took this further with his celebrated input/output analysis that established an industry-level "system" approach to production, used later by scholars to explain innovative processes.

But it was Schumpeter ([1934] 1961; 1939) who laid the cornerstone of the modern innovation systems approach. Distinguishing between invention, innovation, and diffusion, Schumpeter provided the first nuanced definition of technological change. Defining innovation as any addition to the existing body of technical knowledge or know-how that results in an outward shift of the production function and a downward shift of the associated cost curves, he added further nuance to the concept by distinguishing between product, process, and organizational innovation (1939, p. 87; [1934] 1961, p. 66; Blaugh, 1996, pp. 454–455).

In the context of the present study, Schumpeter's most relevant insights are his analysis of the market and institutional conditions that generate innova-

tion. In the Schumpeterian system, technological change results from the innovative activities of large firms that are afforded market power at the expense of short-term social welfare (Nelson and Winter, 1982). Innovation is thus endogenously determined by the behavior of the entrepreneur and his or her financiers, and by the institutions of private property, business traditions, and capitalist competition (Clemence and Doody, 1966, p. 47). Over the long run, technological change results from the continuous market entry of entrepreneurial agents and innovation processes that force older firms and production methods into obsolescence, thereby reallocating resources into new products and processes and reorganizing key aspects of the economy—prices, goods, credit, and so on—to support a new production regime (the "creative destruction," or Schumpeter Mark I model).[1] Movement from one state (characterized by a set of innovations and related institutions employed by society) to the next ultimately results in greater output for unchanged money incomes, interest rates, profits, and indebtedness. This implies an increase in society's control over real consumption, that is, lower prices and higher real incomes that represent economic growth. In sum, Schumpeter suggested that innovation results from the character of social and economic institutions, and that institutions change in response to innovation, thereby implying an endogenously-determined relationship between society and innovation.

The innovation systems framework emerged in the mid-1980s as a neo-Schumpeterian perspective that drew significantly from literature on evolutionary economics and systems theory. Evolutionary economists such as Nelson and Winter (1982)[2], Dosi et al. (1988), Metcalfe (1988), and Andersen (1994) inform the innovation systems framework by emphasizing continuous and nonlinear processes of endogenously determined technological and institutional change, in contrast to the more conventional or neoclassical study of relative factor prices, exogenous technological shocks, and static equilibria. The innovation systems approach takes from systems theory an emphasis on the study of i) the attributes and interactions among diverse elements of a set, ii) how the properties and behaviors of each element influence other elements and the set as a whole, and iii) how interdependence among the elements renders the set indivisible, thereby making analysis of a single element irrelevant (Carlsson et al., 2002).[3]

A comprehensive description of the innovation systems approach was first set forth by Lundvall (1985) and applied to national comparisons of innovation systems by Freeman (1987). The concept was further elucidated in Dosi et al. (1988), Lundvall (1988, 1992), Freeman (1988, 1995), Nelson (1988, 1993), and Edquist (1997), with empirical applications focusing primarily on national industrial policy in Europe, Japan, and several East Asian countries that experienced rapid industrialization during the 1980s. Recent work on innovation systems has added new analytical dimensions, including the study of systems at different spatial (i.e., geographically determined) levels (Saxenian, 1994; Braczyk, Cooke, and Heidenreich, 1998; Fritsch, 2004), different sectoral levels (Breschi and Malerba, 1997; Malerba, 2002), different time periods (Anderson and Teubal, 1999; Andersen, 2000, 2004), and in relation to a given technology set (Carlsson and Jacobsson, 1993; Carlsson, 1995, 1997). Application of the innovation systems approach has since been explored by the Organization for Economic Cooperation and Development (OECD, 1997) and its members (Arnold and Bell, 2001), the United Nations Commission on Trade and Development, the European Commission, and, more recently, the World Bank and International Monetary Fund (Lundvall et al., 2002).

Studies that use an innovation systems framework are able to analyze processes that are typically overlooked in the linear approach to research and development (R&D). Innovation systems studies often open the "black box" of innovation to analyze actors' motives and behaviors; the institutions that shape these motives and behaviors; interactive, joint, and complementary processes of innovation; and the dynamics of institutional learning and change. They also provide analyses that extend beyond single industries or markets, capturing a wider range of agents (public and private), interactions (competition, cooperation, and learning), institutions (social practices and norms), and policies (science, technology, trade, education, and investment) that condition agents' interactions and responses to innovation opportunities. Further, they often provide analyses of policy design from the perspective of policy as a continuous process that adapts to institutional and technological opportunities presented by socioeconomic

change and development (Metcalfe, 1995, 2000). This differs significantly from the neoclassical assumption that policy is the domain of fully-informed social planners who reconcile social and private welfare within a system of rational maximizers.

Today, there is an extensive body of applied literature on innovation systems in industrialized (OECD) and newly-industrialized Asian countries, where the emphasis is typically placed on industry and manufacturing. This does not, however, preclude the need for, or potential value in, applying the innovation systems framework to the study of developing countries. Lundvall et al. (2002) are clear in their call for greater study of national innovation systems in developing countries. But other authors suggest that the framework—in part or in whole—is not necessarily appropriate to the study of technological change in developing countries. For example, Metcalf (2000) argues that innovative capacity is significantly preconditioned by the existence of a strongly capitalist system supported by functional market institutions and processes, implying that developing countries may not meet the basic criteria for possessing what might be described as an innovation system. Similarly, Balzat and Hanusch (2004) describe innovation systems in developing countries as "fragmented," a characteristic that might hamper the application of an innovation systems approach. Viotti (2002), in a study comparing innovation systems in Brazil and South Korea, argues that national "learning" (rather than "innovation") systems are more appropriate to the study of technological laggard countries. Relatedly, Arnold and Bell (2001) argue that innovation in developing countries might be better framed by studying a country's capacity to imitate, adapt, and catch up with innovation processes in industrialized countries. But, as will be discussed later, these arguments should not entirely rule out the application of an innovation systems framework to the study of technological change in developing countries.

An Innovation System Model

Game theoretic modeling based on emerging work in evolutionary economics offers some insight into the value of the innovation systems framework. The models described below illustrate the spontaneous processes of social self-organization and how public policy and organizational structures can affect these processes. This perspective differs significantly from the neoclassical approaches to constitutional design and benevolent social planning. In an evolutionary approach, aggregate social outcomes are not the summation of individual maximizing behavior; rather, they are the result of individual behavior conditioned by the behavior of others and by the institutional landscape that conditions these behavior patterns.

The evolutionary model employed below derives from the biological population models described by Maynard Smith (1982). But it substitutes for the intergenerational selection of biologically inheritable traits the selection of socioeconomic behaviors, both idiosyncratic and intentional, over time. The approach is described in detail by Nelson and Winter (1982) and pursued further by Andersen (1994, 2000, 2004), who models an innovation system with Schumpeterian characteristics to describe the strategic decision-making processes of diverse agents who cooperate, compete, or otherwise interact over time.

A Schumpeterian game theoretic model similar to that described by Andersen (2000) is configured as follows.[4] First, the model is set up with the standard attributes of a noncooperative game: several agents ("players") pursue different behaviors ("strategies") that obtain different outcomes ("payoffs"). Second, the model is initially configured as the classic hawk/dove game. Intuitively, when a hawk and dove meet, the dove is severely injured by the hawk's aggressive nature; when two hawks meet, they are both severely injured because of their equally aggressive natures; and when two doves meet, they both fare well because of their peace-loving nature.

The hawk and dove strategies are respectively renamed Innovator *(I)* and Adaptionist *(A)* to capture the Schumpeterian nature of the game described here. In this game, an Innovator might be an actor who possesses and transforms knowledge into a functional technology. For instance, an Innovator might be a research-based firm or a highly entrepreneurial individual. An Adaptionist might be an actor who applies such knowledge to the production of some good or service. Thus, an Adaptionist might be

a small-scale farmer or a rural entrepreneur—an example used here because of its relevance to innovation in developing countries, where agriculture often is a central component of the economy.

These descriptions provide an appropriate starting point for modeling a simple innovation system because they represent a set of agents that engage in interactions (exchanges) that are subject to coordination failures caused by, say, contracts for appropriating rents from innovation that are difficult to enforce or otherwise incomplete.

We begin with a one-off, static version of the game and describe the payoffs as follows. When a player choosing an Innovator strategy meets another player choosing the same Innovator strategy, the duplication of innovative effort implies that they must equally divide the value of the appropriable benefits *(v / 2)* of their innovative activity and equally divide the transaction costs associated with the meeting *(c / 2)*. These transactions costs—say, expenses incurred in the process of protecting, securing, or obtaining rights to appropriable innovation rents—are prohibitively high *(c > v),* implying that the payoffs are detrimental to each party. However, when an Innovator meets an Adaptionist, the Innovator appropriates the full value of its innovative activity without cost.

Conversely, when an Adaptionist meets an Innovator, the Adaptionist realizes no benefit since the Innovator appropriates the full value of its innovative activity, as mentioned above. When an Adaptionist meets another Adaptionist, however, both share the benefits of the innovation equally, less any transactions costs incurred in the meeting *(z)*. We assume that an Adaptionist's costs are neither prohibitive nor greater than an Innovator's costs *(z < c).*

These strategies can be presented in a strategic (or normal) form model as shown in Table 1. Player 1 is represented by the row strategies and payoffs. Player 2 is represented by the column strategies and payoffs. Note that the payoffs shown in Table 1 are those of Player 1 (the "row" player), while Player 2's payoffs are found symmetrically across the diagonal.

Table 1: Payoff Matrix, Innovator/Adaptionist Game

	Innovator	Adaptionist
Innovator	*(v – c) / 2*	*v*
Adaptionist	*0*	*(v – z) / 2*

Numerically, by assigning values such that *v = 3, c = 5,* and *z = 1,* consistent with the inequalities described above, the payoff matrix is as in Table 2.

Table 2:
Numerical Payoff Matrix, Innovator/Adaptionist Game

	Innovator	Adaptionist
Innovator	*–1*	*3*
Adaptionist	*0*	*1*

The outcomes of a one-off interaction suggest that there is no dominant strategy to this game: we cannot simply predict a single strategy that each player will (or will not) choose. The outcomes shown here are two Nash equilibria, indicating two self-evident outcomes in which neither player can gain without making the other worse off, or in which all players' strategies are best responses to the other available strategies. This implies that neither player has an incentive to alter his or her strategy given the strategies adopted by others: it is always better to be an Innovator when facing an Adaptionist, and always better to be an Adaptionist when facing an Innovator. Both equilibria are Pareto optimal in the sense that the strategic responses leave each player better off than had he or she pursued some other strategy. These outcomes are consistent with the solutions that obtain from the standard payoff *(π)* structure of a hawk/dove game, namely

$$\pi(I,A) > \pi(A,A) > \pi(A,I) > \pi(I,I) \qquad (1)$$

Next, consider this game within the context of an entire population comprised of Innovators and Adaptionists. Here, Innovators and Adaptionists interact randomly on a frequency-dependent basis within a system; that is, they meet up with one another based on the proportion of Innovators *(α 0 [0, 1])* and Adaptionists *(1 – α)* present in the system. Payoffs to the Innovator are the sum of the payoffs of interacting with another Innovator and another Adaptionist, subject to the probability of each interaction occurring within the system, or

$$\pi(I,\alpha) = \alpha\left(\frac{v-c}{2}\right) + (1-\alpha)v \qquad (2)$$

Similarly, the payoffs of the Adaptionist strategy are

$$\pi(A,\alpha) = \alpha(0) + (1-\alpha)\left(\frac{v-z}{2}\right) \quad (3)$$

Equating the payoffs of the two strategies and solving for α yields

$$\alpha^* = \frac{v+z}{c+z} \quad (4)$$

where α^* represents the equilibrium distribution of Innovators and Adaptionists in the system, represented graphically in Figure 1. Using the numerical payoffs given in Table 3, $\alpha^* = 2/3$.

Intuitively, the institutional context (the payoff structure) within which this population evolves obtains a stable equilibrium in which the two types of behaviors (Innovator and Adaptionist) are able to coexist. Using the numerical payoff structure, the system is characterized by a population consisting of two-thirds Innovators and one-third Adaptionists.

Next, consider a dynamic model of this game in which the proportions of Innovators and Adaptionists change over time as agents update their behavior based on learning and positive feedback processes between time periods *t* and *t +1.* Assume that some small proportion of the agents (ω) choose to deviate from their strategy and experiment with new strategies based on what they learn in interactions with other agents. If the payoffs of such a deviation are greater than the payoffs of their existing strategy, then they will change their strategy—Innovators will become Adaptationists and Adaptationists will become Innovators.

More formally, a change in the proportion of Innovators between *t* and *t +1* will result when the payoffs to members of a deviating group are greater than the mean payoffs in the system. By expressing the mean payoff as

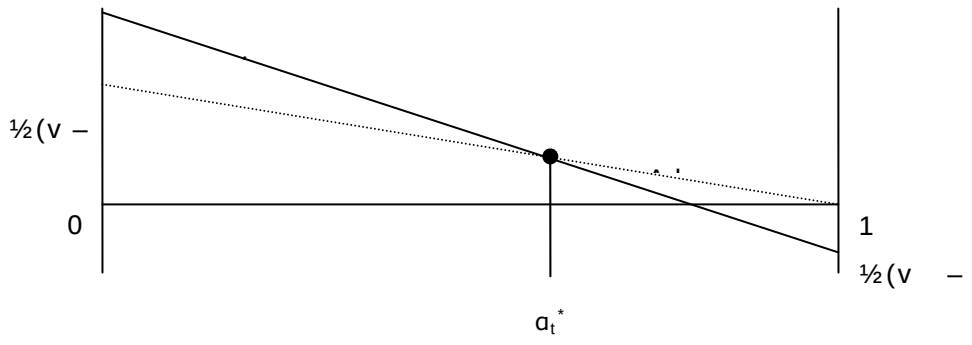
$$\bar{\pi} = \alpha_t \pi(I,\alpha_t) + (1-\alpha_t)\pi(A,\alpha_t) \quad (5)$$

then the change in the proportion of Innovators between *t* and *t+1* is equal to

$$\Delta\alpha = \omega\alpha_t\left[\pi(I,\alpha_t) - \bar{\pi}\right] \quad (6)$$

This equation is commonly referred to as the *replicator dynamic*, or the process through which the frequency distribution of those strategies with higher payoffs increases to an asymptotically stable distribution. In intuitive terms, the replicator dynamic describes the process by which individual behaviors and practices are copied and disseminated (or rejected and rendered extinct) throughout a population via a process of repeated interaction between agents and conditioning by institutional context.

Figure 1: Innovator/Adaptionist Game



The asymptotically stable distribution obtained from this process is referred to as an *evolutionarily stable equilibrium*—analogous to a Nash equilibrium in the one-off game described above—and is obtained where there is no change in the proportions of Innovators and Adaptionists in the system, that is, where

$$\frac{d\alpha}{dt} = 0 \tag{7}$$

In this model, three such equilibria are possible: two are found where the system is comprised exclusively of Innovators or Adaptionists *($\alpha = 1$* or *0).* But these solutions are inherently unstable: any deviation within the system *($\omega > 0$)* will cause movement away from these equilibria. Moreover, these solutions are uninteresting in so far as a homogeneous population tells us little about innovation and evolution. However, the third possible equilibrium is of interest: this is the point at which the payoffs of each strategy are equal, that is

$$\pi(I, \alpha_t) - \pi(A, \alpha_t) = 0 \tag{8}$$

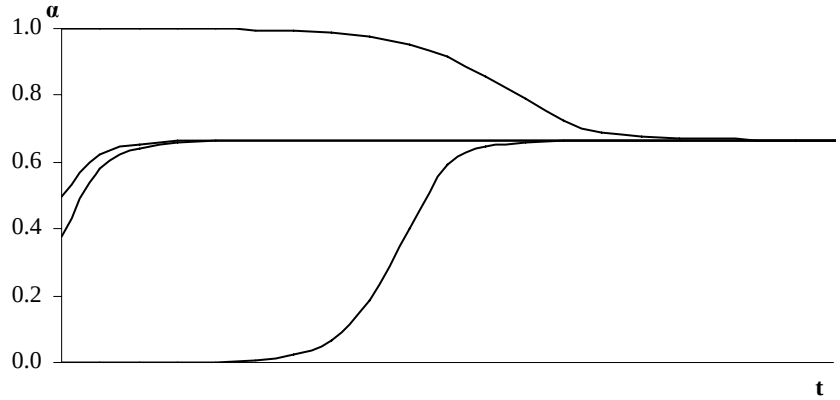
Given the payoffs set forth in the model, this equilibrium solution is evolutionarily stable because any agents choosing to deviate will find that the payoffs of a change in strategy are unfavorable, thus causing them to return to the equilibrium distribution, or

$$\frac{d[\pi(I, \alpha_t) - \pi(A, \alpha_t)]}{d\alpha_t} = -\left(\frac{2v + c - z}{2}\right) < 0 \tag{9}$$

Thus, the point at which this condition is met (for $\alpha \neq 1,0$) is an evolutionarily stable system profile. A graphic representation of the trajectory of the system's replicator dynamic shows an asymptotically stable outcome (Figure 2). Using our numerical example again, a stable population is made up of two-thirds Innovators and one-third Adaptionists.

Next, consider a model of an innovation system comprised of Innovators *(I)*, Adaptionists *(A)*, Complementors *(C)*, and Imitators *(M)*. A Complementor might be described as a small-scale innovator whose marketable product depends on that of the primary Innovator. An Imitator might be more like a pirate, realizing the full value of appropriable benefits with only negligible costs. Through this model, we begin to capture some of the complexities inherent in a more realistic system, and present the possibility of multiple evolutionarily stable equilibria.

Figure 2: Replicator Dynamic of an Innovator/Adaptionist Game



The model's payoff structure between Innovators and Adaptionists is as described above. But the additional interactions posed by this game warrant further explanation. First, when an Innovator meets a Complementor, the Innovator appropriates the full value of its innovative activity without cost, while the Complementor generates its own additional, appropriable value from the meeting *(v)* less its own costs *(r)* that are assumed to be greater than those of an Adaptionist but less than those of an Innovator *(c > r > z)*. When a Complementor meets either an Adaptionist or another Complementor, the two equally divide whatever value is generated in their meeting. Necessarily, since neither agent creates much value independently, the benefits they divide are relatively small and, depending on the cost structure, possibly negative. Finally, when an Imitator meets any other agent, the Imitator appropriates the full value of the Innovator's innovative activity with only nominal cost *(s)*. We assume that the Imitator faces the lowest cost structure, such that $c > r > z > s$. Table 3 describes this payoff structure.

The outcomes of this game again suggest multiple equilibria (Figure 3). When mapped against time, several stable asymptotic solutions (and several unstable solutions) emerge, ranging between 0 and 1.

The relevance of these models becomes apparent when we consider how societies organize themselves over time, how institutional design contributes to determining these evolutionary processes, and how the outcomes of these processes may or may not be optimal.

Numerically, assuming $r = 2$ and $s = ½$, the payoffs are as shown in Table 4.

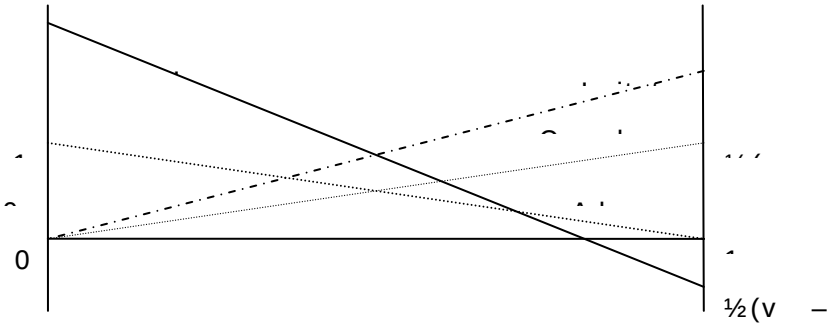
Table 3: Payoff Matrix, Innovator/Adaptionist/Complementor/Imitator Game

	Innovator	Adaptionist	Complementor	Imitator
Innovator	$(v - c) / 2$	v	v	*0*
Adaptionist	*0*	$(v - z) / 2$	$(v - z) / 2$	*0*
Complementor	$v - r$	$(v - r) / 2$	$(v - r) / 2$	*0*
Imitator	$v - s$	$v - r - s$	*0*	*0*

Table 4: Numerical Payoff Matrix, Innovator/Adaptionist/Complementor/Imitator Game

	Innovator	Adaptionist	Complementor	Imitator
Innovator	*–1*	*3*	*3*	*0*
Adaptionist	*0*	*1*	*1*	*0*
Complementor	*1*	*½*	*½*	*0*
Imitator	*2½*	*½*	*0*	*0*

Figure 3: Innovator/Adaptionist/Complementor/Imitator Game



First, the models suggest that institutional design is important. Given a set of n agents in a particular game, any change in the payoff structures may change the outcomes of the game. So, for instance, a sufficiently enforced law against piracy might reduce the payoffs to Imitators regardless of whom they interact with. Likewise, a sufficiently enforced intellectual property rights regime might increase the payoffs to Innovators with or without consequence to Adaptionists' payoffs, depending on the nature of the regime. Institutional design, whether the result of spontaneous emergence or of choices made by system actors, necessarily influences the nature and character of the system.

Second, the models suggest the importance of change over time. Institutional design may spontaneously or consciously change as the system evolves in a given direction. For instance, an innovation system operating in a society that prioritizes the welfare of Adaptionists such as small farmers may, in the early years of agricultural modernization, choose to limit the payoffs of being a private sector Innovator. In the long run, however, the society may choose to replace such policies with interventions that favor the private Innovator by, say, reducing the crowding-out effects of public sector investment in agricultural research, or by reallocating public research to a basic/strategic function only. Changes in institutional design over the long term necessarily influence the nature and character of the system.

Third, the models suggest that optimality is not a necessary outcome of evolutionary processes. It should be obvious that optimality does not necessarily obtain from these models; rather, stability obtains, and only under certain circumstances. Indeed, it is difficult to identify conditions for optimality or paths thereto in a dynamic innovation system that evolves from market inefficiencies, endogeneity, serendipity, and non-market institutions, or from a system that generates multiple equilibria and Pareto-inferior outcomes. But where policies can be designed to affect the evolutionary process of innovation, then the trajectory of a system can potentially be guided toward greater innovative output and more favorable distributions of innovative rents and social welfare.

Thus, the evolutionary models described above suggest that public policy can play a role in transforming an innovation system by changing the rules of the game and by changing the sequence in which the rules are applied. In effect, this implies that there is a role for public policy beyond the correction of imperfect markets as identified by neoclassical economics (e.g., market power) and beyond the correction of imperfect institutions as identified by new institutionalist economics (e.g., coordination failures). Rather, the role of public policy should be to (a) enable an innovation system to remain flexible and diverse enough to avoid becoming locked into a single trajectory, (b) create incentives for innovative activity, and (c) create institutions that respond to and learn from the innovative process.

Finally, note that this model illustrates only one possible set of agents, interactions, and outcomes in an innovation system. Other models can be developed to describe any other set of relationships formed around any other set of technologies and institutions. This flexibility is what makes game theoretic and population game models so useful in analyzing complex systems. Still, the point here is not to describe all possible agents, interactions, and outcomes but to provide a model that helps illustrate the complexities encountered when heterogeneous actors behave strategically, and how their behavior generates certain evolutionary outcomes within a broad system.

Discussion

Returning to the issues raised by Metcalf (2000), Arnold and Bell (2001), Balzat and Hanusch (2004), and Viotti (2002), it is worth discussing whether an innovation systems approach can be constructively applied to the study of developing countries. If models such as the one set forth above suggest that societies and economies are organized differently, characterized by different sets of institutions, and evolve differently over time, then the argument against application of the approach holds only if there is some common characteristic across developing countries that precludes the existence of either innovation processes or a coherent system.

As noted earlier, one argument suggests that developing countries are not characterized by a unified capitalist economy, which is considered a necessary

condition for a functioning innovation system (and the study thereof). But if this were true, then the innovation systems in OECD countries would have long ago been hampered by the continued existence of strongly socialist structures in many of these countries. Moreover, there is sufficient evidence to suggest that both capitalism and innovation are flourishing in many developing countries.

Further, there is limited insight in the argument that the study of developing countries should focus on imitation and learning because they are technological laggards rather than creators of new knowledge. As Arnold and Bell (2001) and Balzat and Hanusch (2004) are quick to point out, innovation itself is often a process of individual, organizational, and societal learning, highlighted by activities such as imitation, emulation, and replication. Thus, the innovation systems approach is just as relevant to the study of technological laggards and how they adopt existing knowledge as it is to the study of technological pioneers.

Finally, it can be argued that because innovation takes many forms and derives from many sources, its study can neither be limited to industry or manufacturing nor to industrialized, capitalist economies. For centuries, farmers in both industrialized and developing countries have innovated to enhance crop yields and output by carefully selecting seeds from plants displaying desirable traits, grafting plant parts from preferred varieties onto other mature plants, or engaging in other traditional selection practices. This has occurred in both traditional subsistence agriculture where markets are few and far between and in highly commercialized agricultural sectors.

To be fair, the innovation systems framework *is* increasingly being applied to the study of agricultural research and technological change in developing countries. This trend is particularly useful for capturing the diversity and complexity of agrarian agents, processes of institutional learning and change, market and nonmarket institutions, public policy, poverty reduction, and socioeconomic development. Yet few applications of the framework to developing-country agriculture have made extensive use of either the theoretical content or methodological diversity available in the literature (see related article in this volume). Thus, there is much more to be done to bring the full value of the innovation systems framework into the study of developing countries.

Conclusion

Implicit in all of these arguments is the fact that, by its very definition, the innovation systems framework has the capacity to analyze both the diversity of socioeconomic institutions and the complexity of relationships and interactions among heterogeneous agents under different institutional scenarios. This should open the door for greater study of innovation systems in developing countries in all levels, sectors, and time-periods in relation to different technology sets and with regard to specific goods and services. With greater understanding of how agents generate, exchange, and use knowledge given the relationships and institutions that condition their behavior, we can learn more about how innovation processes contribute to growth, development, and prosperity in developing countries.

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Notes

1. A secondary Schumpeterian model, typical to more mature firms and industries, obtains from the accumulation of innovation and within-firm changes in the allocation of resources into new products and processes (the "creative accumulation," or Schumpeter Mark II model).
2. Worth noting is the relative distance between the innovation systems approach and new institutional economics (NIE). The NIE approach provides insights into how agents engage in the production, diffusion, and utilization of knowledge and technology where markets fail or are otherwise incomplete. The innovation systems approach, in contrast, emphasizes the study of complex non-market characteristics (organizational characteristics and capabilities, for example) as well as non-market interactions (interactive learning processes and feedback loops, for instance) and how they are embedded in systems and processes of innovation (Lundvall et al., 2002). Despite different areas of emphasis, some leading authors in the innovation systems literature contextualize their work using modes of analysis that are plainly drawn from NIE perspectives. For instance, Metcalfe (1997) examines innovation systems in the context of nonclearing markets for innovative activity; the influence of information asymmetries, property rights, appropriation externalities, indivisible capital investments, and nonrival/nonexcludable (public) goods in innovation markets; the effects of noneconomic forces such as culture, history, and path dependency; and the necessity of technology policy in preserving certain market inefficiencies so as to ensure greater innovative output.
3. The succession of models presented here is loosely based on Andersen (2000). Several changes have been made to the definitions of (and intuition behind) the agents' characteristics, their payoff structures and behavior, and their implications within an evolutionary system.

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