



INNOVATION IN DEVELOPING COUNTRIES TO MEET HEALTH NEEDS

EXPERIENCES OF BRAZIL, CHINA, INDIA, AND SOUTH AFRICA

An overview report to the

Commission on Intellectual Property Rights, Innovation and Public Health

CIPIH

prepared by

The Centre for Management of IP in Health R&D

MIHR

April 2005

Contents

Executive Summary	1
PART 1 – What is Innovation?.....	5
National Systems of Innovation	5
The determinants of innovation: A framework	6
The value of innovation theory	7
PART 2 – Analysis of Findings in Four Countries	8
Evolution of the national innovation systems	8
The determinants of innovation in four countries	9
Measuring innovation	10
Input indicators.....	10
Output indicators.....	11
Government policies and actions	11
Several key issues	13
The impact of the ‘Brain Drain’ on innovation.....	13
The importance of domestic and export markets	13
Traditional knowledge and health	14
Does the private sector accord priority to diseases of the poor?.....	15
IP management and licensing practices to acquire and develop knowledge.....	16
Patents, TRIPS and innovation	16
Main barriers to innovation	20
PART 3 – Implications	22
Determinants	22
Promote dynamic linkage.....	23
PART 4 – Concluding remarks	24

INNOVATION IN DEVELOPING COUNTRIES TO MEET HEALTH NEEDS EXPERIENCES OF BRAZIL, CHINA, INDIA, AND SOUTH AFRICA.

Executive Summary

This paper is for the WHO Commission on Intellectual Property Rights, Innovation, and Public Health (CIPIH). The CIPIH requested The Centre for the Management of IP in Health R&D (MIHR) to report on the experiences of four developing countries with regard to the status and determinants of biomedical innovation in those countries and make recommendations that may assist policy development in those and other developing countries in relation to meeting their health needs. The four countries are Brazil, China, India, and South Africa. Consultants in each country prepared reports and MIHR prepared this overview report of the issues based largely on those country reports:

South Africa	Sibongile Pefile
China	Zezhong Li
Brazil	Claudia Chamas
India	Hiro Bhojwani

This report has four parts. The first part sets the context by reviewing some of the approaches and experiences of studying innovation and innovation policy relating to industry in a variety of countries. Part 2 seeks to answer a number of key questions pertinent to innovation in the health sector in the four countries. This part is mainly based on information from the country reports. The third part presents recommendations for other developing countries and international organisations regarding innovation in the health sector. The concluding part provides some concluding remarks on possible trajectories for development, manufacture and supply of needed health products by the four countries and other developing countries

There is a widely recognised and deep deficiency in availability and access to treatments (drugs), vaccines and diagnostics for the ‘diseases of the poor’ that affect millions of people, particularly in the low-income, developing countries¹. Further it is recognized that health and economic development are integrally linked². New and improved health technologies are needed to address diseases in developing countries. More effort is needed to translate product candidates related to the multifarious ‘diseases of the poor’ into products.

The studies undertaken for this Report throw light on how various organisations can, through the efforts of biomedical research, innovation and production systems, help poor people in the developing world gain improved access to the drugs and vaccines they need.

There are many reasons why access is limited, but three stand out:

1. **Lack of research:** Many of the diseases faced by poor people do not have appropriate medications or vaccines, and few large drug companies are

tackling these problems with a high level of investment due to the inability of poor people to pay.

2. **Lack of resources to procure products:** Even when drugs are available, poor people and poor countries may not have adequate resources to procure them. Drug companies, through their ownership of patents and intellectual property (IP) seek to maintain market prices to recoup the costs of drug discovery, marketing, and distribution. Some companies have introduced tiered pricing and are prepared to sell products at prices which are only marginally above production costs. But even in these circumstances developing country governments often find themselves without the resources to pay for them.
3. **Lack of adequate delivery systems:** Even when drugs and vaccines are available at reasonable prices, the health delivery systems in many poor countries are often inadequate to ensure poor people receive the needed products.

The barriers to access to medicines, vaccines and diagnostics for diseases of the poor has become an important issue in international development. There are a number of proposed strategies for overcoming these barriers. For example, developing countries could improve their capacity to produce drugs, vaccines, diagnostics and medical equipment so that they become less dependant on foreign sources and related pricing structures³. Also, developing countries could seek to innovate new drugs and vaccines appropriate to their needs and seek patent protection to help ensure some control of the market. Indeed, a number of scientifically and technically advanced developing countries – Innovative Developing Countries – have begun to do this. However, there is no clear consensus on which strategies are the most effective and how government policies can be formulated and implemented to ensure success. There is a large body of literature and experience concerning innovation, some of it pertaining to health technologies, but this literature and experience has not been systematically applied to the problems of developing countries. One of the purposes of this report is to explore how the health sector, particularly in developing countries, can build on the recent studies of industrial innovation to create effective health related innovation systems.

Innovation is a complex process that can be measured through various means such as patents, publications, new products, and numbers of R&D personnel. Studies in innovation show that success is achieved through the operation of networks involving certain critical organizations and individuals. Countries seek to develop and implement innovation policies to support economic development. Most developed countries have national systems of innovation (NSIs) and these often focus on science and technology (S&T). The developing countries discussed in this paper also have NSIs but not necessarily directed to health and with little concern for diseases of the poor. There is a need to develop such NSIs that will help to redress health inequities. The development and implementation of an effective NSI requires an understanding of the determinants of innovation. We propose six determinants:

- Creating capacity for and undertaking R&D
- Creating and sustaining capabilities to manufacture products to appropriate standards

- Promoting and sustaining domestic markets including government health systems
- Promoting and sustaining export markets including sales to international organisation such as UNICEF
- Creating and implementing systems of IP management appropriate to the needs of the country
- Creating and implementing systems for drug, vaccine, diagnostic and device regulation to help ensure safety, efficacy and to take into account issues of cost benefit.

The six determinants are assumed to be dynamically linked such that progress in one is facilitated by and dependent upon progress in the others.

The four countries considered in this study have followed similar paths in developing their NSIs. They have generally begun with import substitution through the copying of drugs and vaccines already on the market elsewhere and with trade barriers for foreign products. In this early stage, there was limited support for R&D in both the public and private sectors. More recently they have sought to build up domestic R&D capability in both sectors, and there are early signs of success in innovation but it has become clear that these countries face significant challenges in developing domestic innovation capabilities. The most significant challenges are to build up networks among the key components of innovation including research centres (public and private), manufacturers, buyers (public and private markets both domestically and internationally), intellectual property (IP) systems and policies, and regulatory (drug and vaccine) systems and policies.

All four countries have increased their innovative capabilities as measured by patents, publications, and manufacture of health technologies. A uniform finding throughout this study is that the four countries can be divided into two groups. China and India have consistently been more successful in building innovation capability in health. Brazil and South Africa have lagged behind. Brazil has lagged behind because S&T policy did not emphasize the translation of research into products. South Africa's major challenge has been its relatively smaller market and the brain drain. India and China have been addressing the problems of brain drain by inducing nationals to return home. South Africa has not been able to achieve the same level of success in reversing the brain drain.

The four countries have sizeable domestic markets although South Africa's market has not been as large or robust as the other three countries. The increasing prosperity seen in Brazil, China and India has been a driver of increasing local innovative capability in health. In addition, the four countries have sought to increase their exports of health technologies with India being especially successful. It is one of the world's major suppliers of generic drugs and of vaccines.

The countries have paid special attention to traditional knowledge and are seeking to use this resource as a base for biotechnology. China has had a particular success with Artemisinin – the front line treatment for malaria.

Despite these promising developments, the private sector in all four countries has not been oriented toward diseases of the poor. They seem to have similar decision

making criteria as their developed country counterparts. This reality calls for the development and implementation of government policies to provide incentives to the private sector to address diseases of the poor.

Each of the four countries recognizes the value of good IP systems and effective IP management although there is a lack of trained personnel, institutions, and systems in each country. Efforts are underway to address this need but the challenges are immense. A promising development is the rapidly growing level of international collaboration that helps the private sector to increase rapidly its IP expertise.

It is still too early to determine the impact of TRIPS in these four countries. Each country has embraced TRIPS and there are strong government policies to use TRIPS as a means to enhance R&D capabilities, and to increase trade and investment. There are some early indications of increased foreign investment, particularly in India. However, the question of the impact of TRIPS on access to health technologies by the poor remains unanswered.

These findings lead to a number of possible implications for how these and other developing countries can increase their success in innovation.

- There may be opportunities to increase trade between developing countries and to seek to establish price controls on a regional basis
- As each country develops economically, it should look particularly at the need and opportunity to expand domestic markets to the underserved in rural areas.
- Governments should provide tax incentives for small and medium enterprise (SME) in biotechnology. The government could also promote innovation by supporting the establishment and expansion of R&D centres in both the public and private sectors.
- Governments should encourage the continued growth of the generic drug (and vaccine) production industries. TRIPS has no impact on the production of products for which the patents have expired.
- Governments need to continue their efforts to expand capabilities in IP management and policy formulation and to explore the ways in which they can most effectively work within the TRIPS framework.
- The private sector in these countries should look for niche products, e.g. diagnostics, that may take advantage of particular strengths and needs in the country.
- At all levels governments should seek to promote dynamic linkage among the key institutions for innovation – R&D centres, producers, buyers and users (both domestically and foreign), IP centres and regulators.
- Perhaps the most highly impactful action that governments can take is to promote the formation of public private partnerships (PPPs) focused on the development of health technologies to meet the needs of the poor.

In sum, each of the countries is making important progress in health innovation but there are significant challenges especially with respect to health technologies for diseases of poverty. Government and the private sector can take a number of initiatives to enhance innovation capability especially by promoting dynamic linkage of innovative institutions through public private partnerships.

PART 1 – What is Innovation?

This Part of the Report provides a brief introduction to the field of innovation studies.

National Systems of Innovation

The process of innovation is complex⁴. It used to be thought that by investing in scientific research, new technologies would be generated which would be produced and distributed. However, detailed studies in the last three decades have shown that this linear conceptualization is flawed. It is now understood that innovation involves complex, iterative and changing processes involving many players whose roles may change significantly with time. This more recent conceptualisation of innovation seems to be especially applicable to the development of new drugs and vaccines. Scientific research is important, but, on its own, it is insufficient to generate innovation⁵.

There have been many attempts to measure innovation⁶ but because of its complexity it is difficult to “measure” the process through the indicators that are generally used. These indicators include input measures such as the human resources and special skills that are required, and the financial flows to different elements such as to research and development (R&D) and manufacture. Output measures include counts of publications and citations, and especially important have been patent statistics. Process indicators such as the number of contracts and links between universities and industry try to capture the interactions between the different participants in the innovation process. Although useful for making international comparisons, these indicators provide only a partial measure of a very complex process. Each of these measures is used in this report.

The concept of a National System of Innovation was developed first by a number of academics. The concept was further used by developed country governments, many of which moved to formulating “innovation policy” rather than just R&D policy.

Some developing countries, including South Africa and China in the late 1990s found it helpful to use the notion of a National System of Innovation (NSI) as the basis for policy.

The OECD (1994) defined a NSI as:

“... [a] system of interacting private and public firms (either large or small), universities and government agencies among the production of science and technology within national borders. Interaction among these units may be technical, commercial, legal, social, [and] financial, in as much as the goal of the interaction is the development, protection, financing, or regulation of new science and technology.”

Systems of innovation in the health sector consist of complex networks of universities, research institutes, pharmaceutical companies, medical and hospital

equipment manufacturers and suppliers, government agencies and controlling bodies and hospitals.

For the purposes of this paper and reflecting on the global nature of health, we consider NSI as including activities and organisations both within the country and outside it. The term NSI is appropriate however because it is sovereign governments that make policies and oversee patents, biomedical regulatory institutions, budgets for R&D, the creation and operation of organisations and firms, etc.

A NSI needs to take into account the following functions⁷:

- Policy and resource allocation
- Regulatory
- Financing
- Performance
- Human resource development and capacity building
- Infrastructure

A key component of the NSI approach is that ultimately all of the components of a NSI are designed to promote innovation through the firm or enterprise (public or private). It is the realization that firms or enterprises are the key means by which products reach users that has led to the appreciation of the essential nature of public private partnerships. Thus, a NSI for health should be directed towards ensuring that all components of the system are in appropriate relationship to the firm or enterprise that will produce and distribute drugs, vaccines, diagnostics, or medical equipment.

There are various ways of examining and understanding a NSI. For example, the national knowledge approach⁸ recognises that there are a number of functions regarding knowledge that need to be performed by a firm or enterprise. These include:

- Creating knowledge
- Acquiring knowledge
- Assimilating knowledge
- Using knowledge
- Disseminating knowledge.

Each of these functions requires different skills. Sometimes all of the functions are performed within the same organisation, but more often different, more specialised, organisations are involved⁹. This is especially the case for the creation of knowledge which may take place in another organisation and even in a different country.

The determinants of innovation: A framework

A new approach^{10, 11} has built on this innovation literature and developed a framework which is intended to be particularly relevant for understanding innovation in the health sector. This framework has six determinant of innovation.

- Creating capacity for and undertaking R&D
- Creating and sustaining capabilities to manufacture products to appropriate standards
- Promoting and sustaining domestic markets including government health systems
- Promoting and sustaining export markets including sales to international organisation such as UNICEF
- Creating and implementing systems of IP management appropriate to the needs of the country
- Creating and implementing systems for drug, vaccine, diagnostic and device regulation to help ensure safety, efficacy and to take into account issues of cost benefit.

The six determinants are assumed to be dynamically linked such that progress in one is facilitated by and dependent upon progress in the others.

All government and private sector initiatives and policies are designed to influence decision makers in firms on the best way to innovate. Ultimately it is these decision makers who must choose the best way in which to acquire the technology they will use in producing the new drug, vaccine, diagnostic or equipment. There are several alternative ways to acquire technologies:

- Develop it within the firm
- Acquire from another domestic company
- Acquire from a public laboratory or university
- Acquire from a foreign firm through a licence
- Form a joint venture with another, usually foreign, firm.

In addition the government may provide for a foreign company to set up manufacturing facilities within the country either as an independent undertaking or a joint venture. Sometimes several of the different routes are used as the local firm builds up a portfolio of technologies.

The value of innovation theory

The innovation literature provides a firm basis on which to assess and understand the development, manufacture, introduction and distribution of health technologies needed in developing countries. Innovation theory points to the essential nature of interactions among the different component parts of innovation systems, and to the recognition that R&D is only one of the activities necessary to ensure that innovation takes place. It also helps us identify the questions which must be answered before recommendations can be made on how developing countries can design their innovation systems to meet their health needs.

PART 2 – Analysis of Findings in Four Countries

The four commissioned reports from Brazil, China, India and South Africa provide comprehensive surveys of innovation in the health sector in each country. This overview report poses a number of questions and examines a number of issues relevant to innovation in developing countries. It attempts to do this based largely on the material contained in the four reports.

Evolution of the national innovation systems

The evolution of the innovation systems in each country has followed a surprisingly similar path given their differing economic and political systems. China and India followed a command economy approach during the 1950s, 60s, and most of the 70s. Both governments gave priority to building public scientific and technical institutions and creating indigenous scientific and technological capabilities. Both have built atomic bombs, thus demonstrating their ability to make military innovations. However, during the late 1960s to late 1970s the Chinese scientific system underwent considerable disarray due to the Cultural Revolution and its aftermath.

China and India began to move from command economies to market economies in the mid 1980s. Both opened their doors to foreign investment and began to encourage the private sector. By the late 1990s, both countries recognised the importance of innovation through the workings of a market economy and China, in particular, began to use the concept of a NSI to promote reforms.

South Africa also had built a strong science and technology system and it too used this capability to build an atomic bomb. Also, like China and India, it went through a lengthy period of self-reliance during the Apartheid era. It was only after the African National Congress (ANC) came to power in 1995, that the country's 'first world' science system became more oriented to 'third world' problems, and the new government embraced the NSI approach to policy making.

Brazil followed a very different policy, but with broadly similar results. During the 1960s, 70s and 80s it followed an import substitution policy and, in this regard, was similar to China and India. This import substitution strategy included an emphasis on self-reliance and a strengthening of the domestic research system. However, the strategy also included the erection of barriers to the import of foreign technology – a vital source of learning and capacity enhancement – as well as critical inputs to technological innovations. The government changed its policy in the 1990s when it adopted a free market approach including deregulation and privatisation. Much of the motivation to adopt this revised market strategy was to attract foreign investment

In the last decade, the four countries have opened their economies and embraced globalisation. All have joined the World Trade Organisation (WTO) and set up patent systems that are compliant with TRIPS

The four countries considered in this review have each made important progress in health technology innovation. The University of Toronto¹² has recently undertaken a review of biotechnology innovation in Brazil, India and South Africa and other

countries that highlights much of this progress. In summarizing some of the key points of the University of Toronto study, the Economist states “Brazil needs better links between academia and industry. [...] India’s regulatory system is slowing down product development. South Africa needs to do more to reverse its brain drain, and train more researchers to boost their ranks”¹³. These are just a few of the problems still facing these countries as they seek to improve their innovative capabilities.

A number of issues relating to innovation need to be addressed and appropriate policies developed and implemented before these countries can more fully contribute to health innovation both for themselves and for other developing countries. The purpose of this section is to identify these key issues and discuss ways in which to address them.

The determinants of innovation in four countries

As noted earlier, Mahoney has proposed a framework that includes six determinants of innovation in the health sector. In this section we apply this framework using one country, South Africa, as an example.

The South African report lists the main components* of innovation as:

1. Innovation infrastructure.
 - Attractiveness of the natural environment for exploiting S&T
 - Intellectual property protection
 - Government tax credits and subsidies for R&D
 - Company spending on R&D
 - Procurement of advanced technology products
2. Cluster specific conditions:
 - Production process conditions.
 - Extent of product and process collaboration
 - Local supplier quality
 - State of cluster development
3. Quality of linkages:
 - Absorptive capacity for new technology
 - University/industry research collaboration
 - Venture capital availability

Within each of these components, the South African report highlights both the positive and negative features which have influenced that country’s ability to innovate in the health sector. An important aspect of this analysis is the way in which it emphasises the importance of dynamic linkage as in our framework. In addition, this

* The author uses the term “determinants,” but to avoid confusion with our framework we have employed the term “components.”

approach emphasises qualitative aspects of innovation, e.g. “absorptive capacity,” and our framework provides the key areas for analysing these qualitative issues. For example, one needs to look at absorptive capacity with respect to R&D (the ability to learn new R&D methods), manufacture (the ability to learn new manufacturing processes), building domestic markets (the willingness and the ability of the local market to take up the new technology), building export markets (the ability of local institutions to absorb and use policies and practices that will allow them to play internationally), developing IP systems and regulatory systems (the ability to manage IP and operate regulatory systems in accord with best international practices). Venture capital availability depends on an assessment of feasibility of the R&D plan, of the potential to manufacture the product, of the size and profitability of domestic and export markets and of the ease of obtaining necessary IP and moving through the regulatory system to licensure.

Thus, the two approaches are consistent and complementary.

Measuring innovation

Indicators of innovation include input, output and process indicators. Especially significant are international comparisons and analyses of how the indicators vary with time. The four country reports provide some measures of input and output indicators. There are uncertainties about comparability of data that constrain the ability to make comparisons. However, the indicators are suggestive of improvements over time in innovative capacity in the four countries.

Input indicators

The main input indicator is the amount of funding allocated to R&D.

India: In 2003/4, the pharmaceutical industry in India spent approximately 13.2 billion Rupees on R&D (US \$1 = 44 Rupees) and representing 3.6% of turnover. Mashelkar (2005) estimates that the Indian pharmaceutical industry has increased its spending on R&D by 400% over the past four years. In addition, in 2003 the public sector spent 2 billion Rupees on pharmaceutical R&D.

The Brazilian private sector, in contrast to the Indian, spent very little on R&D in pharmaceuticals. In 1998 the amount was only 0.59% of turnover. In 2001, its total expenditure on health research was only US \$167 million.

In China, pharmaceutical firms invest between 0.5% and 3.0% of turnover on R&D. This is substantially less than Indian firms but more than Brazilian companies. In the biopharmaceutical sector, expenditures on private sector R&D on new products increased from US \$5.3 million in 1998 to US \$21.4 million in 2002.

Data are not available for research and development funding in health by the four governments.

Output indicators

There are two types of output indicator, bibliometric and patent:

Bibliometric

The principal bibliometric indicators are counts of published papers and citation indicators (the number of times published papers are cited in other articles). Recently, Mashelkar has computed the number of publications or citations per GNP per capita. This measure seeks to account for both the economic status of a country and its relative size. It is a measure of “efficiency,” viz. how well can a large and poor country use its limited resources compared to large and wealthy countries. The calculations show that China and India are very efficient.

With regard to the total number of scientific papers in the health sector Brazil ranked 23rd in the world for the period 1997 to 2001. China was 22nd for the period 1991-93, but moved to 14th place by 2000-2002. Indeed, China and India had the greatest increase in highly cited papers over the periods considered. Brazil and South Africa have had much less satisfactory increases in the numbers of highly cited papers.

Patents

Patents may be a more accurate measure of innovative capability because they represent work that is directed to development of specific products or processes. Comparative statistics are difficult to compile but one measure that is widely used is the number of US patents that have been granted to applicants from different countries. A paper emerging from a meeting at Bellagio in May 2004¹⁴ shows the dramatic rise in patenting in the U.S. for China and India between 1999 and 2003.

US patents issued to Chinese inventors for drugs, vaccines or pharmaceuticals rose from 21 to 34 whereas US patents for Indian inventors rose from 33 to 90. These are still small numbers compared with the patenting by many developed country inventors, but when the patents per GNP per capita are calculated, India ranks third in the world and China fourth. Brazil ranks 11th and South Africa 14th.

These indicators, although only partial measures of innovation, do suggest that India and China are making rapid progress in the health sector. Brazil and South Africa are not far behind.

Government policies and actions

Health biotechnology has been a priority for the four countries over the past decade, with the Indian Government nurturing the subject for more than twenty-five years. By the mid-1970s both the Indian Council of Medical Research (ICMR) and the Council of Scientific and Industrial Research (CSIR) supported biotechnology programmes. In 1982, the Indian government established a National Biotechnology Board with the objective of building human resources and building infrastructure. In 1986 this Board became the Department of Biotechnology (DBT) in the Ministry of Science and Technology and had the task of co-ordinating biotechnology programmes

across government departments, developing human resources, and building a biotechnology information system. Six new research centres were established. Over 25 years the Indian Government invested approximately eight billion rupees (US\$ equals 44 Rupees) in health biotechnology. In addition, three State governments developed policies to encourage the development of biotechnology parks and biotechnology clusters.

In South Africa, the Government established biotechnology as one of five priority topics within its national R&D strategy, and gave priority to developing its NSI. A Biotechnology Commission was established and attention has been given to institution building, to legal and regulatory frameworks, and to research capacity, and to funding mechanisms and business ventures.

In 2002 China established its pharmaceutical S&T policy covering the period 2002 to 2010.

Policies in the pharmaceutical and biotechnology sectors in all four countries have been designed to strengthen all aspects of the national innovation system in the health sector. They have addressed:

- Institution building
- Funding of S&T
- Development of appropriate regulatory mechanisms
- Direct support to industry in the form of tax incentives and the development of science parks and biotechnology clusters.

As a result, both the public and private sector sectors have grown substantially, although innovation in the private sector in these developing countries still lags behind that of the private sector in most industrial countries.

The main contribution of the governments to private sector innovation has been the creation of appropriate human resources. The private sector uses these resources for creating, acquiring, assimilating and using new technologies.

The public sector research programmes have also produced knowledge that has been available for use by private sector scientists. For example, the CSIR in India has the specific goal of collaborating with the private sector to accelerate innovation^{*15}.

Direct assistance has been provided through tax incentives to stimulate R&D and innovation. National and state/provincial governments have encouraged interaction between firms, and between firms and universities and government laboratories, by establishing science parks and biotechnology clusters. There is good evidence from all the countries that the development of clusters of firms has been an important activity for stimulating innovation[†].

* Evaluating the economic contributions of public sector research is extremely difficult.

† This is congruent with findings from research on biotechnology and clusters in the USA and Europe and in other industrial sectors.

Several key issues

The impact of the 'Brain Drain' on innovation

All four countries have experienced substantial emigration of their scientific and technical personnel. With respect to China, it is estimated that only about one third of students who go abroad for training return to China when their training is completed. For India, Mashelkar¹⁶ cites a UNDP report that estimates that 100,000 Indian professionals leave the country every year to take up jobs in the United States. South Africa suffers substantial emigration of highly qualified professionals.

At first sight this loss of highly skilled human resources represents a major economic loss to the countries. However, as China and India develop, they are able to attract back large numbers of their diaspora. These returning scientists and industry managers bring advanced technical skills, knowledge and managerial practises. In the same article, Mashelkar also cites the case of General Electric's new Indian R&D laboratory where 700 of the 2,300 employees are young Indians who returned from the US.

In China the number of returning expatriates has grown considerably in the last few years.

The South African report states that between 1989 and 1999 approximately 10,000 professionals emigrated. There is no evidence to suggest that there is any major return of professionals such as is happening in China and India.

The evidence from the four countries shows that although each of the countries has experienced a substantial loss of highly qualified individuals through emigration, the picture over the long term is more complex with both short and long term contributions from the emigrants and an increasing number of returnees in the case of China and India.

The importance of domestic and export markets

The four countries have large domestic markets, with South Africa having the smallest, comprised of diverse economic groups and wide-ranging health needs. These markets are the basis for the growth of the pharmaceutical industry in each country. However, whilst all four countries have large and growing domestic markets, the extent to which these markets affect each country's innovative capabilities varies.

Export markets have clearly been an incentive to innovators in India, which is a key supplier to many African countries and increasingly to European and US markets. Significant levels of sales in both domestic and export markets are enabling Indian firms to generate profits to invest in R&D. Indian firms have acquired marketing skills, production capabilities, IP management expertise, and the ability to address regulatory requirements, i.e. manage the determinants of innovation. Consequently, these capabilities generate confidence and entice foreign direct investment which spurs further innovation.

The policy of the Brazilian government to meet domestic demand for Anti-Retroviral (ARV) drugs has promoted increased levels of manufacture and collaboration for *production* of ARVs. However, this has not yet translated into increased *innovativeness* in this therapeutic area. The tropical diseases prevalent in Brazil, together with the biodiversity of its natural resources, has however, spurred the emergence of a biotechnology region in Minas Gerais and the founding of a number of biotechnology firms.

The Brazilian policy of import substitution, combined with a strong public health focus on vaccines, has ensured that there is an identifiable market and production of essential vaccines. The public sector has developed impressive vaccine production capacity. Investment in R&D has been modest, but is now growing, as evidenced by the recent purchase by the Brazilian government of an R&D facility owned by GlaxoSmithKline.

South Africa's public health services, particularly for the poor majority of citizens, are of low quality in relation to other middle income countries, contributing to an under-developed domestic market. Despite having the largest pharmaceutical industry in Africa, South Africa is a net importer of products such as diagnostics and medical equipment for which there is local manufacturing capacity.

Like Brazil, in the area of vaccines, India's large domestic market - and the accumulated ability (including the development of a capable national regulatory authority) to supply foreign markets, has allowed an especially impressive growth in the private vaccine industry. One Indian company is now the world's largest supplier to UNICEF.

In China, the increasingly dynamic import and export markets (coupled with improvements in production, regulatory and scientific investment) may be tightly connected to increased levels of innovation, as the opportunities for generating profits through exploiting such markets become increasingly clear to local industry. However, China has not become as active in the vaccine market as India perhaps as a result of less attention to its regulatory system.

Traditional knowledge and health

With regards to Traditional Medicines, India and China in particular are engaged in large-scale manufacture of medicines to meet the needs of the large populations that use them. Indeed, these areas of knowledge are being integrated into modern medicinal pharmaceutical production, delivery methods and developmental research. This is an area in which the healthy domestic markets may be seen to be spurring overall innovative capability in the biopharmaceutical sectors.

The protection and domestic commercial exploitation of traditional knowledge is now a widely recognised issue in the four countries and is an important issue in many other developing countries. There are two critical issues pertaining to traditional health systems and traditional medicines. The first is to develop policies to protect the traditional knowledge used by communities in developing countries from being

inappropriately exploited by foreign corporations. The second is how the techniques of modern science can be applied to make innovations in traditional medicines.

The Indian report addresses both of these issues. In 2002, India established a national policy on ISM and H (Indian System of Medicine and Homeopathy). This policy sets out how IP of ISM and H will be protected. The policy calls for the recording and documenting of knowledge in this field so that it is in the public domain and cannot be patented. An earlier case where an American company had patented the use of turmeric for the healing of wounds was successfully challenged in the U.S. courts by the CSIR. The challenge was based on the fact that turmeric had been used for healing purposes in Indian medicine for generations. A National Medicinal Plant Board has been established to encourage innovation with herbal drugs. This aims to apply the methods of modern science to improve standardisation, concentrate liquids and improve shelf life.

Not all developing countries are proposing to document and publish their traditional knowledge. The issue is being debated in South Africa. One proposal is for the South African Government to document the technology, but then licence it for commercial gain to South African companies, with the revenues potentially being fed into Community Trust Funds which can decide how best to benefit the Community, e.g. through investment in health-care systems.

China has blended its modern and traditional knowledge to modernise traditional medicines. One of the most successful examples has been with the development of Artemisinin. This is a herbal derivative from the sweet wormwood plant and has for long been used for the treatment of malaria. Now Chinese scientists have isolated its primary active ingredients and produced an effective new drug for malaria treatment. A Chinese firm and foreign firms (especially Novartis) have co-operated to make Artemisinin a first-line treatment for malaria in endemic countries.

Does the private sector accord priority to diseases of the poor?

It is widely assumed that the private sector in all countries is motivated by the maximisation of profits and the closeness of projects to institutional core competencies¹⁷, and that consequently it will direct its innovations to those diseases which affect people who can pay for medication¹⁸ and to technological areas where it has accumulated know-how. Some have queried whether developing country firms may be either more publicly minded, or can find sufficient profit from high volume production that they will produce drugs and vaccines that will benefit poor people¹⁹.

There is some evidence in the reports that a few companies believe it to be worthwhile to produce high volume low cost drugs. The majority, however, behave as firms in the developed countries and cater primarily for individuals (and countries) that can afford to pay high prices. The main evidence for this conclusion comes from the Indian report. A table in that report shows that of some 50 drugs in the pipeline of Indian pharmaceutical firms less than 5 are drugs or vaccines which address the diseases of the poor.

It seems that even in developing countries it will be necessary for the government to introduce policies that will provide incentives to the private sector to contribute more to the development and manufacture of technologies for diseases of the poor. These should include schemes that would guarantee public purchase of new drugs if developed and support for Public Private Partnerships to develop and manufacture drugs. Each of the four countries considered in this study are pursuing these and related policies.*

IP management and licensing practices to acquire and develop knowledge

As South Africa and Brazil import relatively high levels of technology compared to India which increasingly generates its own, there is a relative lack of experience in outward licensing. In contrast, India has begun to license its technologies overseas, leading to increased IP capability. Work in India to develop IP policies and systems is enabling classification of Traditional Medicines for protection of knowledge and may be an important source of revenue and innovative activity. China has much foreign direct investment (FDI) so has benefited from learning from use of the inward flow of technologies, but has much less experience in managing IPs.

Despite an identified need for improvement, India has relatively good technology transfer and negotiations skills, fostered by involvement in partnerships overseas. Brazil's skills are not refined in this area due to a lack of experience in exporting home-grown technologies. However, several recent contracts between the private and public sectors have been signed to foster increased access to ARVs. Brazil's strength and experience lies also in negotiations at the international level and mobilizing developing countries to ensure their rights are protected against technologically and economically stronger powers, e.g. the US.

South Africa is relatively experienced with international research partnerships but not with managing negotiations of IPs. Despite being TRIPS compliant for some time and having a relatively evolved IP system, South Africa is new to the area of technology transfer, and only a few institutions have any capability. Indeed, awareness of technology's role in competing globally is rising from a low level in South Africa. As such there is a reliance on importing international sources of technology and a low level of indigenous technology development partnerships, in comparison to India (which is at the opposite end of the spectrum in this regard). However, relatively high levels of international and regional research partnerships have lead to higher levels of learning in South Africa, which is harnessed by access to up-to-date knowledge thanks to good information and communication technology.

Patents, TRIPS and innovation

* Both the large multi-national (MNC) pharmaceutical companies and smaller biotechnology firms have displayed keen interest in certain product development PPPs, and Moran's work (2005) reveals that firms in developing countries see an opportunity for profit with \$100M markets that have otherwise been too small and risky for the MNCs.

Despite a relative lack of experience in technology transfer, South Africa's IP systems are possibly the most advanced and well-developed among the four countries, although this is not matched by its innovation capabilities as measured in terms of output of new biomedical therapeutics, diagnostics or vaccines (as measured in both new product introductions and patents). In contrast to Brazil, foreign businesses have a greater level of confidence in the South African IP system. Despite this greater level of confidence, there is a dearth of private sector local or foreign investment in innovative activity. This circumstance reinforces the notion that IP is only one of a range of determinants of innovation and probably not the most important. In health, the existence of markets is the most important followed by support for R&D.

All four countries are now TRIPS compliant. As a result of measures taken to strengthen patent regimes and to increase research capabilities, patenting has risen in all four countries, although, measured per capita, remains relatively low in South Africa and Brazil. This lack of growth reflects a number of factors including brain drain, emphasis on academic rather than commercial objectives, and relative importance accorded to patents. It is also a result of the relative lack of corporate (private sector) investment in R&D, combined with the resilience of the 'publish or perish' paradigm at universities which lowers incentives to patent and often hinders the innovation process.

It is unknown what impact TRIPS will have on these four countries in terms of investment in research, innovation of new health technologies, and prices of proprietary products. Some predict that Brazil, South Africa, India and China will face a 'survival of the fittest' scenario whereby non-innovators will fail. Companies without R&D and without the ability to manage IP will fall by the wayside, be purchased or become contract manufacturers of non-proprietary products. India's patent system is relatively cumbersome but patenting is increasingly steadily; Brazil's is slow and under-resourced and patent activity still remains low; China's is evolving slowly but at an acceptable pace whilst patenting is rising steadily; South Africa's system appears to be effectively operated but only deals with low levels of patenting.

It appears that achieving TRIPS compliance has led to some increased foreign investment and a higher level of international partnerships in India and Brazil, and, to a lesser degree, China. There are fewer signs of this in SA.

All four countries have included some TRIPS flexibilities such as compulsory licensing in their IP laws, but none of the flexibilities are being applied.

The Compulsory Licensing (CL) provisions in India are perceived as cumbersome and thus not yet an effective safeguard against high pricing of on-patent essential health products (however this is under review). India's pricing controls mechanisms are, however, empowered to prevent high prices (and reduced access to medicines for the poor) that arise from respecting product patents. Its effectiveness is not yet proven, but the government's intention is to strike a balance between stimulating innovation and investment, and human welfare (access to medicines).

As regards CL, Brazil has proven notable due to its ability to use it as a threat to MNCs, which has led to the voluntary lowering of prices on essential pharmaceutical

products. No other country has instituted compulsory licenses, but all have integrated them into their IP laws.

Increases in –and support for - technology transfer, one of the TRIPS provisions, is not yet manifest in any of the four countries. India, however, is witnessing increased foreign activity in the country, including increased R&D partnerships with local firms in tropical and infectious disease research. TRIPS compliance is acting as a support to other incentives to foreign investors, such as relatively cheap and sophisticated human capital, access to a diverse ethnic populations beneficial for clinical trials, and availability of supporting contractors who recognise the importance of technological development in economic success and have experience of dealing with northern business culture thanks to the brain drain of previous decades.

From the analyses provided, the patent system does not appear to have affected the conduct of basic research in any of the four countries studied, although there is a dearth of specific data to verify this.

It is clear that, like in India and Brazil, prior to the strengthening of the patent system in China the government was concerned with making public health products available and affordable to the poor (revealed explicitly in its investments in national institutes dedicated towards the development and manufacture of biological products in China and Brazil and in the 1970 India Patent Act in India). The notable difference brought about by the strengthening of the patent system, however, is manifest in the increase in the volume, distribution and quality of applied research, leading to an actual increase in marketable health product innovations by these countries. That is, there are more firms investing higher amounts of time and money into product innovation. The IP system is believed to have reinforced the move towards product R&D, but cannot be said to be wholly responsible for it.

As regards South Africa, because of the unfavourable investments conditions^{*}, the patent system has had a relatively lower effect on innovation in public health products.

The majority of product R&D activity in India and China is for the chronic diseases of the growing middle class markets such as cardio-vascular related ailments, cancer and diabetes, which are accounting for an increased share of the public health burden (relative to infectious diseases)²⁰. We do not yet know whether investment into diseases that have become those of the poor, such as leishmaniasis, malaria, and Chagas (Brazil), will be affected by the market incentives provided by the patent system.

The distribution of research in China has been affected by the opening up of its markets globally (part of which includes, *de facto*, the regulation of the IP system) in that there is an increase in public and private sector product development activity in the area of traditional medicines. This is true of India and Brazil and, increasingly, South Africa.

^{*} Due to issues described in the study such as insufficient funding, inadequate linkage between the private and public sectors and lack of awareness about the importance of science, technology and innovation.

In all four countries, traditional medicines are used by large portions of the population, and have a significant role in public health. Weak patent policies and regulations as regards traditional medicines have led to a loss of materials to foreign research. Increasingly, developing countries are acknowledging the importance of robust and inclusive IP policies in this area to ensure protection of its indigenous and traditional knowledge and, often, return of rewards to communities (sometimes in the form of Trusts funds) that have nurtured this knowledge.

One indication that a reliable patent system may provide an incentive for MNCs to invest some resources in the poor sector of developing country markets – which are characterised by high volume, low profit sales and also affect relatively smaller volumes of wealthy country populations - can be identified in Astra Zeneca's TB research initiative in India. Additionally, the strengthening of China's patent system has, overall, increased levels of FDI, including in pharmaceuticals, although it is not clear whether these new sources of investment have had any impact on innovative activity in relation to public health needs.

It should be noted that an alternative view holds that with a strong patent system in place in developing countries, MNC activities in those countries are being radically reduced as their role in monitoring and policing the activities becomes less necessary. It is too soon to say, however, whether or not those 'policing' activities will in time be supplanted with more innovative investments, although there are clear signs that bioprospecting activities by MNCs in developing countries have been rising as the search for new molecules continues. Additionally, there are indications that clinical trials activities by Northern-based firms (either the MNCs themselves or, increasingly, the Contract Research Organisations (CROs) that they sub-contract) are rising. In some developing countries, interactions with such CROs catalyse learning and familiarity with the regulatory process and international standards in biomedical research, and enhance exposure to issues such as IP management*.

Another effect of the improvement of adherence to IP rules has been the enhanced viability (demonstrated in increased frequency) of collaboration with developed country firms outside the home country. This practice is increasingly being seen in Chinese and Indian firms which are engaging with other firms in countries such as the US and UK. Adherence to patent rules is perceived to enhance the potential to build trusting relationships between partners, and thus enhances opportunities for learning and returning know-how back to the home country. Again, it is too soon to see whether this will be the case, but history reveals that wide-ranging interactions with overseas firms have been an effective mode of learning for technologically emerging economies or IDCs†.

* One notable example of this can be identified in the dispute between the University of Nairobi and the University of Oxford as part of their work for the International AIDS Vaccine Initiative

† One example of this was in the case of Japanese scientists seconded to US laboratories on exchanges, who returned with a wealth of knowledge that enabled Japanese companies to compete directly with US technologies.

In cases of research into infectious diseases, there is relatively little investment or patent activity in these areas – the main reason for this is that patenting is costly, and the expected return from sales of products by MNCs in infectious disease markets is relatively low. As such, there has not been a great deal of patenting activity in neglected disease areas, and so research into such diseases ought to remain relatively unencumbered, although the data is not available to demonstrate whether this is the case.

Main barriers to innovation

Brazil's earlier policies of import substitution meant that whilst, in some areas, e.g. aircraft manufacture, it became technologically self-reliant and scientifically strong, capabilities to interact within global value chains, often important to health R&D, were not developed.

Brazil has faced delays in the development of innovative capability because of a lack of integration between S&T, economic and health policies, i.e. it has failed to address the six determinants of innovation in the framework. A resulting fragmentation between sectors has occurred, and correspondingly, there is a notable lack of capacity in negotiating contracts for technology transfer, which is an essential component of innovation processes and technological upgrading.

In addition, the importance accorded by the Brazilian government to S&T for development has not filtered into the private sector. As such, technological innovation has been less of a priority than straightforward manufacture of generic products, reflected in relatively low levels of R&D investment by the private sector. Similarly, despite strong governmental focus on S&T in South Africa, small and medium size enterprises (SMEs) engage in low levels of R&D.

A lack of adequate effective policies on the part of the South African and Brazilian governments concerning innovation of new products has meant that the 'publish or perish' paradigm in the academic institution remains central, and that protecting inventions, consideration of the commercialisation process, and linkage with the private sector are largely neglected, having an overall negative effect on innovation, the development of spin-out ventures, and product-development contracts. The university sectors in India and China are not producing a significant level of spin-out companies in biotechnology. On the other hand, the presence of an entrepreneurial 'culture', relatively high levels of skilled and inexpensive professionals, and availability of, and support for, ICT, clinical research organizations and regulatory services ensures that a culture of innovation is growing steadily within firms.

Furthermore, 'brain drain' from South Africa has led to a substantial shortage of highly skilled professionals that are essential for innovation in the biomedical sector. In India and China there are substantial and increasing incentives for departed professionals to return. In South Africa, there is an absence of adequate support, human and financial resources, and sectoral dynamism that would allure significant numbers of its departed professionals back.

South Africa also suffers from low levels of engagement in the formal education sector, particularly in mathematics and the sciences. Additionally, low levels of support for education in Brazil means that the R&D-based pharmaceutical sector suffers from a shortage of skilled personnel. In contrast, India and China have high and increasing levels of skilled professionals emerging from relatively well-resourced education sectors.

Despite deep and focused public sector investment in education and biomedical scientific research in the Chinese public sector, the Chinese private pharmaceutical sector remains fragmented and has suffered from substantial shortages of investment capital to undertake risky product R&D. Public sector focus has been strongly on the 'Research' rather than 'Development' end of R&D.

Historically lax IP laws and an absence of effective regulatory processes in China meant that production of generic 'copycat' drugs was widespread and innovation was not a necessary component of competitive market success: as such, the innovativeness of the sector suffered*. With regards to IP regimes, the cumbersome nature of India's existing IP and regulatory system has to a limited extent hampered the pace of innovation. Further, Brazil's IP regime is poorly resourced, slowing patent activity by R&D professionals in the country.

Reliance on imported technologies is also a barrier to innovation in South Africa and Brazil. Furthermore, sporadic and un-sustained government investment in the biomedical R&D endeavour has also hampered the evolution of dynamic innovation processes in Brazil.

* However, with the strengthening of the patent regime due to the implementation of the WTO TRIPs Agreement, a number of Chinese firms appear to have recognised the importance of investing in R&D for survival. There are signs of consolidation within the Chinese industry, which may also increase the levels of investment in innovation.

PART 3 – Implications

We know very little about the way in which specific policies affect innovation and the effective development of a technologically dynamic bio-pharmaceuticals industry in emerging economies, especially with respect to the diseases of the poor. We can see that work to build linkages across sectors, provide investment and develop effective IP systems is important but insufficient without adequate human capital and supporting infrastructures that mitigate risk. History reveals that these are important foundations, which take several decades to reveal their full benefits. More specific research needs to be undertaken to identify which combinations of policies can ensure the emergence of successful pharmaceutical sectors. For instance, we need more clarification on which biotechnology sectors are most dynamic before we can speculate about how innovation occurs.

The four country consultants were asked to suggest implications for other countries and for international organisations about ways to strengthen innovation capabilities. Many of their recommendations were directed to their countries with some having implications for other countries. In this overview report, we summarise the main recommendations which have general significance. We organize these recommendations according to individual determinants of innovation and to achieving dynamic linkage.

Determinants

- Markets: Establish sub-regional pharmaceutical price control mechanisms. TRIPs does not prohibit price controls. But small countries do not have the negotiating strength to impose price controls. It is therefore suggested that developing countries join together to develop regional approaches to price control. Perhaps WHO can help.
- Domestic markets: Even when drugs and vaccines are available there is frequently a problem in marketing these products in rural areas in poor countries. When this is the case local MNCs might be used to help with marketing as they frequently have more market outreach.
- R&D:
 - Provide tax incentives including for small enterprises to invest in new technologies for diseases of the poor.
 - Build R&D facilities
- Manufacture and export markets: Encourage local manufacture of off patent drugs to provide regional needs.
- IP management:
 - Governments should develop greater clarity about, and competence for making use of the compulsory licensing clauses in TRIPs.

- Improve the capacity of developing countries to negotiate on intellectual property issues with MNCs and in international fora such as WTO.
- Niche products that take advantage of relative ease to address issues of R&D, markets, manufacturing, IP management and regulation. There is a strong case for developing countries to develop innovative capability in diagnostics.

Promote dynamic linkage

- Mashelkar has proposed that governments consider ways of co-ordinating the public sector research in developing countries so that a concerted attack can be made to develop health technologies that would be of particular benefit to poor people.
- Capacity building should include training in innovation management and the delivery for health care services, in addition to support for R&D.
- The firm structure in pharmaceuticals in many developing countries is fragmented. Innovation would be strengthened if there was more consolidation through mergers and acquisition.
- Develop closer relations and information sharing among government departments in order to minimise duplication and competition and promote effectiveness.
- Provide and promote venture capital mechanisms for R&D and manufacture
- Promote local PPPs and establish science parks for R&D and prototype manufacture.

PART 4 – Concluding remarks

In this part, we explore whether a capability to innovate in the development and manufacture of drugs, vaccines, diagnostics and medical equipment in developing countries could provide major health and economic benefits to those countries.

There are four main progressive objectives for innovation in this area. The first objective is to establish manufacturing facilities to produce generic drugs which are competitive in quality and price with generics produced elsewhere. The second objective is to develop and manufacture new drugs, vaccines and diagnostics for illnesses which have largely been neglected by the international pharmaceutical companies, but which are of particular significance for poor people in developing, often tropical, countries. The third objective is to protect and build on indigenous knowledge in health and medicine by a blending of modern and traditional knowledge. The fourth objective is to develop and manufacture new drugs, vaccines and diagnostics for chronic diseases such as heart disease, cancer, and diabetes, which could meet both domestic and international needs.

The evidence from the four countries covered in this study suggests that they are making good progress in meeting objectives one and three. There has been some progress in meeting the second objective, especially through public sector interventions. There is also a substantial amount of work trying to meet the fourth objective of addressing chronic diseases. In this area the pioneering work of South Africa in heart transplants is well known. Some 90% of all Indian private sector drugs in the pipeline are for chronic diseases, and Chinese regulators have just approved the first gene therapy cancer drug*.

In short, the lessons from the four countries are quite encouraging as to the health and economic benefits to be derived from building innovative capacities. It is likely that even more benefits would flow from a more cohesive set of policies to further develop national health innovation systems in each country. This will require them to identify their own determinants of innovation, and for this they could usefully apply our proposed framework of six determinants.

Similar advice to strengthen innovation capabilities in the health area could be given to other developing countries with relatively advanced scientific and technological capabilities. Mexico, Argentina and possibly Indonesia would fall into this category.

It is less clear as to what recommendations can be made to the scientifically weaker countries which do have some area of public research strengths, but have little research and development capability in the private sector. Perhaps these countries might explore developing collaborative programmes with more scientifically and technologically advanced countries than themselves so that useful research results from these countries can be exploited elsewhere for mutual benefit.

* Financial Times, April 1st 2005

References

- ¹ Kettler, H. (2000), "Narrowing the Gap between provision and need for medicines in developing countries", Office of Health Economics (OHE), London, UK
- ² Report of the Commission on Macroeconomics and Health (2004)
- ³ Mashelkar, R. A. (2005) "India's R&D: Reaching for the top". *Science*, Vol.307, Issue 5714, p.1415-1417, 4 March 2005
- ⁴ Lundvall B.A. (ed) *National Systems of Innovation : Towards a Theory of Innovation and Interactive Learning* (Pinter publishers, London, UK 1992)
- ⁵ Bezanson, K. and Oldham, G. (2005), "Rethinking Science Aid", SciDev.net, Editorial, January 2005, www.scidev.net
- ⁶ Mansfield, E. (1991), "Academic Research and Industrial Innovation", *Research Policy*, 20(1), pp. 1-12
- ⁷ OECD 1994 Nation systems of innovation: general conceptual framework. OECD, Paris, France DST1/STP/TIP(94)4.p.3
- ⁸ National Academies of Science, (1996) "Prospectus for National Knowledge Assessment", National Academies of Science, Office of International Affairs, 1996, www.nas.edu
- ⁹ Pammolli, F. and Riccaboni, M. (2000), "Technological Competencies in Networks of Innovators – The case of Biopharmaceuticals", http://www.unisi.it/epris/abstract/pdf/paric_netcomp.pdf
- ¹⁰ Mahoney, RT. "Determinants of Innovation: A Proposed Framework. PowerPoint presentation". Bellagio. May 2004.
- ¹¹ Mahoney RT, Lee K, Yun MK. "Intellectual property, drug regulation and building product innovation capability in biotechnology: the case of hepatitis B vaccine in Korea". Submitted, 2004.
- ¹² Thorsteinsdóttir, H., Quach, U., Martin, D. K., Daar, A.S. & Singer P.A. (2004), 'Health Biotechnology Innovations in Developing Countries', *Nature Biotechnology*, Vol. 22, Supplement, December 2004
- ¹³ 'Third-world biotechnology: Southern comfort, Eastern promise', *The Economist*, December 11, 2004

¹⁴ Morel, C. et. Al, (2004) “Health Innovation in Developing Countries to Address Diseases of the Poor”. Unpublished report based on Discussions in Bellagio, May 2004

¹⁵ Nelson R.R. (1977), “The Moon and The Ghetto. An Essay on Public Policy Analysis”, WW Norton, New York, USA

¹⁶ Mashelkar (2005), see iii. Above

¹⁷ Patel, P. and Pavitt, K., (1997) “The technological competencies of the world's largest firms: complex and path-dependent, but not much variety”, *Research Policy*, Vol. 26, Issue 2, May 1997, Pages 141-156

¹⁸ OHE, Kettler (2000), see i. above

¹⁹ Prahalad, C.K., (2005), *The Fortune at the Bottom of the Pyramid: Eradicating Poverty through Profits*, Wharton School Publishing, Upper Saddle River, New Jersey.

²⁰ World Health Organisation (WHO), World Health Report, (2004)