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**REPORT OF THE COMMISSION ON INTELLECTUAL PROPERTY RIGHTS,
INNOVATION AND PUBLIC HEALTH**

The Director has the honor to transmit to the 47th Directing Council of PAHO, 58th Session of the WHO Regional Committee for the Americas, the Report of the Commission on Intellectual Property Rights, Innovation and Public Health.

Public health

Innovation and Intellectual Property Rights

Report of the Commission on Intellectual Property Rights,
Innovation and Public Health

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¹ All Commissioners were appointed in their individual capacity and not as representative of an institution or government. The Commissioners have disclosed any conflicts of interest to the other members and to the WHO Secretariat.

Terms of Reference

- Summarize the existing evidence on the prevalence of diseases of public health importance with an emphasis on those that particularly affect poor people and their social and economic impact;
- Review the volume and distribution of existing research, development and innovation efforts directed at these diseases;
- Consider the importance and effectiveness of intellectual property regimes and other incentive and funding mechanisms in stimulating research and the creation of new medicines and other products against these diseases;
- Analyse proposals for improvements to the current incentive and funding regimes, including intellectual property rights, designed to stimulate the creation of new medicines and other products, and facilitate access to them;
- Produce concrete proposals for action by national and international stakeholders.

Origins

In May 2003, WHO Member States agreed at the World Health Assembly to set up a time-limited body to consider the relationship between intellectual property rights, innovation and public health. The operative part of the text of the resolution establishing the Commission (WHA56.27) read as follows:

"...collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries..."

The Commission was established by the Director-General of WHO in February 2004.

The Commission was supported by a small Secretariat in WHO under the overall direction of Dr Tomris Türmen, representative of the Director-General. Dr Charles Clift was Secretary of the Commission.

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PREFACE

Against the background of an ongoing international debate concerning the relationship between intellectual property rights, innovation and public health, in international organizations and more generally among governments and civil society organizations, the World Health Assembly decided in May 2003 to give an independent Commission the task of analysing this key issue.

The World Health Organization considered that its mission demanded it should play a part in this debate, with the objective of illuminating how intellectual property rights might affect public health. There was the need for governments in the north and south, pharmaceutical companies, scientists and other stakeholders to consider how diseases which disproportionately affect developing countries could best be addressed, and to seek solutions.

Our terms of reference made it clear that the focus of our enquiry should be the development of new diagnostics, vaccines and medicines to treat these diseases. But we quickly concluded that innovation was pointless in the absence of favourable conditions for poor people in developing countries to access existing, as well as new, products. The price of medicines is an important factor in determining access, but so also are poverty and the lack of infrastructure for delivering health care to poor people. It is not just neglected diseases, but rather neglected people, that should be our main concern.

The international debate has strengthened awareness and produced some very positive effects. Many stakeholders have responded to the challenge of promoting more research and development (R&D) relevant to the needs of developing countries. New partnerships have been formed, and initiatives taken, to create new products for developing countries, and to promote their delivery.

Resources have been mobilized on an unprecedented scale from charitable foundations for these purposes. Governments have also contributed to the financing of R&D and, in ways they have not done before, to the purchase of vaccines and medicines for the treatment of diseases prevalent in developing countries. Nongovernmental organizations have played an important part in sustaining this impetus through their own field programmes and through their advocacy on behalf of the sick in developing countries. Industry has created new programmes of R&D devoted to the specific needs of developing countries. Private–public partnerships for product development are the most visible manifestation of collaboration between the different partners to promote relevant research and development for diseases that predominantly affect developing countries. All this has created a real momentum of change, but it would be complacent to think that it is sufficient, or commensurate with the scale of that suffering.

It is in these circumstances that our Commission has undertaken its work – encouraged by willingness of so many to respond to the plight of sick people in developing countries suffering from preventable and treatable diseases. Even so, we noted not only the great possibilities offered by recent and ongoing scientific

advances, but also the difficulty of translating them into products and delivering them in ways that can benefit poor people. It is overcoming this divide, between the possibilities offered by science and the lack of present means to realize them, that animates our report.

What value can we add to this debate from the perspective of public health? We thought it necessary to look at the bigger picture. Even if our mandate referred principally to intellectual property rights, we had to examine many other factors that contribute to the improvement of public health in developing countries. We placed this issue in a broader perspective, including for example regulation, and issues such as the importance of political commitment, in both developed and developing countries, in promoting access to new and existing products. We analysed the complexity of scientific challenges in biomedical innovation and sought reasons why, in spite of a greater effort, R&D has not yet produced the results hoped for, or even expected, for the people of developing countries.

Intellectual property rights are important, but as a means not an end. How relevant they are in the promotion of the needed innovation depends on context and circumstance. We know they are considered a necessary incentive in developed countries where there is both a good technological and scientific infrastructure and a supporting market for new health-care products. But they can do little to stimulate innovation in the absence of a profitable market for the products of innovation, a situation which can clearly apply in the case of products principally for use in developing country markets. The effects of intellectual property rights on innovation may also differ at successive phases of the innovation cycle – from basic research to a new pharmaceutical or vaccine. We considered the impact of TRIPS, the flexibilities in TRIPS confirmed by the Doha Declaration, and also the impact of bilateral and regional trade agreements as they might affect public health objectives.

Whereas there is an innovation cycle in developed countries which broadly works to provide the health care required by their inhabitants, this is far from being the case in developing countries to meet the needs of their people, in particular poor people. Our task was to consider how this difference might be addressed.

In successive phases of the innovation cycle – from fundamental research to the discovery, development and delivery of new products – the multiplicity of financial and other incentive mechanisms, and the scientific and institutional complexities of biomedical innovation have had to be considered. At each phase intellectual property rights may play a greater or lesser role in facilitating the innovation cycle. Other incentive and financing mechanisms to stimulate research and development of new products are equally necessary, along with complementary measures to promote access.

In spite of the progress made in the last decade, exemplified by the formation of numerous new public–private partnerships and greatly enhanced funding from foundations and governments, the basis for continued progress in the development of new products needed by developing countries remains fragile. To assure their sustainability, and guarantee that medicines, vaccines and diagnostics produced reach the people who are in need of them, additional efforts are needed. Much more needs to be done to increase the funds available on a sustainable basis and to promote

synergy among the efforts of the different partners. Governments have the major responsibility to mobilize funds and promote new financing and incentive mechanisms to meet our shared goals.

WHO deliberately constituted the Commission to bring together a large spectrum of different experiences, opinions and scientific disciplines. A necessary prerequisite for our work was for different points of view to be declared and interdisciplinary exchange to occur, before common denominators could be identified. We tried to achieve this through an extensive process of consultation and research.

The Commission held its first meeting in Geneva in April 2004. Subsequent meetings were held in Washington, DC (October 2004), Rio de Janeiro and Brasilia (February 2005), and Brussels (March 2005) where there were also intensive interactions with stakeholders. Further meetings were held in Geneva (June and September 2005, January 2006).

Members of the Commission also met stakeholders in other cities: Ottawa (October 2004), Mexico City and New Delhi (November 2004), and Johannesburg and Pretoria (May 2005). I also participated in a dialogue with leaders of the pharmaceutical industry at the World Economic Forum in Davos in January 2005.

We held a series of workshops and an open forum at WHO in Geneva in early summer 2005. Our web site, and the associated electronic discussion forum, has also proved a useful means of stimulating constructive debate and dialogue. We also received nearly 50 submissions from individuals and organizations.

We commissioned 22 studies to inform ourselves about the state of knowledge, and to generate some new evidence, allowing us to enlarge somewhat the knowledge base on intellectual property and health. However, we had neither the means nor the time to undertake in-depth studies, while the field of intellectual property is continually evolving in many ways, including as a result of TRIPS, the Doha Declaration and new bilateral treaties covering intellectual property rights. Thus the evidence is necessarily imperfect, but reflects our state of knowledge in 2005.

We would like to recognize the contribution of those who have enriched the Commission's work, as an expression of their commitment to the fight against diseases that disproportionately affect developing countries. This includes, not least, our principal sponsors, the governments of Switzerland and the United Kingdom of Great Britain and Northern Ireland, the Ford Foundation and, of course, the World Health Organization.

Our efforts are now complete. This report is the result. All members of the Commission have played a part to the very end in shaping this report. I think the report is a substantial one. Inevitably there have been compromises which reflect the different strands of opinion present in the Commission. It is no surprise, given that members of the Commission exercised and continue to exercise diverse responsibilities in different fields (the pharmaceutical industry, public-private partnerships, government departments, research institutions, regulatory authorities,

and medicine), that some of us would have preferred different emphases or analyses at particular points.

The Commission accepts this report as a solid contribution towards continued international dialogue, and progress towards the objectives for which the Commission was established. However Carlos Correa, Trevor Jones, Fabio Pammolli, Pakdee Pothisiri and Hiroko Yamane have expressed specific concerns which are set out briefly in the Annex to this report.

Our own experience reflects a more general one: that finding a way forward depends on overcoming differences concerning the appropriate road to take. Even so, I am persuaded that the time for action is now favourable, and the need urgent. Never before have the same possibilities existed to address the problems of public health of the developing countries, and more particularly of their poor populations: heightened international consciousness, the possibility of additional financing for development, new scientific advances and new institutional forms, such as public-private partnerships. Each one of these four elements is essential, and interdependent. If one of them suddenly weakens, the current momentum, still insufficient, could be lost. It is in the hope of contributing to this synergy that we submit our report to the World Health Organization, which we hope will carry this beacon forward.

Ruth Dreifuss
Chairperson of the Commission

CHAPTER 1

THE HEALTH INNOVATION CYCLE: MAKING IT WORK FOR POOR PEOPLE

INTRODUCTION

The world faces a fundamental dilemma. In recent years there has been a rapid increase globally in technological and economic potential, implying an enhanced ability to overcome problems related to poverty and poor health. But there has also been an actual deterioration in health status in many developing countries, largely as a result of HIV/AIDS but also because of a resurgence in other infectious diseases and a growing burden of noncommunicable diseases.

In the past 25 years, scientific and technological changes have accelerated. Just 25 years ago, the personal computer was in its infancy, as was the biotechnology industry. Genomics barely existed. The advances in biotechnology, underpinned and enabled by the parallel revolution in digital information technologies and the Internet, have opened up enormous opportunities to promote human health.

Throughout the world, economic policies have moved in the direction of liberalization since 1980, and international institutions (particularly Bretton Woods) have reflected this change in economic philosophy in their advocacy and lending policies. During the same period, the world has seen the fall of the Soviet bloc of centrally-managed economies and the pursuit of liberalization policies in China and India, the world's two largest developing economies. These events continue to have a massive impact on the structure of the world economy.

It was within this context that the World Trade Organization (WTO) was created in 1995 as a global body to promote liberalization of trade in goods and services. Of particular importance for our enquiry, the global application of minimum standards for intellectual property under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) has been the subject of controversy, particularly in regard to its potential impact on public health. As a result of this controversy, governments meeting at Doha in 2001 clarified some aspects of the relationship between the TRIPS Agreement and Public Health in the Declaration on the TRIPS agreement and public health.

HEALTH, WEALTH AND POVERTY

The impact of these economic and political trends on global health is complex. While the relationship between poverty and globalization is beyond the scope of this report, evidence that correlates poverty with high disease burden is compelling and stands at the centre of the issues we are addressing. Poverty, disease burden and research capacity all intersect to create an array of challenges and opportunities for countries. Poverty affects purchasing power, and the inability of poor people to pay reduces effective demand, which in turn affects the degree of interest of for-profit companies.

The complexity of factors that affect the ability of poor people to benefit from both the potential, and the actual, fruits of progress in health-related research should not be underestimated. By 2003, the number of people living in developing countries had grown to an estimated 5.3 billion – more than 80% of the total world population of nearly 6.3 billion (1). The World Bank categorizes developing countries as low or middle income countries, where (in 2004) low income countries had a per capita income of US\$ 825 or less, lower middle income countries up to US\$ 3255, and upper middle income countries up to US\$ 10 065 (2). These are the definitions we use throughout this report. Within the category of developing countries, there is thus a wide spread (more than ten-fold) in average national incomes, while the degree of social and economic inequalities also varies widely within countries. This heterogeneity has important implications for our analysis, because not only do countries have different disease burdens, they also have widely varying resources and capacities to address them.

Although economic status is a very important determinant of health status, both between countries and within countries, it would be a mistake to be too deterministic. Countries with quite high levels of per capita income may have lower indicators of health (such as child mortality or longevity) than countries further down the income scale. The pursuit of appropriate policies in terms of the delivery of health care, and of other correlates of good health such as water and sanitation, can make a large difference to health status even at low levels of per capita income. As Marmot notes:

...there is little correlation between gross national product (GNP) per person and life expectancy. Greece for example, with a GNP at purchasing power parities of just more than US\$ 17 000, has a life expectancy of 78.1 years; the USA, with a GNP of more than \$ 34 000, has a life expectancy of 76.9 years. Costa Rica and Cuba stand out as countries with GNPs less than \$ 10 000 and yet life expectancies of 77.9 years and 76.5 years... There are many examples of relatively poor populations with similar incomes but strikingly different health records. Kerala and China, famously, have good health, despite low incomes. The social processes that lead to this beneficial state of health need not wait for the world order to be changed to relieve poverty in the worst-off countries (3).

Table 1.1 Proportion of disability-adjusted life years (DALYs) lost by disease group, 2005 (% of total DALYs lost)

Cause	High income	Low income	Low and middle income countries by WHO region ^a					
			African	Americas	South-East Asia	European	Eastern Mediterranean	Western Pacific
Communicable ^b	5.6	53.5	71.7	21.8	39.3	12.1	43.6	18.7
Non-communicable	85.7	35.0	19.2	62.4	47.1	71.5	43.3	67.0
Injuries	8.7	11.5	9.1	15.8	13.6	16.4	13.1	14.3

^a For more information about WHO regional classification, see http://www3.who.int/whosis/member_states/member_states.cfm?path=whosis,inds,member_states.&language=english.

^b Includes maternal and perinatal conditions, and nutritional deficiencies.

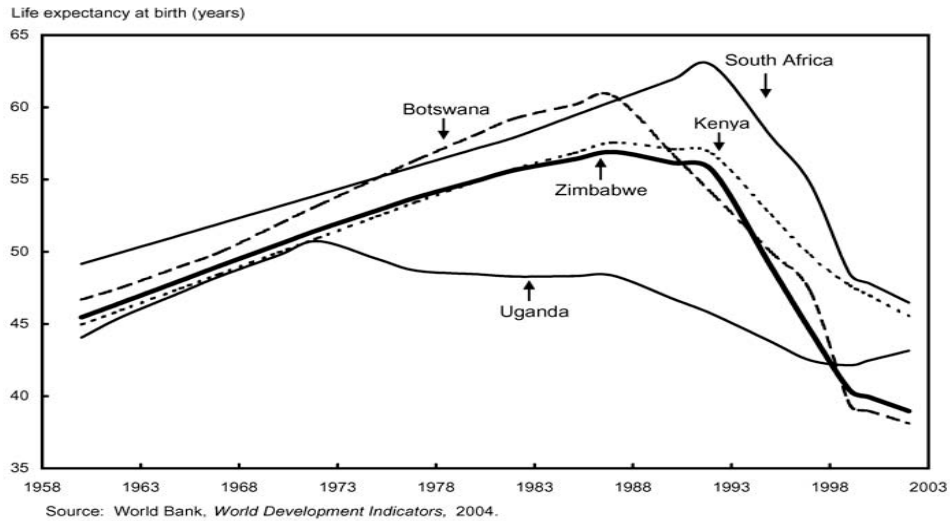
Source: reference (4).

CHANGING DISEASE TRENDS

At the same time as major changes in the global economy and in technologies have been taking place, we have seen the emergence of the HIV/AIDS pandemic beginning in the early 1980s, which has been accompanied also by the resurgence of tuberculosis (TB) and, separately, malaria in the developing world in the past 20 years or so. There are many possible indicators of the impact of these trends, but none more dramatic than the wholesale reversal of life expectancy in badly affected countries, which until the late 1980s or early 1990s had been on a steadily rising curve (Figure 1.1). Overwhelmingly it is countries in Africa and in Eastern Europe that have suffered from this increase in adult mortality. The probability of dying between the ages of 15 and 60 years in Africa has increased since 1990 for both males and females, largely as a result of HIV/AIDS, while in all other parts of the world (apart from Eastern Europe) mortality rates have continued their long-term decline.

Worldwide, so-called diseases of poverty (i.e. communicable, maternal, perinatal and nutrition-related diseases) contribute to over 50% of the burden of disease in low income developing countries – nearly ten times higher than their burden in developed countries. WHO projections of the burden of disease up to 2015 indicate that population ageing and other factors will increase the importance of noncommunicable diseases globally. In developing countries, both the proportion of older people and of noncommunicable diseases are rising more rapidly than in developed countries. Death rates from noncommunicable diseases will remain much higher in developed countries than in developing countries for the foreseeable future, but noncommunicable diseases are now the predominant cause of disability-adjusted life years (DALYs) lost in most developing country regions, with the notable exception of Africa (see Table 1.1) (4). This means that, in contrast to developed countries, developing countries are increasingly suffering from the *double* burden of disease because of the continuing scourge of communicable, maternal, perinatal and nutritional diseases, combined with injuries and noncommunicable diseases.

Figure 1.1 Changes in life expectancy in selected African countries, 1960–2002



Source: reproduced, with permission, from reference (5).

As regards communicable diseases, these are, and will remain, far more devastating – in terms of mortality or lost DALYs per capita – in developing countries than developed countries (Table 1.2). Nevertheless, deaths from communicable diseases in developing countries are projected to fall 13% by 2015, despite HIV/AIDS. Partly as a result, deaths from noncommunicable diseases in developing countries are projected to be more than twice as high as those from communicable diseases by 2015.

Regional factors are also very important. The proportional burden from infectious diseases combined with maternal, perinatal and nutritional conditions in sub-Saharan Africa is substantially greater than that found in low income countries as a whole, largely as a consequence of the HIV/AIDS epidemic ravaging the African continent. Particular groups are also highly vulnerable to ill-health and mortality. At the heart of the high-level global commitments agreed upon at the start of the new millennium were reducing child mortality and improving maternal health.

Every year there are 529 000 maternal deaths, and no less than 3.3 million babies are stillborn, 4 million die within 28 days of birth, and a further 6.6 million young children die before their fifth birthday (10). Today, 58% of malaria cases occur in the poorest 20% of the world's population, a greater proportion than that of any other disease of major public health importance in developing countries – and among poor people, the hardest hit by far are sick children and pregnant women (7). Meanwhile, rotavirus is the most common diarrhoeal pathogen in children around the world, but 82% of rotavirus deaths occur in the world's poorest countries (8). Furthermore, 80% of cervical cancer cases are in the developing world, where it is the leading cause of death from cancer for women, but it has been estimated that only about 5% of women in developing countries have been screened for cervical dysplasia in the past 5 years, compared with 40–50% of women in developed countries (9).

Table 1.2 Burden of disease by income group (per head of population)

Cause		Persons, All ages			
		High income 2005	High income 2015	Low and middle income 2005	Low and middle income 2015
<i>Population (millions)</i>		947	976	5495	6121
Total	Deaths^a	859	918	912	903
	DALYs lost^b	126	124	248	232
Communicable diseases^c	Deaths^a	57	55	308	268
	DALYs lost^b	7	5	103	86
Noncommunicable diseases	Deaths^a	753	812	515	545
	DALYs lost^b	108	109	113	115
Injuries	Deaths^a	50	51	90	90
	DALYs lost^b	11	10	32	31

^a Per 100 000 population.

^b Per 1000 population.

^c Includes maternal and perinatal conditions, and nutritional deficiencies.

Source: reference (6).

The *World health report 2005* notes:

There is no doubt that the technical knowledge exists to respond to many, if not most, of the critical health problems and hazards that affect the health and survival of mothers, newborns and children (10).

Even in wealthier countries, there are groups that are clearly worse off. For instance, in the United States of America, diabetes and its complications disproportionately affect African Americans and Hispanic Americans: nearly 12% of the former and 14% of the latter are affected by diabetes, almost double the prevalence among European Americans (11). Aboriginal populations around the world also tend to have very high prevalence of diabetes, attributable to both lifestyle and genetic factors (12, 13).

In summary, the impact of noncommunicable diseases on developing countries has been insufficiently emphasized. Noncommunicable diseases are projected to be responsible for more than twice as many deaths in developing countries in 2015 than communicable diseases. Reducing the very high incidence of communicable diseases in developing countries is an overriding priority, but it is also important to consider how the high burden of noncommunicable diseases in developing countries can be

addressed. The health needs of the poor and vulnerable, in particular women and children should remain a priority.

MANY WAYS TO BETTER HEALTH

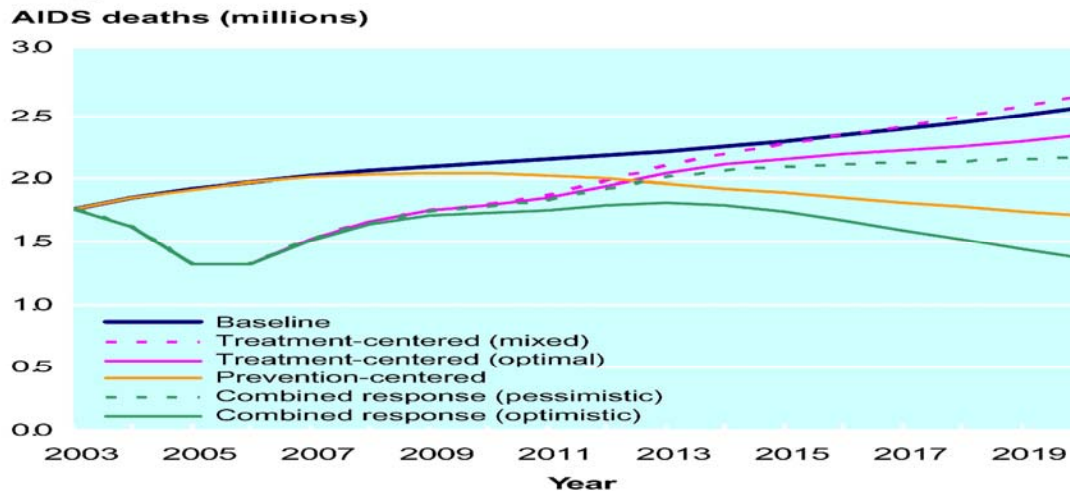
Within the health sector, health outcomes can be pursued through a variety of means, not mutually exclusive, including:

- prevention of various kinds, which itself may involve a choice among biomedical interventions;
- behavioural change or the eradication of a disease vector;
- cure with existing treatment;
- amelioration of conditions with an existing treatment;
- search for an improved method of prevention, diagnosis or treatment.

Achieving sustainable results in the management and control of most diseases requires a strategy that incorporates prevention, diagnosis and treatment, as well as overall health promotion and education. In theory, incentives to promote innovation, including funding for research and development, need to balance the extent to which more R&D would be the appropriate and cost-effective means to achieve given health outcomes (e.g. because adequate treatments do not exist), with the need for more investment in prevention or delivery systems (e.g. where effective vaccines and treatments exist but are not being widely used by those who need them). An appropriate balance, for example, needs to be struck between treatment and prevention in HIV/AIDS. Figure 1.2 predicts that antiretroviral treatment alone will be able to save a large number of lives over the next ten years, but in the long run a combined response of treatment and prevention is the most effective strategy.

Malaria presents another example. Early malaria eradication campaigns successfully employed a combination of spraying, elimination of mosquito breeding sites, and mass treatment to free 500 million people from the threat of disease (14). Today, the African continent, largely left out of eradication campaigns, is home to 90% of the malaria burden and the overwhelming majority of malaria-related deaths. A number of tools exist to prevent and treat the disease, including bednets, indoor residual spraying, and artemisinin-based combination therapies. New possibilities also lie on the horizon, most notably preventive vaccines, but these require the investment of considerable funds and human capital to bring them into being, and then further funds to secure their procurement at levels that will meet global demand. With the reality of limited funding sources, one of the challenges is striking the right balance between investing in the improved uptake of existing knowledge and practices, and investing in avenues that could give rise to important new interventions – and even breakthroughs – of the future. What makes this process even more difficult is the need to make funding and research decisions in the face of considerable uncertainty, because of the high-risk nature of R&D, and far ahead of knowing the actual features of the final product.

Figure 1.2. HIV/AIDS mortality among adults in sub-Saharan Africa, 2003-2020, under different intervention scenarios



Source: reproduced, with permission, from reference (15).

HEALTH, DEVELOPMENT AND THE MILLENNIUM DEVELOPMENT GOALS

The promotion of better health also involves far more than a focus on particular health targets, using health sector interventions. For instance, the goals of improving environmental sustainability are equally important for health and the reduction of waterborne diseases. WHO estimates that over 4% of the global burden of disease is accounted for by diarrhoeal diseases, mainly concentrated in children, and that 88% of this burden is caused by unsafe water supply, sanitation and hygiene (16). A recent estimate suggests that burning wood for fuel in sub-Saharan Africa, apart from contributing to climate change, could cause the premature deaths of 8 million children and 2 million women by 2030 (17).

The reality is that health outcomes depend on a multitude of factors outside, as well as inside, the health sector. In now developed countries, increased life expectancy has been attributed to a wide variety of factors including: economic growth and rising living standards; fairer income distribution; improved nutrition; better education; sanitation and housing improvements; and public health measures and medicines (18,19). While our terms of reference require us to focus mainly on the availability and affordability of medical interventions of various kinds, we need to keep firmly in mind that improved health also depends critically on improvements in the other determinants of health; and that if these are not addressed, then the impact of medical interventions will be limited. It is therefore appropriate that WHO has launched a companion Commission on the Social Determinants of Health which will specifically address policies aimed at reducing inequalities in health within and between countries caused by social conditions (3).

The reduction of poverty itself is therefore one of the most important contributions to improving health. However, while poverty predisposes people to ill-health, ill-health also reinforces poverty. The essential contribution of the WHO Commission on Macroeconomics and Health in 2001 was to demonstrate that investing in health research and health care was central to the promotion of economic and social

development and the reduction of poverty. This message was reinforced by the recent conclusions of the United Nations Millennium Project on what was required if the Millennium Development Goals (MDGs) were to be achieved by 2015 (20). Promoting health and promoting development are complementary – one cannot be achieved without the other. The MDGs, agreed upon at a meeting of world leaders in 2000, represent an historic commitment to a time frame for addressing some of the world's greatest development challenges.

A number of the MDGs specifically relate to health, namely the reduction of child (under 5 years of age) mortality by two thirds between 1990 and 2015 (Goal 4, target 5), the reduction of maternal mortality by three quarters (Goal 5, target 6), halting by 2015 and beginning to reverse the spread of HIV/AIDS (Goal 6, target 7), halting by 2015 and beginning to reverse the incidence of malaria and other major diseases (Goal 6, target 8), and, in cooperation with pharmaceutical companies, providing access to affordable essential drugs in developing countries (Goal 8, target 17) (21).

There are also other goals that bear directly on the present task. In particular the overarching goal, halving the proportion of people living in extreme poverty or hunger (Goal 1, targets 1 and 2), is central to the improvement of health status in developing countries. Achieving universal primary education (Goal 2) and eliminating gender disparities in education (Goal 3, target 4) are similarly critical for achieving improved health, particularly among girls and women. Quite clearly environmental sustainability, in particular providing sustainable access to safe drinking water and basic sanitation, and improving the lives of slum dwellers, are also directly linked to the reduction of waterborne and other diseases related to poor living conditions (Goal 7, targets 10 and 11).

Moreover, the United Nations Millennium Declaration itself echoes a number of the themes of this report. Section 5 in particular is worth highlighting:

We believe that the central challenge we face today is to ensure that globalization becomes a positive force for all the world's people. For while globalization offers great opportunities, at present its benefits are very unevenly shared, while its costs are unevenly distributed. We recognize that developing countries and countries with economies in transition face special difficulties in responding to this central challenge. Thus, only through broad and sustained efforts to create a shared future, based upon our common humanity in all its diversity, can globalization be made fully inclusive and equitable. These efforts must include policies and measures, at the global level, which correspond to the needs of developing countries and economies in transition and are formulated and implemented with their effective participation (22).

So far, the record in progressing towards the achievement of the MDGs is very mixed. As of 2005, the most prominent shortfall is in reaching the goal of halting and then reversing the spread of HIV/AIDS. There are now over 40 million cases worldwide, and over 3 million deaths annually. Progress in halting and then reversing the spread of TB is hardly better, although North Africa, West Asia, and Latin America and the Caribbean are broadly on track. But there are still some 2 million TB deaths a year, many of them as a result of opportunistic infection in HIV/AIDS sufferers. In respect of malaria, there is still a very long way to go to meet targets in the face of rising

resistance to drugs and other factors. Progress towards the target of reducing child mortality, as noted above, is also very mixed. Apart from 14 countries where downward trends have reversed since 1990, there are 29 countries where rates are stagnating. Overall progress in reducing maternal mortality by three quarters is poor, particularly in sub-Saharan Africa, east and south Asia, and Oceania.

A key conclusion is that innovation for “medicines and other products” must be situated within a wider picture of efforts across sectors to improve health and development. Another is that “other products” should include those for improved diagnosis and prevention – including existing well proven but low-technology interventions that can be brought to bear on complex public health challenges.

While fully recognizing the importance of reducing poverty and addressing the social determinants of ill-health, our emphasis has necessarily to be on the specific contribution that innovation in the public health field can make to the improvement of human health in developing countries, and how the appropriate level and composition of R&D, responding to the needs of developing countries, can be mobilized. Above all, the contribution that innovation can make will be meaningful only if we can find ways to make it affordable and accessible to poor people.

A MORAL IMPERATIVE

Although much of this report is couched in the language of science, medicine, economics or law, it should not be forgotten that there is an underlying *moral* issue. While we have the technical capacity to provide access to lifesaving medicines, vaccines or other interventions, which are indeed widely available in the developed world, millions of people, including children, suffer and die in developing countries because such means are not available and accessible there. Governments around the world have recognized the force of this moral argument, but there is still a large gap between rhetoric and action. In Okinawa in 2000, the G8 leaders said:

Health is key to prosperity. Good health contributes directly to economic growth whilst poor health drives poverty. Infectious and parasitic diseases, most notably HIV/AIDS, TB and malaria, as well as childhood diseases and common infections, threaten to reverse decades of development and to rob an entire generation of hope for a better future. Only through sustained action and coherent international co-operation to fully mobilise new and existing medical, technical and financial resources, can we strengthen health delivery systems and reach beyond traditional approaches to break the vicious cycle of disease and poverty (23).

An acute concern is that of sustainability, particularly in respect of HIV/AIDS treatments. Now that the welcome step has been taken of providing international funds for the treatment of HIV/AIDS, there is an obligation through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), as well as other initiatives such as the United States President's Emergency Plan for AIDS Relief, to sustain that treatment. Donors make annual and ad hoc commitments to the GFATM, while current and future beneficiaries require treatment with antiretrovirals for years or decades if they are to survive. Therefore, the short-term financial obligations are out of kilter with the moral obligation created to continue treatment as medically required. The head of the GFATM noted in 2005:

Scale-up brings the world to a phase of long-term very substantial morally binding commitments. For the first time in the business of development finance, you can't have fashions to move money elsewhere. We have to live with millions of people who will stay on antiretrovirals for the rest of their life. To turn off funding would lead to their death in a few weeks or months (24).

In spite of increased recent contributions to the GFATM, the funds available still fall far short of what is required to meet the needs of those who require access to existing treatments in developing countries. The vision of sustained and coherent international action has not yet fully materialized.

The moral obligation is backed by a *legal* imperative. Most governments have committed to take steps ensuring that various fundamental human rights are fulfilled. Human rights have an authority that is not trivial; most countries have already acknowledged the primacy of human rights by signing and ratifying the international agreements in which they are enshrined, and many have further made provision in national constitutions and legislation (25). In this context, the relevant human right agreed in the International Covenant on Economic, Social and Cultural Rights (article 12.1) is "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" (26). This language reflects the overarching objective in WHO's Constitution, which is "the attainment by all peoples of the highest possible level of health" (27).

Governments' obligations are not meant to be utopian. The notion of progressive realization is an essential part of the discourse on social and economic rights, because it acknowledges the inevitability of resource limitations on governments and other actors. Nevertheless it also imposes a responsibility to move forward in as effective and expedient a manner as possible, and through concrete and targeted measures, towards the realization of these rights (28). At a minimum, human rights, and the right to health in particular, prescribe that States have an obligation to give consideration to the health implications of their policies. Health policies, as well as inter alia those addressing trade, the environment and commerce, should be equally subject to assessments as to their impact on the right to health.

In its General Comment No. 14 on Article 12, the Committee on Economic, Social and Cultural Rights enumerates core obligations, which include the provision of essential biomedical innovations (29). However, the Committee makes it clear that the right to health is not to be understood as a right to be healthy. The right to health contains both freedoms and entitlements. The freedoms include the right to control one's health and body. The entitlements include the right to a system of health protection which provides equality of opportunity for people to enjoy the highest attainable level of health. Moreover, the Committee emphasizes that it is incumbent on States and "other actors in a position to assist" to provide international assistance and cooperation, especially economic and technical, to enable developing countries to fulfill their obligations under the Covenant. Although the General Comments of the Committee do not have legally binding effect, they are considered authoritative guidance on clarifying the contents of rights and obligations enshrined in the Covenant. They therefore constitute an important foundation for arguments that treat access to essential treatments, preventives and diagnostics as a right, and entail

particular obligations on States. Access to these products is, therefore, a legitimate and core component of the right to health, as is the right to benefit from the fruits of scientific progress.

The Covenant also recognizes in Article 15 the following rights and obligations:

1. The States Parties to the present Covenant recognize the right of everyone:
 - (a) To take part in cultural life;
 - (b) To enjoy the benefits of scientific progress and its applications;
 - (c) To benefit from the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.²
2. The steps to be taken by the States Parties to the present Covenant to achieve the full realization of this right shall include those necessary for the conservation, the development and the diffusion of science and culture.
3. The States Parties to the present Covenant undertake to respect the freedom indispensable for scientific research and creative activity.
4. The States Parties to the present Covenant recognize the benefits to be derived from the encouragement and development of international contacts and co-operation in the scientific and cultural fields (26).

For the purposes of this report, a key question relates to the relationship between the set of policies which could stimulate biomedical innovation relevant to developing countries, and the ability of countries to make available the products of innovation, which would contribute to fulfilling people's right to the highest attainable standard of human health.

Governments which have ratified the Covenant have a duty to take concrete steps towards the realization of the right to health, a core element of which is access to biomedical innovations. Moreover, "other actors in a position to assist", whether in

² On 21 November 2005, the Committee on Economic, Social and Cultural Rights at its Thirty-fifth session, clarified, in the General Comment No 17 (paragraph 1), that the rights recognized in this provision are not intellectual property rights: "The right of everyone to benefit from the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he or she is the author is a human right, which derives from the inherent dignity and worth of all persons. This fact distinguishes article 15, paragraph 1 (c) and other human rights from most legal entitlements recognized in intellectual property systems. Human rights are fundamental, inalienable and universal entitlements belonging to individuals and, under certain circumstances, groups of individuals and communities. Human rights are fundamental as they are inherent to the human person as such, whereas intellectual property rights are first and foremost means by which States seek to provide incentives for inventiveness and creativity, encourage the dissemination of creative and innovative productions, as well as the development of cultural identities, and preserve the integrity of scientific, literary and artistic productions for the benefit of society as a whole" (30).

the public or the private sector, share a responsibility to cooperate in the advancement of the right to health.

A framework for analysis

A useful framework for analysis is set out in General Comment No 14, which considers four interrelated components which together define what the right to health means: availability, acceptability, accessibility and quality (29). According to this framework, interventions should be:

- **available in sufficient quantities.** In the first place, the right kinds of interventions should exist. If they do not exist, then the principal challenge is to spur the needed innovation to create a product that fills the identified need. Where a suitable intervention already exists but is still unavailable in adequate supply, the question may be soluble through research – such as by creating a synthetic version of artemisinin, the antimalarial drug, because the natural product is in limited supply. Alternatively, an existing intervention may be inadequate, such as current TB treatments that take six months and are very cumbersome, or the drugs for sleeping sickness. Or an intervention may chiefly require effective procurement strategies for existing products to finance or subsidize the scaling-up of production and distribution, and the putting in place of effective delivery infrastructures.
- **acceptable, both in terms of their usability and their appropriateness, given cultural and other factors.** This requires the right kinds of products, tailored to the specific technical and social needs of the group in question. Knowledge is a critical element of creating acceptable interventions: knowledge of existing gaps in scientific know-how and clinical outcomes, and knowledge of behavioural and cultural norms that prevail within the communities in question. Obtaining this kind of knowledge requires its own kind of research, and relies in many instances on classic epidemiological or social anthropological study to weave together a picture not only of the scale of the impact of a disease on a community but also of means to more effectively achieve uptake of interventions. Education may also be important in addressing lack of acceptability. Health systems research has an important part to play here (31).
- **effective and of good quality.** This requires appropriate standards for testing new products, as well as incentives to conduct clinical trials in key populations. There are particular ethical and technical challenges for the testing of products in pregnant women and very young children, particularly those who are poor and marginalized, which are often the groups that are most at risk. In the present report, this dimension is incorporated into the analysis of acceptability (Chapter 4).
- **the lowest possible cost to facilitate access.** This requires not only the financing of research, but also affordable prices of medicines and the financing of procurement. The first kind of financing drives the direction of research; HIV/AIDS, for instance, has greatly benefited from the active involvement of public sector institutions in setting the research agenda for the development of new products. On the other hand, R&D for noncommunicable diseases has generally been directed at interventions appropriate to conditions in developed countries (with their strong resource position) rather than towards research to develop interventions suitable for

poorer populations in developing countries. Financing – at the other end of the chain – can help with efforts to scale-up and manufacture new products, and with access to existing products.

This schema frames the problem in a way that points to particular gaps and challenges that exist for different conditions, and to appropriate remedies. In addition, it emphasizes the degree to which vulnerable or poorer groups benefit from interventions. It is therefore one that links products with key features of poverty, and focuses the lens on groups of principal interest to the Commission.

Part of what this framework demonstrates is that "access" alone is an inadequate determinant of the extent to which interventions reach the desired groups. Very often, the term "access" is employed in a manner that confounds and obscures problems that are fundamentally different in nature, thereby impeding the application of appropriate remedies. This model provides a useful framework for analysing the nature of the challenges that exist, as well as possible solutions.

DEFINING THE PROBLEM

THE TYPES OF DISEASE

It is necessary to define the scope of the Commission's remit in respect of diseases that "disproportionately affect developing countries". The Commission on Macroeconomics and Health (CMH) in its report distinguished among three types of diseases:

Type I diseases are incident in both rich and poor countries, with large numbers of vulnerable population in each. Examples of communicable diseases include measles, hepatitis B, and *Haemophilus influenzae* type b (Hib), and examples of noncommunicable diseases abound (e.g. diabetes, cardiovascular diseases, and tobacco-related illnesses)...Many vaccines for Type I diseases have been developed in the past 20 years but have not been widely introduced into the poor countries because of cost.

Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in the poor countries...HIV/AIDS and tuberculosis are examples: both diseases are present in both rich and poor countries, but more than 90 percent of cases are in the poor countries...

Type III diseases are those that are overwhelmingly or exclusively incident in the developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). Such diseases receive extremely little R&D, and essentially no commercially based R&D in the rich countries. When new technologies are developed, they are usually serendipitous, as when a veterinary medicine developed by Merck (ivermectin) proved to be effective in control of onchocerciasis in humans...Type II diseases are often termed *neglected diseases* and Type III diseases *very neglected diseases* (32).

The implications of the WHO projections above suggests that many of the CMH Type I diseases are, in fact, taking on the characteristics of Type II diseases – prevalent in

developed countries but beginning greatly to affect developing countries, in particular because of the rapid ageing of populations in developing countries, and because interventions based on developed country situations may not be technically feasible or affordable in developing country settings. Whereas, for example, deaths attributable to heart disease have started falling in much of the developed world (but not eastern Europe) in the past 25 years, this is not the case in developing countries. It is possible that most diseases – that is, diseases across all three types described above – are liable disproportionately to affect developing countries unless measures are taken to prevent, diagnose and treat them in ways that are feasible in the conditions of developing countries. In addition there is a large range of conditions, in particular relating to maternal and child health, and to reproductive health, that deserve special consideration for developing countries because they are major causes of morbidity and mortality for women and children (see Table 1.3).

Our remit is to cover the range of diseases and conditions that currently affect developing countries, from Type I to Type III, taking account of those that will increase in importance in coming decades. The criterion should be diseases or conditions of significant public health importance in developing countries for which an *adequate* treatment does not exist for use in resource-poor settings – either because no treatment exists whatsoever, or because, where treatments exist, they are inappropriate for use in countries with poor delivery systems, or unaffordable. The focus of innovation should not only be on particular diseases that are mainly confined to developing countries, but also on tackling the health problems of developing countries in the light of their circumstances.

Table 1.3 Examples of status quo for Type I, II and III interventions

	Accessible <i>Is it affordable?</i>	Acceptable <i>Is it well-adapted to the clinical setting?</i>	Available <i>Does it exist? If so, is it within reach of poor people?</i>	Quality <i>Is it safe and effective?</i>
Type I (Cervical Cancer)	In situ stage cervical cancer is treatable; invasive stage cervical cancer, where surgery or radiation is unavailable, is fatal. However, costs for both Pap screening and treatment of precancerous conditions, as well as for the treatment of advanced disease (i.e. surgery and radiation) are expensive, some have argued prohibitively so.	The Western model of regular screening of all sexually active women with regular follow-up, and treatment of women with even mild dysplasia is not appropriate for the developing world context. Pap smear programmes are complex and costly to run, and have failed to reach a significant proportion of women in countries where health systems and infrastructure are poor. In addition there are cultural reasons why such programmes may fail, e.g. because of stigma.	80% of cervical cancer cases are in the developing world, where it is the leading cause of death from cancer for women. The Pap smear test, treatment for precancerous conditions, and surgery and radiation treatment for advanced disease exist, and a vaccine for cervical cancer, <i>Cervarix</i> , is currently in clinical trial. But it has been estimated that only about 5% of women in developing countries have been screened for cervical dysplasia in the past 5 years, compared with 40–50% of women in developed countries.	Pap smear screening and treatment of precancerous conditions have resulted in up to a 90% decrease in cervical cancer incidence and mortality in some developed countries (9, 33).
Type II (HIV/AIDS)	The price for lamivudine, stavudine and nevirapine has come down from over US\$ 10 000 per year to approximately US\$ 182 per year for both the original and generic versions of these drugs. Paediatric and other second-line antiretrovirals remain more expensive.	There is a great need to further develop fixed dose combination therapy (because of ease of use, distribution advantages, and affect on compliance), and for adapted paediatric drugs. Current diagnostic tests and monitoring tools, as well as methods for diagnosing opportunistic infections, are relatively difficult to use in poorer settings.	Antiretroviral treatment has extended the lives of HIV-positive individuals in both the developed and developing world. But only 15% (970 000 of 6.5 million) of those needing antiretroviral treatment in developing and transitional economies receive it.	Today, there is inadequate clinical monitoring for side-effects and opportunistic infections. Safety and efficacy of triple-combination regimens for the prevention of mother-to-child transmission in women who do not require antiretrovirals for their own health has not been assessed in resource-constrained settings. There is serious concern about the risk to women if possible toxicity cannot be carefully monitored (34–39).
Type III (Human African Trypanosomiasis)	Several companies have pledged to produce and donate existing medicines for the treatment of human African Trypanosomiasis (sleeping sickness) from 2001 to 2006. Eflornithine is the only trypanosomiasis drug developed in the past fifty years, and is much safer than the arsenic derivative melarsoprol for treating West African trypanosomiasis. *	Case detection is difficult, requiring major human, technical, and material resources (blood samples, spinal tap, etc.). This problem is magnified as the disease primarily affects poor, rural populations, with little access to health facilities. There is a need for new easy to use, accurate diagnostic tests (including ability to determine stage of disease), as well as drugs that can be administered orally.	Currently there is no vaccine or drug available to <i>prevent</i> infection. There are drugs available for <i>treatment</i> of the disease, but these drugs are old, difficult to administer in poor conditions, and not always successful. Trypanosomiasis threatens 60 million people but only about 4 million people are under surveillance and only about 40 000 receive diagnosis and treatment. There are an estimated 300 000 cases per year.	There have been significant concerns about the safety of the drugs used for treatment. For instance, whereas pentamidine (used for treatment of West African trypanosomiasis) is mostly well tolerated by patients, <i>melarsoprol</i> (at present the only drug available to treat the advanced stage of trypanosomiasis), kills one in twenty patients receiving it, and serious neurological sequelae are common side-effects (40–42).

* Production ceased, from 1995 to 2000, until a cosmetic use was discovered for it (facial hair removal).

THE ECONOMICS OF INNOVATION AND ACCESS

World sales of pharmaceuticals are very highly skewed to developed world markets. Table 1.4 indicates that developing countries, accounting for more than 80% of the world's population, are responsible for only about 10% of global sales. However, it should be noted that in terms of volume, the share of developing countries could be significantly higher because average prices of pharmaceuticals tend to be lower in developing than developed countries. Nevertheless, the overall picture demonstrates very clearly the extreme differences in access to health-care products between

developed and developing countries. It is helpful to consider the issues raised from two perspectives: lack of effective demand for products; and lack of supply.

Table 1.4 World pharmaceutical market by region (US\$ billion, ex-manufacturer prices)

Region	2004	2005	Global share of sales 2005 (%)
North America	249.0	268.8	44.4
Europe	169.2	180.4	29.8
Japan	66.1	69.3	11.4
Oceania	7.1	7.7	1.3
CIS ^a	4.2	5.0	0.8
South-East Asia	25.3	28.8	4.6
Latin America	24.4	26.6	4.4
Indian subcontinent	6.6	7.2	1.2
Africa	6.3	6.7	1.1
Middle East	4.7	4.9	0.8
Total world market	562.9	605.4	100.0

^a Commonwealth of Independent States.

Source: reference (43).

Demand

The fundamental problem is the lack of effective demand in the market for products that are required to prevent, treat or cure illnesses that affect poorer people in developing countries. On the one hand, this is evidence that poor people in developing countries are simply not getting the treatments they need, in spite of a much higher disease burden. On the other hand, it is also an indicator of how existing incentive structures encourage companies to invest in the creation of products targeting those with purchasing power, mainly in developed countries.

For Type I diseases, such as diabetes and cancer, companies have a strong incentive to invest in the development of preventive, diagnostic and therapeutic tools oriented towards Europe, the United States and other developed markets. For people living in developing countries, a major problem is the price of medicines and the overall cost of treatment: poor patients most often pay out-of-pocket, and governments generally lack the resources or the will to cover the cost, in whole or in part, of essential medicines on their behalf. There is, therefore, a lack of incentive to invest in the search for preventive, diagnostic and curative interventions adapted to the resources and social and economic conditions of developing countries.

The CMH suggests that, left to market forces, there will be an inadequate volume of research on Type II diseases, such as malaria and TB, and, in some cases, that research is insufficiently attuned to the disease conditions in developing countries. This is not the case where there is significant developed country demand for treatments and vaccines. For example, antiretrovirals would not now be available for use in developing countries without the incentive offered by demand from rich countries. However, this argument does not apply to malaria and TB, where rich country demand is smaller, and is for prophylaxis rather than treatment.

An important point is that the type or strain of the disease in developing countries frequently differs from that in developed countries (e.g. different clades of HIV are common in developing countries, and the immune system may react differently to TB vaccines) (44) so that solutions in developing countries may need to be different. In the case of antiretrovirals, currently available drugs, when used in appropriate combinations, may cover such differences. In the case of vaccines needed by developing countries, including for HIV/AIDS, market forces have generally been insufficient to stimulate R&D. That is why new international initiatives have sprung up in recent years to focus on the development of vaccines (as well as treatments) specifically tailored to developing country needs. Also, because TB and HIV/AIDS are now so commonly found in the same patients, new treatments for TB need to take account of possible interactions with antiretrovirals.

For Type III diseases, such as dengue fever and leishmaniasis, where there is no rich country demand, the problem of lack of incentives for innovation is particularly evident. In some cases, such as ivermectin for river blindness, the product was initially developed to meet veterinary demand, and only latterly for human demand. As noted above, current treatments, such as melarsoprol for sleeping sickness, have serious side-effects. The major challenge is that clinically effective interventions either do not exist at all, or where they exist, are wholly inadequate.

For all types of disease there is a need to find ways to encourage the development of medical technologies appropriate to the circumstances of developing countries. The development of diagnostics, vaccines and treatments need to take account of the resource constraints in developing countries, the social and cultural factors that may affect acceptability, and the implications of inadequate systems and infrastructure for delivery. For example, it is estimated that less than 3% of those who need them in developing countries have hearing aids which may cost from US\$ 200 to US\$ 500. Development of an appropriate and affordable form of hearing aid would be of enormous benefit to the hard of hearing (45).

Where there is no purchasing power – either on the part of the government or the patient – the market is not an adequate determinant of value. Thus too few resources are likely to be devoted to developing drugs, vaccines and diagnostics that address the needs of people living in developing countries, because they are inherently unprofitable, or the relationship between investment and risk, in relation to potential profit, is unattractive to the private sector. The market alone, and the incentives that propel it, such as patent protection, cannot by themselves address the health needs of developing countries. That is the principal reason why new initiatives have sprung up in recent years, such as public–private partnerships.

Supply

In the pharmaceutical industry, the process of drug development typically begins with investigations on the results of basic research largely conducted by public sector research institutions and universities, followed by the synthesis, screening and testing of possible compounds with therapeutic effect (the "discovery" phase). For a promising compound, there follows a period of further chemical and pharmaceutical development. This includes tests for possible toxicity to body organs and how the product is absorbed and metabolized by the body. Extensive tests will also be

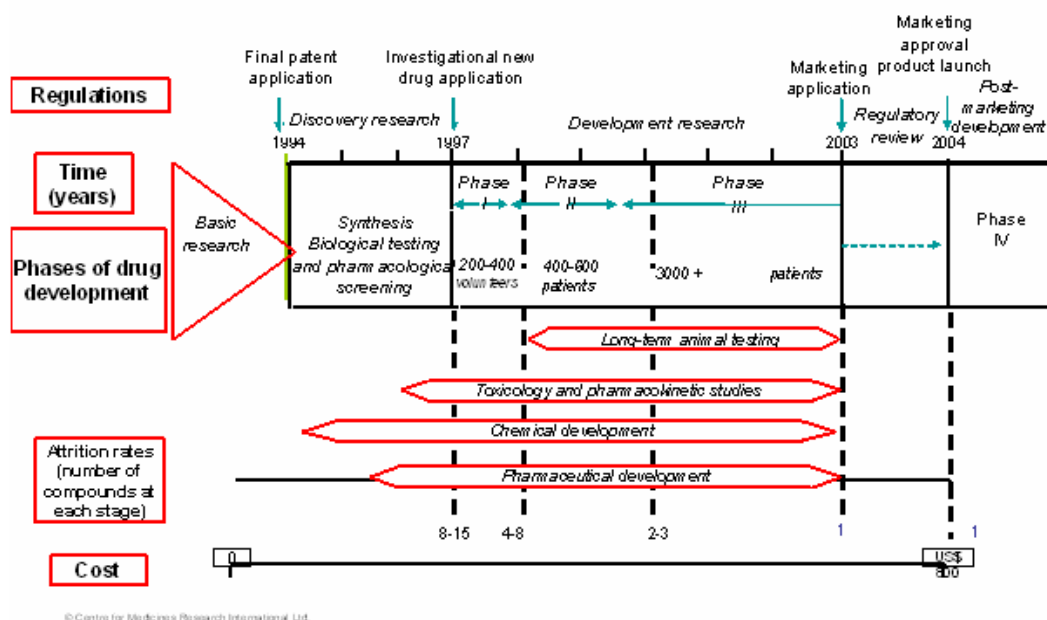
necessary in animal models and finally in humans (the "development" phase). If all these tests are successful and the product meets the standards set by the regulatory authority (that it is safe, efficacious and of good quality), the product can then be made available to patients (the "delivery" phase). At each stage, there is a process of attrition, so that only a small proportion of compounds examined in the discovery phase reach the delivery phase. Even after delivery, further trials may be undertaken for various purposes, including extending the use of a product to new indications, or determining rarer side-effects that may only become apparent when the product is used by large numbers of people.

Thus, drug discovery and development is a complex, lengthy and costly activity. Widely quoted figures for a sample of medicines produced by the industry suggest that the average cost of developing a new drug is US\$ 800 million, or even much more (46). These figures, however, include the cost of success and failure, and the cost of capital, and have been questioned on methodological grounds and because the raw data for independent verification have not been made available (47). Figure 1.3 below, provided by the Centre for Medicines Research International Ltd (CMRI), and based on data collected by CMRI from industry, provides a diagrammatic view of the development process from the industry point of view at a particular point of time.

However, the direct costs of developing a particular drug are much lower depending upon the therapeutic area, geographical focus and regulatory requirements. This is particularly the case for products developed by public-private partnerships as discussed in Chapter 3. The evidence suggests that they may have the potential to develop products at much lower costs than the pharmaceutical industry can, partly because of the nature of the diseases they cover and the prior investment in discovery research in universities, public research institutions and the pharmaceutical industry.

Whatever the exact cost, there is a need to think very seriously about how this cost can be reduced, if such products are to be made available and affordable in developing countries. This involves looking carefully at the process of product development, at the various incentives provided by the market or by governments, and at the way the structure of the industry is evolving. Without doing everything possible to reduce the cost of product development, the chance of these products being accessible to the majority of people in developing countries is much diminished. In addition, it is important that policies ensure that any reductions in cost are passed through to patients in reduced prices.

Figure 1.3. The pharmaceutical industry depiction of the discovery and development of a new medicine.



Source: reproduced, with permission, from reference (60).

Despite high cost and risk, from 1995 to 2002 the pharmaceutical industry was the most profitable industry in the United States, measured by the median net profit after tax as a percentage of revenues. In 2003 it witnessed a decline, falling to third place behind mining, crude oil production and commercial banks, but retained profitability at a margin of 14%, three times higher than the median for all *Fortune 500* companies that year (49). A still authoritative discussion of costs, risks and rewards in pharmaceutical R&D, and a review of the literature, can be found in a 1993 report of the United States Office of Technology Assessment (50). A main issue, from our point of view, is that market mechanisms and incentives, as well as allocative decisions of companies, lead to insufficient investment in R&D specifically directed to the needs of developing countries.

Because the market fails to induce adequate investment in products needed by developing countries, it is necessary that other measures be put in place to promote relevant innovation. While the large-scale pharmaceutical sector remains an important partner in public-private ventures, in practice many collaborations are with small biotechnology or pharmaceutical companies, public sector research institutes or universities, contract research organizations, and developing country partners in the public or private sector (48). Just as the pharmaceutical industry is seeking to reduce costs by partnering more closely with these other industry players, public-private partnerships are perhaps leading the way in developing a new business model. However, they are still at an experimental stage as their sustainability remains uncertain. A response to the problems posed by the lack of innovation on the diseases

of the poor requires a deeper involvement of governments themselves in finding and implementing solutions.

Ensuring adequate supply depends on at least two factors: improving the efficiency of product development; and improving its direction – that is, the extent to which it is oriented towards social goods and not only lucrative products. On the one hand, there is the challenge of reducing the cost and the period of product development, in order to generate better products faster and at a lower cost. On the other hand, there is a need to encourage sustainable supply in areas where the market has failed to bring it forth. Ventures already exist to address the important challenges for TB, malaria and HIV/AIDS, which together afflict millions of people worldwide, particularly in developing countries; but nothing yet exists to bring new or adapted tools to developing countries for the other half of their double burden – chronic noncommunicable diseases, such as cancer, diabetes and cardiovascular disease, which in many countries are combining with diseases of poverty to cripple already burdened health systems.

The economic problem is a lack of effective demand for health products needed by developing countries. This means that the market fails to stimulate the development and supply of these goods, or their adaptation to the circumstances of developing countries. It is the responsibility of governments to find solutions to this problem.

THE ROLE OF PATENTS

Patent protection has been historically credited with a variety of functions, the most widely acknowledged of which is the **incentive function**. This justification rests on the hypothesis that, in the absence of patent protection, inventors would be unable to appropriate the returns from their intellectual creations, with negative consequences in terms of innovation incentives for society as a whole. There would be less innovation than society desires. Society is thus ready to grant a time-limited monopoly on new inventions on the assumption that the costs in terms of higher prices to consumers, arising from the monopoly granted, are more than outweighed by the benefits of innovation (51–53).

An implicit assumption in the justification for patents is that they are applied in an economic and technological context where they can induce innovation, principally by the private sector. But the validity of this assumption depends on the context such as, for instance, the nature of the industry concerned (54). The assumption may be generally correct in developed countries and in a few developing countries which have the required capital and innovative capacity, but this is not the case in those developing countries which lack both a significant scientific and technological infrastructure and a private sector capable of innovation. It is also assumed that society at large will be able to benefit from present and future innovation. But where most consumers of health products are poor, as are the great majority in developing countries, the monopoly costs associated with patents can limit the affordability of patented health-care products required by poor people in the absence of other measures to reduce prices or increase funding. Thus the overall effect of intellectual property regimes is context-specific – the impact in a country such as India may differ from that in Thailand or in Ghana.

A second possible function of patents is a **transactional function**. The availability of patent protection has been identified as a necessary precondition, in some cases, for the emergence of markets for technology and specialized technology suppliers. This is not always the case, since there are other mechanisms (such as lead time and advantages over the learning curve) that in some sectors are more relevant than patents. The existence of patent protection over the inputs to a collaborative research endeavour is commonly held as a factor facilitating inter-firm R&D collaboration (e.g. when a company licenses a patented invention to another better able to bring it to market). In practice, the incentive and the transactional functions are intertwined. Patents can facilitate the division of profits among contributors to a given stream of research. This in turn affects the extent of incentives available to successive inventors. The assignment of patent rights may constrain the duplication of innovative effort while preserving, in some cases, sufficient incentives for further product development under the patentee's control. Some studies have shown that strong and broad protection, particularly of early "upstream" research, could also deter downstream and follow-on innovation by successive inventors, limiting technological progress. This is discussed further in Chapter 2 (55).

Patents also perform a **disclosure function**. Disclosure of technical information that would otherwise be kept secret is an important aspect of all scientific research and development and acts as the *quid* for the *quo* of legal protection in a bargain between the inventor and society. It is a requirement that the information disclosed in patent specifications should enable a skilled person to reproduce the invention. In practice, specialist skills, know-how and ancillary technology may also be required to achieve this. Limitations in the patent examination process and the quality of disclosure by the applicant in some cases may not enable reproduction of the invention.

Finally, patents are valuable for their **signalling function**. Possession of patents may serve the purpose of signalling a firm's innovative capabilities and increase its ability to raise the necessary capital, especially through venture capital financing. This function has been particularly crucial in the biotechnology sector, where start-ups rely on their protected intellectual capital to raise funding.

Patent laws are territorial in nature, and their operation reflects national needs and circumstances. Changing circumstances, including economic and technological developments, may require adaptation of the system. The functioning of the patent system has been the subject of a number of studies and reviews. For instance, in the United States recent academic work and reports by the Federal Trade Commission and the National Academy of Sciences have examined a number of ways in which the patent system in that country operates (56, 57, 67). Partly arising from these reviews, and because of pressure from various sections of industry, a bill has now been introduced into Congress seeking to enact various reforms in the United States system (58).

The patent system is subject to strain in some jurisdictions, particularly in adapting to new technologies, such as software and biotechnology. The low standards of patentability applied in some jurisdictions, and shortcomings in the machinery for

examining patents, have led to a proliferation of patents of poor quality or dubious validity.³

In regard to our enquiry, a key issue is whether or how the patent system is relevant to encouraging innovation in the biotechnology and pharmaceutical industries.

For developing countries that are members of WTO, the TRIPS agreement now provides a framework of minimum standards of intellectual property protection, although least developed countries (LDCs) have the option of delayed implementation (until at least 2016 in the pharmaceutical sector). The impact of implementing the TRIPS agreement in developing countries, particularly in respect of access to medicines, has been controversial.

The TRIPS agreement allows countries a considerable degree of freedom in how they implement their patent laws, subject to meeting its minimum standards including the criteria for patentability laid down in TRIPS. Since the benefits and costs of patents are unevenly distributed across countries, according to their level of development and scientific and technological capacity, countries may devise their patent systems to seek the best balance, in their own circumstances, between benefits and costs. Thus developing countries may determine in their own ways the definition of an invention, the criteria for judging patentability, the rights conferred on patent owners and what exceptions to patentability are permitted, provided these are consistent with the relevant articles of TRIPS (for WTO Members). Under TRIPS they may also exempt from patentability, should they so wish, therapeutic methods for the treatment of humans and new indications of known products which amount to a therapeutic method. As also recognized in the Doha Declaration, they may – on various grounds – provide for measures such as parallel imports, government use and compulsory licensing. However, an emerging development is the growing number of bilateral and free trade agreements which include higher standards of protection that erode these flexibilities.

In this regard, several resolutions passed by WHO Member States in 2003 and 2004 have emphasized the importance of the flexibilities in the TRIPS agreement. A resolution of the World Health Assembly in 2004 urged Member States:

...to encourage that bilateral trade agreements take into account the flexibilities contained in the WTO TRIPS Agreement and recognized by the Doha Ministerial Declaration on the TRIPS Agreement and Public Health (66).

In the context of our work one of the important points is that, where the market has very limited purchasing power, as is the case for diseases affecting millions of poor people in developing countries, patents are not a relevant factor or effective in stimulating R&D and bringing new products to market. Moreover, because most poor people in developing countries have to meet the cost of treatments from their own very limited disposable income, in contrast to people in most developed countries where governments and private or government insurance schemes play a major role,

³ The possible implications in respect of pharmaceutical patents are discussed further in Chapter 4.

any impact that patents or indeed other policies may have on prices paid need to be carefully considered.

Intellectual property rights and patents interact in rather complex ways with other policies, both nationally and internationally. While policies on intellectual property rights are national, they have international implications which are now manifested in the TRIPS agreement and in numerous other bilateral and multilateral trade agreements. Nationally, the impact of intellectual property rights may be affected by numerous other policies, including those related to competition, to pricing policies on pharmaceuticals, to government purchasing policies and others.

Intellectual property rights have an important role to play in stimulating innovation in health-care products in countries where financial and technological capacities exist, and in relation to products for which profitable markets exist. In developing countries, the fact that a patent can be obtained may contribute nothing or little to innovation if the market is too small or scientific and technological capability inadequate. In the absence of effective differential and discounted prices, patents may contribute to increasing the price of medicines needed by poor people in those countries. Although the balance of costs and benefits of patents will vary between countries, according to their level of development and scientific and technological infrastructure, the flexibility built into the TRIPS agreement allows countries to find a balance more appropriate to the circumstances of each country.

THE INNOVATION CYCLE

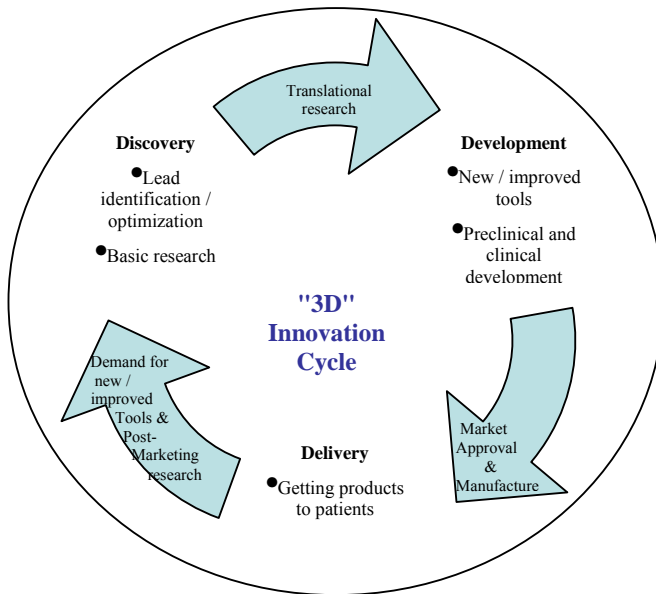
The depiction of the industry model earlier in Figure 1.3 does not focus on the connection between basic research and the development of vaccines and medicines valuable for human health. The scientific and technical components of the discovery and development process represent only one aspect. Whether the whole process actually delivers products needed by poor patients in developing countries at prices that are potentially affordable depends on a host of political, economic, social and cultural factors.

We prefer to consider innovation as a cycle. This cycle⁴ depicted in Figure 1.4 represents a schema that applies principally to developed countries and the diseases which predominantly affect them, where effective demand and the population's health needs most closely coincide. For conditions such as cancer and asthma, incremental improvements are commonplace, and companies have a reasonable assurance that health-care providers and patients will purchase their products. That provides the basic economic and financial incentive for innovation. Whatever the various problems encountered in the innovation cycle, either technical or in terms of the policy framework (which we examine in the following chapters), it broadly works for the developed world and sustains biomedical innovation directed at the improvement of public health.

⁴ The United States National Cancer Institute (NCI) has developed a similar model, which it calls the discovery-development-delivery continuum. According to NCI, "The research process spans a continuum from discovery of new knowledge about the process of cancer, to development of new interventions, to the ultimate delivery of new, more effective, and safer interventions to all who need them" (61).

For developing countries, where the demand is weak – but not the need – there is little incentive to develop new or modified interventions appropriate to the disease burden and conditions of the country. This economic reality introduces an important gap in the innovation cycle: either no products exist in the first place, or if they do, then there is often disproportionately small effort, globally, to make them more effective and affordable in poorer communities. Broadly speaking, the innovation cycle does not work well, or even at all, for most developing countries.

Figure 1.4 The innovation cycle



Making the innovation cycle work in developing countries depends on improving the efficiency of the innovation process by addressing both technical and policy challenges at each stage of the cycle (discovery, development and delivery). Special issues arise at the interfaces between the stages of the process, and within each stage.

For example, improved research tools and platform technologies could go a long way towards streamlining innovation, both leading up to and within the discovery stage. Many of the approaches used in the development stage have not changed significantly in decades. The regulatory

framework poses specific challenges in the process of development, and in facilitating delivery. The purpose of our investigation is to seek ways to make the innovation cycle work better to develop and supply health-care products needed by poor people in developing countries.

Our concept of innovation sees the process as a cycle consisting of three major phases that feed into each other: discovery, development and delivery. This is in contrast to conceiving of innovation as an entirely linear process that culminates in the launch of a new product. Within the innovation cycle, public health need creates a demand for products of a particular kind, suited for the particular medical, practical or social context of the group in question, and feeds into efforts to develop new or improved products.

The Commission's main task is therefore to consider measures that might be appropriate at different stages of the innovation cycle to promote sustainable innovation of the kind needed by developing countries.

CHANGING PLAYERS IN THE INNOVATION PROCESS

This report is concerned with how better to orient health innovation so that it benefits poor people. Over the past decades, the face of innovation has changed in ways that are important for any discussion of access. The pharmaceutical industry has been through many transformations in its more than 100-year history. From its early days, it has strongly depended on developments in chemistry and biology, and benefited from a symbiotic relationship with academic laboratories. From the apothecaries and chemical companies of the late 19th century to the multinational pharmaceutical giants of today, the structure of the industry has tracked changes in the realm of science as well as being profoundly affected by the economic and regulatory environment. Today, the global pharmaceutical industry has focused on the translation of basic scientific discoveries, largely deriving from basic research in public-sector research institutions and universities, into drugs and vaccines. More than many industries, the financial performance of the pharmaceutical industry is dependent on the economic policy framework set by governments, in particular the patent regime, and the regulatory arrangements designed to ensure that products are safe, efficacious and of good quality.

Pharmaceutical research has evolved from a reliance on the extraction and concentration of useful compounds from nature and the creation of synthetic chemicals, to an ability to relate chemical structure to pharmaceutical activity and thus block disease-causing pathways. Most recently, the automation of laboratory work through combinatorial chemistry and high-throughput screening seemed to have offered the possibility of speeding up drug discovery, and has led to the creation of vast libraries that can be "mined" for molecules with the greatest potential. In practice this approach has yet to live up to expectations.

In recent years, there has been a process of concentration in the global pharmaceutical industry, driven to a considerable extent by the search for new potential products in development to boost their product pipelines in the quest to maintain sales and profit growth. While the largest firms have grown through mergers and acquisitions, they have also sought to increase the productivity of in-house R&D through structural reorganization. At the same time, many large pharmaceutical companies have now moved towards a more focused role: more potential products are licensed in from biotech and other small companies; and clinical research is increasingly outsourced to specialist research organizations, with an increasing emphasis in recent years on trials in developing countries such as India and China. It was estimated that 35% of drugs in Phase III trials in 2001 were either licensed in or the product of collaborative research, and two thirds of clinical trials involved contract research organizations (62). The number of players in the R&D process has increased and, with this evolution, more opportunities have opened up, as have the complexities of coordinating and negotiating activities between the different parts of this evolving system. Importantly, developing country R&D expertise, in both the public and the private sector, is being used increasingly at all stages of the innovation cycle. In Brazil, China, India and elsewhere, foreign collaborations are increasing.

The rise of a biotechnology industry, often comprising companies spun-off from university laboratories, has offered additional opportunities for the discovery of new classes of drugs, and – coupled with the emergence of firms specialized in clinical

trials – is resulting in significant changes in the structure of the industry. Universities themselves, particularly in the United States, have become key players in the development of new biotechnologies. Intellectual property rights have been central in this development, and increasingly universities have developed extensive patent portfolios.

Of particular note, the past 20 years have witnessed the emergence of several new key players and changing roles for others.

- The **biotechnology sector**. In the United States, three events in 1980 laid the groundwork for the industrial application of biotechnology: the Supreme Court's decision, *Diamond v. Chakravarty*,⁵ to accept the patentability of genetically modified microorganisms; the Bayh–Dole Act⁶ permitting universities to obtain patents on the products of federally-funded work; and the success of Genentech, the first publicly-traded biotech firm.⁷ The biotechnology industry, now 1500 companies strong in the United States, has brought with it new competencies in gene-based techniques, and become an important strategic partner of the pharmaceutical industry. For biotechnology companies, their proprietary claims on upstream inputs, such as genetic sequences, and the databases that make them available, are essential tools for the acquisition of capital.
- The **generic drugs industry**. In the United States, the 1984 Hatch–Waxman Act⁸ significantly reduced regulatory barriers to market entry for generic drugs following the expiry of the patent on the original product. Many developed countries now have thriving producers of generic drugs and cheaper access to off-patent drugs. In some developing countries, a generic sector has also developed. India, which until 2005 permitted only process patents on pharmaceuticals, has emerged as a major producer and exporter of bulk drugs, active ingredients and products still patented in other countries. China has also been a major supplier of bulk drugs and active ingredients for some time.
- **Civil society groups**, including advocates representing patients with specific disorders. These groups have put pressure on companies, both nationally and internationally, to lower prices or accelerate product development, on regulators to speed up the regulatory process, and on governments to provide adequate health-care facilities (63).
- A **group of developing countries** that are successfully fostering innovative capacity in biomedical research, including in biotechnology. This group includes countries such as Brazil, China, Cuba, India and several others. Increasingly these countries are

⁵ *Diamond v. Chakravarty*, 447 U.S. 303 (1980).

⁶ The Bayh-Dole Act (P.L. 96-517, Dec. 12, 1980).

⁷ See <http://www.gene.com/gene/about/index.jsp>.

⁸ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended 21 U.S.C. ' 355 (1994)).

becoming active participants in global R&D networks, on account of their scientific and technological expertise and cost advantages.

- **Universities**, particularly in the United States where a considerable proportion of global public and private sector funding for health R&D originates, have pursued patents as a new source of revenue and to encourage commercial application.
- **Governments**, throughout the evolution of the industry, have played a significant role in the promotion of outcomes by setting up incentive systems such as intellectual property rights or tax credits, and more directly through their funding decisions, both in providing funds for research in the university or public sectors, and in the decisions they take on the purchase of products and the prices they are prepared to pay. In addition, governments provide a regulatory framework to ensure the quality, efficacy and safety of new products. The way these regulatory institutions function has important implications for incentives to invest in product development, and for how quickly new products get to market, or whether they get to the market at all. Increasingly, governments' domestic policies in areas such as intellectual property rights are affected by multilateral and bilateral trade agreements.
- **Non-profit foundations**, alongside governments and the private sector, have also played a very significant part in the funding of biomedical research principally in developed countries – the Howard Hughes Medical Institute in the United States and the Wellcome Trust in the United Kingdom are good examples. In respect of diseases that particularly affect developing countries, the emergence of public–private partnerships for product development has been a very significant development within the past decade. These new partnerships have developed in a number of ways but usually with the significant involvement of non-profit foundations and industry, and often with support from WHO. Their largest source of funds remains the non-profit sector, in particular the Bill and Melinda Gates Foundation. They have significantly increased the number of products in development for diseases and conditions predominantly affecting developing countries.

INNOVATION SYSTEMS IN DEVELOPING COUNTRIES

In recent years there has been much discussion about appropriate ways to stimulate innovation, particularly in the developed world. The linear model, discussed in the next chapter, whereby universities or public research institutions did basic or fundamental research and the private sector picked up and developed what was capable of commercial application has become regarded as outmoded. One reason for this is the large number of actors now involved in different stages of the innovation process, for instance biotechnology companies and contract research organizations. Another is the recognition of the need for much greater interaction, in a number of different ways, between these different participants. Basic research, for instance, may

be done in, or sponsored by, universities and pharmaceutical companies. At the same time, universities and public research organizations have also been responsible for the development of products with a more or less direct commercial application (either as an input into further research or as a completed medical technology), which they may then license to others. This suggests that a “systems” approach that emphasizes networks and coordinated efforts is needed for effective R&D. In the specific context of African science, a recent editorial noted:

The new approach sees science as part of an innovation system that contains many feedback loops and opportunities for interaction with the broader society. These, for example, ensure that scientific priorities are selected according to social and economic priorities (for example, through the use of 'technology foresight' exercise to determine the allocation of research resources).

The new paradigm does not see science as an end in itself, but places every aspect of science in a social context. Research institutions, programmes and training are all designed accordingly. Scientists' work is valued not only for its intellectual merit, but also for its potential contribution to society's social and economic needs (for example, in the number of patents it has stimulated). And the process of priority setting has become a public dialogue between scientists and broader community.

It does not take much imagination to see that this new, 'mode 2' science, is the one that best fits the needs of Africa (indeed of most developing nations). The science required as a central component of development strategy is one that is built not around intellectual curiosity (essential though this is), but around social need. Research priorities must not be determined by the likely number of publications in academic journals, but by their relevance to this need. And publication rates should not become the principal determinant of professional success in the academic world, even if they continue to play an important part (64).

Developing countries, which have hitherto relied heavily on public sector research, can take advantage of this perspective in developing their own innovation systems. The Science and Technology Adviser for Africa's New Partnership for Africa's Development (NEPAD) noted:

Scientific and technological capacity for health cannot, thus, be reduced to equipment, funding and number of health scientists and technicians. It is the configuration of skills, policies, organizations, non-human resources, and overall context to generate, procure and apply scientific knowledge and related technological innovation to identify and solve specific health problems. The capacity is built through interactive processes of creating, mobilizing, using, enhancing or upgrading, and converting skills/expertise, institutions and contexts. It is not about isolated activities and products (65).

Indeed, developing countries have a rich source of medical knowledge in what is commonly known as “traditional knowledge”, either oral or written. This encompasses systems for treatment and knowledge about the medical properties of plants and genetic resources. The opportunity exists to use this knowledge much better, both as a source of treatments, and to accelerate the development of new

“modern” products based on the ingredients in “traditional” treatments which are known to have some efficacy.

THE REPORT

The following chapters of the report address these issues.

Chapter 2 covers the discovery stage. **Chapter 3** discusses the development stage. **Chapter 4** deals with the delivery stage.

In each of these three chapters we address the specific scientific, technical, economic, patent and resource issues that affect the innovation cycle.

In **Chapter 5** we consider policies to improve innovative capacity in developing countries.

Chapter 6 concludes and considers the need to move towards a better financed and more sustainable system for promoting innovation directed at diseases that disproportionately affect developing countries.

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CHAPTER 2

THE DEEP WELL OF DISCOVERY: EARLY STAGE RESEARCH

INTRODUCTION

The introduction of new products for the diagnosis, prevention and treatment of diseases depends on a long chain of scientific research and development.



The foundation of all innovation leading to the discovery of new health-care products is basic research in the life sciences. In most countries, basic research is supported by the government and takes place in public and private research institutes or universities. In addition, private foundations such as the Wellcome Trust in the United Kingdom and the Howard Hughes Medical Institute in the United States provide important support and impetus to the academic research enterprise.

In the United States, the most successful country in biomedical innovation, a seminal report by Vannevar Bush in 1945 laid the basis for large government investments in basic research through institutions such as the National Institutes of Health (NIH). Bush noted that:

Progress in the war against disease, depends upon a flow of new scientific knowledge...This essential, new knowledge can be obtained only through basic scientific research (*1*).

Bush is regarded by many as the father of the “linear model” of scientific innovation. Public investment in basic research, without immediate regard to commercial or industrial objectives, would be the best guarantor of future technical progress:

Scientific progress on a broad front results from the free play of free intellects, working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown. Freedom of inquiry must be preserved under any plan for Government support of science... (*1*).

Although influential worldwide, this model of innovation has been increasingly questioned in recent years for a number of reasons. First, much basic science is actually motivated by thoughts of practical application. For example, Louis Pasteur in the 19th century made path-breaking scientific discoveries in the fields of microbiology and immunology, even though he was clearly motivated by the need to address practical medical problems. As a result, he gave the world, among other things, pasteurization and its first rabies vaccine. The Pasteur Institute was created subsequently in 1888, as a private not-for-profit state-approved foundation, to build on Pasteur’s vaccine research. Second, the practical evidence of how basic science and applied technology interact has suggested the need to look at them as

interdependent, with scientific priorities being influenced by considerations of where opportunities for solving human problems exist.

Many of these trends are visible in the life sciences. In recent years the revolution in molecular biology and the development of wholly new branches of scientific investigation, such as proteomics (the science of proteins expressed by genes), has offered the prospect that the process of biomedical innovation could be accelerated and made more effective. In practice, as we discuss in Chapter 3, the transformation of basic science has not yet resulted in any comparable transformation in the rate of innovation as measured, for instance, by the number of new drug molecules being approved by regulatory agencies. There are, therefore, a host of scientific issues that affect how advances in basic science get translated into products needed to protect and improve human health.

As noted in the previous chapter, the process of drug discovery is not only a matter of science. It involves a complex interaction among a wide range of economic, social and political actors. These include governments (for example, through their medical research councils), foundations and other nongovernmental bodies, such as the Bill and Melinda Gates Foundation in the United States, and the Pasteur Institute in France, academic scientists in universities and public sector research organizations, biotechnology companies and large pharmaceutical companies. Of particular relevance in our context, are the public–private partnerships set up to develop diagnostics, vaccines and drugs directed at the needs of developing countries. Governments play a critical role in providing the policy framework, funding and tax and other incentives, while the other actors in the public and private sectors are essential components of this complex system.

In this chapter we review the evidence concerning the science and the economic and policy choices faced. In particular, we will focus on scientific, institutional and financial issues arising between basic research and the identification of lead compounds with possible therapeutic effect.

- What are the gaps in this process for diseases principally affecting developing countries?
- What policy measures might be appropriate to address those gaps?

In addressing these questions, we look at the experience and evidence from the developed world, in particular the United States, because of its predominant influence on the subsequent development of policies elsewhere. However, we pay special attention to what this implies for developing countries.

EARLY STAGE RESEARCH

THE IMPACT OF SCIENTIFIC ADVANCES

The pharmaceutical industry, as it is known today, emerged over a century ago as a result of basic advances in chemistry and biology, allied to the development of the new discipline of pharmacology. The pharmaceutical industry began, in fact, as a new line of production in the chemical or dyeing industries. In the 20th century, the discovery of antibiotics was central to the development of the industry. Further advances in biology occurred which, in turn, enabled a better understanding of how drugs had their effect in the body. For example, scientists discovered the existence of "receptors" in different body organs where therapeutic agents could attach themselves, either stimulating desirable changes (such as lowering blood pressure) or blocking undesirable changes (such as the growth of tumours). They also recognized the central role played by enzymes in the causation of disease, and as targets for potential drugs.

In the past 30 years, advances in molecular biology gave rise to the biotechnology industry and have become a key driver of R&D methods in the pharmaceutical industry. One result of this has been the development of recombinant DNA and recombinant proteins and monoclonal antibodies derived from them. For example, erythropoietin (EPO) is a leading example of a synthetic hormone, produced by recombinant DNA technology, which addresses deficiencies in the amount of natural EPO produced by the body, leading to low red blood cell counts. It is used widely in medicine as a treatment for a number of serious illnesses, including kidney disease, various types of anaemia, certain types of cancer, and also in the battle against AIDS.

Potentially the most important consequence of these scientific advances is the opportunity to understand the causation of disease at the level of the gene and, on that basis, to determine more accurately the optimal medical intervention. The publication of the draft of the human genome sequence in 2000 (subsequently completed in 2003) was accompanied by a wave of optimism about how this would accelerate the discovery of ways to diagnose, prevent and treat disease. It was thought that the combination of new gene sequencing techniques and the advent of new drug discovery technologies, such as combinatorial chemistry and high-throughput screening of compounds, along with the possibilities for early stage research using bioinformatics, could dramatically accelerate drug discovery. One of the scientific leaders of the project claimed that "this set of power tools that the genome project is producing will accelerate this discovery process rather dramatically, and we're going to see the consequences of that in the next three to five years" (2).

The subsequent years have demonstrated that the power of genomics rapidly to transform the process of R&D and the discovery of new treatments has been overestimated. The wealth of new genetic knowledge has rather served to underline the complexity of the causation of disease. For instance, in 1999, ten large pharmaceutical companies and the Wellcome Trust established a consortium (3) to find and map 300 000 common single nucleotide polymorphisms (SNPs), which are alterations in the basic building block of DNA that may be connected to the causation of diseases. As a result of that work, it is now thought that over 10 million SNPs exist, and only a fraction of these are likely to be implicated in disease causation. A

successor project, called HapMap, has been established with support from the SNP Consortium and others to compare the genetic sequences of different individuals to identify chromosomal regions where genetic variants are shared (4). A further initiative, the Structural Genomics Consortium, has now been formed to determine the three-dimensional structures of proteins of medical relevance. The Consortium is expected to enhance the understanding of relevant proteins and supply new targets for therapeutic intervention thereby providing the structural framework for the rational design of new or improved drugs that can inhibit or enhance protein function (5).

Thus, untangling this complex web of information relating genetic variation to diseases has proved more difficult, and will take more time, than many people originally thought. Nevertheless, all this new information should eventually bear fruit, if the necessary human and financial resources are devoted to translating this fundamental knowledge into interventions that will diagnose, prevent or treat disease.

This general consideration about the impact of genomics applies also to diseases disproportionately afflicting developing countries. For instance, in 2002 the genome sequences of both the main mosquito species responsible for malaria (*Anopheles gambiae*) and the main parasite (*Plasmodium falciparum*) were published. These have provided a very important tool for identifying new approaches in treatment helping, for instance, the Medicines for Malaria Venture (MMV) identify three new projects in their drug discovery portfolio.

Similar sequencing exercises have taken place for a large number of pathogens. For example, major advances in our understanding of mycobacterial pathogenesis have been achieved through the sequencing of the genome of *Mycobacterium tuberculosis* in 1998, the causal agent for TB. Research in this field has been partly driven by the genomics revolution, resulting in the development of tools for gene deletion and gene exchange between mycobacteria. The sequencing of the *Mycobacterium tuberculosis* genome has also helped scientists to start to identify genes that are responsible for latency in TB (6).

However, in the opinion of the Malaria Vaccine Initiative (MVI), genome maps will not, in the short term, have a great impact on malaria vaccine development:

Mapping the malaria genome has identified several thousand potential targets for a malaria vaccine. It will take several years (and perhaps decades) of research to assess these targets and turn promising ones into vaccines that can be evaluated. In the short term, genome maps will not have a great impact on malaria vaccine development (7).

Most recently the genomes of the three trypanosomes which cause sleeping sickness, Chagas disease and leishmaniasis have been published, the result of a cross-national collaboration including researchers in Africa and South America. While these advances are critical, the *Science* editorial accompanying publication captured the dilemma well:

The Tritryp genomes are thus intrinsically interesting—but what will they contribute to the amelioration of disease? Because of their distinct evolution, trypanosomes present a plethora of potential drug targets, and potential drugs are almost certainly languishing in the chemical libraries of pharmaceutical

companies...But we need resources and commitment on a far larger scale to transform drug targets into clinical successes. It is clear that the traditional pharmaceutical industry will not become effectively involved in this area, and the current promotion-and-reward system in academia does not attract or sustain the necessary human and financial resources. Consortia move slowly and are frequently restrained by similar problems, compounded by the egos of scientists and sponsors (8).

In the case of an HIV/AIDS vaccine, specific recognition has been given to the need for a more globally coordinated research effort that focuses on surmounting the fundamental scientific and operational difficulties in translating basic research knowledge into vaccine candidates. G8 leaders in 2003 endorsed the Global HIV/AIDS Vaccine Enterprise, modelled in part on the public sector coordinated Human Genome Project (9). In the words of the International AIDS Vaccine Initiative (IAVI):

... a critical gap exists between basic research and product development efforts: applied research and vaccine design. What is lacking are effective mechanisms to harness the necessary global talent and infrastructure for an applied research problem solving agenda...Solutions to these challenges will require multidisciplinary involvement from various sectors of HIV research and vaccine design; long-term commitment to a systematic problem solving agenda; and creative mechanisms linking basic research scientists with vaccine designers, in fields as diverse as structural biology, robotic crystallization, glycobiology and large-scale non-human primate testing (10).

Each disease and intervention, whether for diagnosis, prevention or treatment, presents its own specific scientific challenges although there is a common thread in almost all the disease areas of interest to the Commission. The fact is that advances in biomedical science, and genomics in particular, offer the prospect of comparable progress in the discovery of new and effective interventions. How quickly the translation of this promise into reality will occur depends on how effectively the world addresses scientific, institutional and resource issues, particularly for those diseases or conditions that predominantly afflict developing countries.

INSTITUTIONAL CHANGES

Advances in the scientific process have been closely linked to changes in the institutions involved in that process. Existing institutions have had to adapt to these advances, while new institutions have arisen to capitalize on them.

As noted above, the crucial issues arise at the interface of what are often called basic research and applied research. In the Vannevar Bush schema, basic research is seen as curiosity-driven (or "blue skies") research and applied research as directed to a particular application (such as the creation of a new drug, vaccine or diagnostic test). The distinction between these two kinds of research, always difficult to define precisely, has been further blurred in the wake of the rise of genomics-based research. For example, useful products (e.g. a diagnostic test) may arise directly from basic genomic research. A more useful distinction, for that reason, may be between upstream and downstream research because the products of upstream research may

include research tools or platform technologies which are required by downstream researchers in the course of their further R&D.

Research tools are difficult to define as a category because of their heterogeneity. They can be an object or a process for laboratory use for drug, diagnostic or other inventions. They include animals used in the laboratory, which may be genetically modified. The so-called Harvard mouse, genetically modified to be susceptible to cancer, is a famous example of an animal research tool which has been patented in a number of countries. Research tools may also be databases – at the United States National Center for Biotechnology Information, part of the NIH, 200 000 researchers every day ask for their sequence to be compared with those in GenBank, a DNA database. This particular database is freely available but other databases may require user fees. Commonly, research tools are a cell line, a vector, an antibody, a protein or gene or its expression, a screening method and so on. Such tools, again, may or may not be patented. A classic example is the recombinant DNA technology invented at the Universities of California and Stanford (known as Cohen–Boyer after the two inventors), which is central to further research on DNA and has uses across the whole field of biomedicine. This technology, which was patented, was widely licensed on a non-exclusive basis and earned US\$ 255 million in licensing revenues for these universities (11).

At the institutional level, the upstream/downstream interface arises between the primarily upstream research carried out at universities or public research institutes, mainly funded by governments, and the downstream research entities, mainly funded privately. Thus, another important interface is between public and private research enterprises. At the risk of oversimplifying history, “basic” science was traditionally viewed as the main activity of the public or university sector and “applied” science the activity of the private sector. The private sector was given the task of using the knowledge produced by universities, and made freely available, to develop it further and find commercial applications. Incentives for scientific advance in the public or university sector were the established systems of open disclosure, publication, peer review and promotion, the prestige associated with being first to make a discovery, and a desire to make the world a better place. In industry, while individuals responded to many of the same incentives as researchers in basic science, the fundamental incentives for companies were commercial and financial. There was a symbiotic and finely balanced relationship between these two systems (12). The universities provided not only the scholarship to advance the progress of science but also the skilled people required by the private sector.

In reality, this picture of the innovative process was always a simplification. Historically, universities and public research institutes have been considerably involved in downstream research, often in partnership with the private sector. For instance, at the NIH, the search for treatments for malaria began in the 1930s, when malaria was still a major public health research problem in the United States. In fact, research on malaria and a host of other tropical diseases began much earlier at the Walter Reed Army Institute of Research, based on the health hazards faced by the United States military fighting overseas. Many products, such as vaccines and antimalarials, have been principally developed by the public sector, although industry has usually collaborated in the development and delivery phases.

More recently, this distinction has been further blurred. For example, in 2005, the NIH awarded a large multi-year grant to a consortium of academic institutions in order to design, develop and test improved HIV vaccines, with elements that range from the basic understanding of the body's immune response in the earliest stage of HIV to conducting clinical trials with HIV vaccine candidates (13). In the same year, the Bill and Melinda Gates Foundation, with the Wellcome Trust and the Canadian Institutes of Health Research, awarded the "Grand Challenges" grants of nearly US\$ 500 million to 43 projects in 33 countries, ranging from the basic to the applied. For instance, one of these grants was awarded to an international consortium of universities and private firms, for studying the fundamental biology of latency in TB and the development of drugs to combat it. Of these grants, 40 were awarded to projects led by public research institutes or universities, and three to those led by private sector pharmaceutical or biotechnology companies (14).

Pharmaceutical companies may undertake or sponsor research of a basic nature, as in the case of the SNP Consortium. Developments in biotechnology have resulted in genomics being perceived as having potentially large commercial value. Thus, a major change at the upstream/downstream interface has been the emergence of the biotechnology industry as a major contributor to the R&D process in biomedicine. The rise of the biotechnology industry owes much to concomitant changes in the universities, out of which emerged many biotechnology start-up companies.

The nature of the revolution in science has placed a premium on interdisciplinarity. New disciplines, such as bioinformatics, proteomics and expression genomics, which also needs to be linked with chemistry, require the coordination of multiple and diverse actors, both horizontally and vertically. If these actors are in different institutions, both public and private, then this requires an effective means to bring about efficient transactions between them. Intellectual property rights, licensing and contracts are the currency of these transactions.

POLICY CHANGES

In the United States, several linked economic and legal developments helped to solidify new institutional arrangements for R&D. A landmark case in the Supreme Court in 1980, *Diamond v. Chakrabarty*, confirmed that genetic inventions (in this case a genetically engineered bacterium capable of breaking down crude oil) were patentable (15). The application of the patent system in this way facilitated the development of a viable business model for the biotechnology industry. With the development of revenue-earning products a long way off for many companies, they could nevertheless raise money, or realize value, through the patents taken out on upstream genetic technologies. Start-up companies have a higher share of biotechnology patents than do large, established pharmaceutical companies (16).

In the same year, the Bayh–Dole Act permitted universities to take out patents based on inventions arising from publicly funded research, with the objective of encouraging the further development and application of technologies based on university research. This technology transfer, as it is known in the United States, has resulted in a rapid growth of patenting in universities, and a new source of potential revenue through licensing. Patents relevant to biomedicine predominate in patenting activity by universities in the United States, in part because of the enormous size of

NIH funding on which much university research depends, and in part because the potential commercial value of such patents is higher than in most other sectors. Indeed, in the United States, the holder of the largest number of DNA-based patents is the University of California, and the second largest is the United States Government through the NIH. Public institutions in Europe and the United States owned 30% of all the patents for DNA sequences filed between 1996 and 1999 (17).

In this new environment, universities and public institutions have become significant players in patenting and licensing in biomedical R&D. In the United States and increasingly in other countries, universities are now active in taking out patents and in enforcing their own patent rights, including through litigation (18). University scientists receive a share of licensing revenues, and may also have dual roles in start-up companies spun out of their university. Thus, not only has the interface between upstream and downstream research become blurred, but also the relative roles of the different parties at this interface, both as individuals and as institutions, have changed.

Upstream research in the public and private sector has traditionally depended on maintaining the appropriate combination of scientific competition and collaboration. Competition to be the first person or team to reach a particular goal is a very powerful spur to progress. A good example of this was the race between a public sector consortium and a private company to sequence the human genome. Another was the rapid sequencing of the SARS genome in 2003. Nevertheless, as the human genome case also illustrates, collaboration between different teams, the sharing of knowledge, and the avoidance of unnecessary duplication, are important factors in the advance of science in both not-for-profit and profit-oriented research endeavours.

Recent changes in the policy framework have implications for the balance between collaboration and competition. In particular, the patent incentive may facilitate the early disclosure of scientific information that otherwise would remain secret and, in consequence, can stimulate competitive innovation. However, the pursuit of patenting and of commercial funding may have the effect of encouraging secrecy rather than knowledge sharing, exacerbating rivalry, and reducing cooperation among research groups. Too much competitive behaviour may be counterproductive for the overall research effort, but so too may be its absence. Indeed, there are a number of important collaborations between private sector companies, foundations and public sector institutions, such as the SNP Consortium. These collaborative efforts tend to be directed at upstream or basic research which is a necessary prerequisite to facilitate the subsequent development of products. Thus, the companies recognize that, at certain stages of the innovation cycle, collaboration to produce upstream knowledge which all parties will require to make use of is in their interest, and in the interest of hastening the application of new technologies for human health. Moreover, like the public sector Human Genome Project, the knowledge generated by these collaborations is generally put into the public domain directly. This means that it is freely available for use by any scientist, and that the data as such cannot be patented.

The opposite applies in respect of the compound libraries held by pharmaceutical companies, as they are regarded as a trade secret. Annotated proprietary compound libraries are one of the most important elements of a company's competitive strength. They may contain a million compounds, both natural and synthetic, and are repeatedly tested against newly emerging therapeutic targets. Because of their potential value for

developed country markets, companies do not generally provide access to their compound libraries, even for public or non-profit researchers working on diseases of low or no commercial value. Some universities have also developed publicly available compound libraries.

Providing access to such facilities may involve a high opportunity cost for firms competing in the research market, although deals have been done in the right circumstances (see Box 2.1). High-throughput screening of biological assays against the compounds in these libraries could provide essential leads for potentially efficacious compounds. Actions are needed to overcome the difficulties experienced to date in accessing this resource by finding ways to bring together the neglected disease researchers and the companies that hold these libraries. Only with novel approaches can private, public and not-for-profit entities expand research efforts on neglected diseases in a manner that ensures continuing protection of these valuable company resources.

Box 2.1 Compound donations

Two drug companies have given away rights to two key compounds, so that they can be developed into gels that protect against HIV. Experts say that a microbicide applied to the vagina before sex could save 2.5 million lives in just three years.

But progress to develop such gels has been slow. Only one microbicide trial has been completed in humans, with unfavourable results — the women became more susceptible to HIV because the gel, essentially a detergent that destroys the virus, damaged their vaginal tissue. Five other microbicides are in clinical trials in Africa after proving moderately successful in monkeys, although critics point out that the virus used in those animal tests infects cells in a different way from the one that causes AIDS.

John Moore from Cornell University in New York and his colleagues tried a different approach. They combined three compounds that each uses a different mechanism to block the virus's entry into cells. Merck's compound CMPD167 competes with the virus for cell receptors inside the vagina. Bristol-Myers Squibb's BMS-378806 interacts with the virus itself, stopping it binding to cells. And a peptide developed by Moore's team inhibits the process used by the virus to enter a cell.

When the researchers tested combinations of the compounds in macaques, they found that they offered at least partial protection against a virus closely resembling HIV. Three animals that received the three compounds together were all protected against infection. These results were enough to persuade the drug firms to give away rights to the compounds, said Moore. "This is the first time there has been a joint announcement like this," added Mark Mitchnick, chief scientific officer of the International Partnership for Microbicides, the public-private-partnership that will develop the gel.

Partners, including the Bill and Melinda Gates Foundation and the NIH, are helping to fund a clinical trial, set to start in 2007. This is estimated to cost between US\$ 150 million and \$ 200 million and will involve about 10 000 women in Africa.

Source: reference (19).

PUBLIC FUNDING AND RESEARCH PRIORITIES

The most important determinant of what research gets done is how funding is distributed. At a global level the overwhelming bulk of early stage research is funded by governments through their equivalents of the United Kingdom Medical Research Council or the United States NIH. In 2001, according to estimates by the Global Forum for Health Research, the total estimated global spending on health research by the public sector was nearly US\$ 47 billion (Table 2.1). Of this amount, nearly US\$ 29 billion (61%) was spent in the United States, predominantly by the NIH. The amount spent by the public sector in developing countries is estimated at US\$ 2.5 billion (20).

Table 2.1 Estimated global health R&D funding, 2001 (in current US\$ billion)

	US\$ billion	%
Total	105.9	100
Total public sector	46.6	44
Total private sector	59.3	56
Total private for-profit	51.2	48
Total private not-for-profit	8.1	8
High income countries		
Public sector	44.1	42
Private for-profit	49.9	47
Private not-for-profit	7.7	7
Total high income countries	101.6	96
Lower middle income countries		
Public sector	2.5	2
Private for-profit sector	1.8	2
Total lower middle income countries	4.3	4

Source: reference (20).

However, these figures should be regarded as indicative only, and include all stages of research spending from discovery to delivery. A recent careful estimate of all types of biomedical research in the United States suggested that in 2004, R&D expenditure in the United States alone amounted to US\$ 94.3 billion. Of this total, US\$ 54 billion represented expenditure by pharmaceutical, biotechnology and medical device companies, and US\$ 37.4 billion by federal, state and local governments. The balance of US\$ 2.5 billion came from non-profit sources. Total expenditure in both the public and private sectors has nearly doubled in the past decade (21).

Important questions about funding include:

- How much money is available and how it is distributed between disease areas or types of research?
- How do funders exercise their influence on the content and conduct of research?

The significant fact about public funding of R&D is that its focus is predominantly shaped by domestic priorities. Thus, the priorities for public sector R&D funding in developed countries will necessarily be shaped by their own disease burden (mainly Type I diseases and HIV/AIDS), and on finding solutions that reflect the resources they have available for new methods of diagnosis, prevention and treatment. Although accurate figures are hard to come by, the global imbalance in publicly funded research in relation to the health needs of developing countries is likely to follow the same trends as the global imbalance in private funding driven by market forces.

There is some developed country interest in international health, dating back to the beginning of the 20th century for former colonial powers such as France and the United Kingdom. In these cases, the infrastructure for research on diseases mainly affecting developing countries remains strong, with links existing between researchers in several parts of the developing world. Thus, for example, the Medical Research Council in the United Kingdom maintains a significant portfolio of research relevant to developing countries. In 2002–2003, the Medical Research Council spent an estimated £22.5 million on research relevant to developing countries, representing over 6% of its total expenditure. The NIH in the United States was specifically empowered to conduct research on tropical diseases in 1993, whereas previously any international research was required to be specifically of benefit to United States citizens. One of our studies estimated that the share of R&D expenditure on tropical diseases by the NIH had increased to as much as US\$ 1 billion (4% of total R&D) in 2004, whereas in the 1990s the share averaged well under 1% of a much smaller total investment (22).

One reason for this improving trend is that recent experience has demonstrated the indivisibility of health priorities. With globalization and the increased movement of people around the world, no infectious disease can be regarded as geographically confined. Demographic and economic trends have increased the world's vulnerability to epidemics (e.g. SARS, TB, influenza and avian flu) which could affect millions of people in the developed and developing world.

Apart from infectious diseases, there is the concern of the rapidly rising rates of noncommunicable disease. Some of these diseases can be treated by a number of older medicines, which are relatively cheap (e.g. diuretics to lower blood pressure). However, many of the newer treatments for cancer and cardiovascular disease, of potential benefit to patients in the developing world, are expensive and complex to deliver. In these instances, in addition to therapy, other approaches, such as inexpensive tools for early diagnosis, and epidemiological research into causation and preventive strategies, could pay bigger overall dividends in terms of health improvements in developing countries. Thus, the priorities for research on Type I diseases, from the point of view of developing countries, with their particular resource constraints, are likely to be different from those in developed countries.

For Type II diseases, such as TB or malaria, the search for solutions applicable in the developing world needs to be built in at the earliest stage of research. In the words of the Global Alliance for TB Drug Development (TB Alliance):

We have a two-fold bottom-line: accelerating research and development and ensuring affordability of the drugs developed, especially in the more impoverished countries with a high burden of TB (23).

Organizations such as the TB Alliance, as will be seen in Chapter 3, operate mainly in the development phase of the innovation cycle, although the issue of how most effectively to translate the results of basic research into usable health-care products arises throughout the research cycle. The UK Medical Research Council put it well in a recent "vision" statement:

However, the right balance has to be struck between short-term 'pay-offs' and promoting the longer-term development of fundamental science that will in time lead to improvements in health and wellbeing. We therefore anticipate that the research the MRC supports will have an increasing relevance to disease, with a greater priority given to translational approaches at the basic/clinical interface (24).

A similar emphasis on translational research is evident in recent policies of the NIH. In particular, the NIH Roadmap Initiative seeks an ambitious restructuring of the methods of basic research. The first component of this initiative aims to create new pathways to discovery. Important elements of this component include the study of the proteins expressed by genes, and metabolic components and networks within cells. NIH will also develop molecular libraries to facilitate the screening of drug targets and compounds, focus on structural biology, and promote the development of bioinformatics, computational biology and nanomedicine. A second component encourages interdisciplinary research and risk-taking (through a new award scheme). A third component focuses on the transformation of clinical research (see Chapter 3) (25).

While these initiatives are focused generally on how to improve basic science to facilitate discovery and then development, this rethinking of the process is relevant to tackling the health problems of developing countries. For example, similarities (or homologies) in the structure of, for example, DNAs or proteins, can be important in identifying drug targets and compounds for diseases with common origins. Moreover, as more and more databases have become available, and software is developed, it has become feasible to use bioinformatics, inter alia, to investigate homologies. For instance, as part of its commercially driven research, Novartis identified a new antibacterial target (for respiratory infections) which bioinformatics showed was also present in the tuberculosis pathogen. This lead is now being pursued in Singapore at the Novartis Institute for Tropical Diseases (26). Homologies may also be important for another reason: investigations of neglected diseases such as tuberculosis may have pay-offs for diseases where there is a significant paying market. For instance, a new drug currently undergoing trials to tackle AIDS-related and paediatric diarrhoea prevalent in developing countries, might also address irritable bowel syndrome, a condition for which there is a very large and profitable market in the developed world (27).

The above discussion draws largely on the experience of developed countries because that is where most R&D has hitherto taken place and where policy responses have been developed. Developing countries, albeit in very different circumstances, may be able to take advantage of developed country experience in making their own policy choices. Some developing countries have a solid scientific infrastructure, largely based on the development of public sector capacity, and devote considerable resources to biomedical research. However, an uncritical application of the linear model and a low participation of the private sector in R&D have handicapped them in translating scientific capacity into useful innovations. This has resulted in a model that has not been well attuned to the application and commercialization of any inventions they might make. The private sector in most of the developing countries reviewed for this report has, until very recently, been a weak source of innovation in the biomedical field.

A number of countries with well-developed scientific infrastructures are now seeking to develop new policies to stimulate innovation, which we discuss further in Chapter 5. The challenge for all developing countries is to fashion innovation policies appropriate to their particular circumstances.

POLICY PROPOSALS: FINANCING AND PRIORITY SETTING

The discussion above covers a wide range of scientific, technical, institutional and financial issues that may affect the progress of early stage research. In what follows we discuss particular policy proposals to address the various gaps in the current process.

In the past few years, the amount of money flowing into R&D for the benefit of developing countries has increased substantially. Interest among public funders in developed countries has increased for both upstream and downstream research. Indeed, it is estimated that non-profit foundations have contributed US\$ 900 million to public-private partnerships for product development from their inception, nearly ten years ago, until the end of 2004, without including initiatives such as the "Grand Challenges" mentioned above and recent NIH investment in a vaccine for HIV/AIDS.

There are, as has been seen, many challenges in translating advances in our much enhanced knowledge at the level of the genome into diagnostics, vaccines and treatments relevant to the disease profile and resource constraints of developing countries. To achieve that goal, more resources need to be devoted to translational work for these indications in the fields of proteomics, structural genomics, bioinformatics, computational biology and nanotechnology.

Recent reports on health research for development have made a number of recommendations on resource flows and coordination. The 1990 Commission on Health Research for Development recommended that governments should spend 2% of their health budgets on what it called essential national health research and that donor nations should spend 5% of their aid for health in developing countries on research and the strengthening of research capacity. Finally, it recommended that there should be an international mechanism to monitor progress and bring greater coherence to research on health problems of developing countries, which would also

have the potential to mobilize greater long-term funding in support of such research (28).

Subsequent reports (e.g. the CMH report) have repeated similar calls focusing on the need for more resources and a number of services that might be more appropriately provided globally than locally. As recently as 2005, WHO Member States passed a resolution in the World Health Assembly which urged Member States to "consider implementing" the (financing) recommendations of the 1990 Commission on Health Research for Development (29). The more ambitious recommendations of the CMH, for a new Global Health Research Fund of US\$ 1.5 billion annually and for an equivalent increase in the amount of money going through existing channels to bodies such as WHO or public-private partnerships, have not materialized. In spite of recent encouraging signs from governments and foundations, much more research needs to be done at the upstream/downstream interface that is so important in translating promising science into products needed to address health problems in developing countries.

This is not just a question of money. The need for an effective balance between competition and collaboration has already been noted. Duplication of effort is, in principle, undesirable but maintaining competition to some extent requires it. The tension between desirable coordination and collaboration, and equally desirable competition, is inherent. Initiatives such as the Global HIV/AIDS Vaccine Enterprise are attempts to reconcile these potentially conflicting objectives.

What is also clear is that, in each disease, different approaches to diagnosis, prevention or treatment may be required. It is, therefore, impossible to make other than very general points about priorities without considering the landscape for each indication and intervention. Even then, there will inevitably be divergent, but equally legitimate, views about priorities in each disease area. In all fields there is a very heterogeneous collection of academics, small and large companies in pharmaceuticals or biotechnology, governments in the form of aid donors or medical research councils, foundations, and patient and civil society groups. One solution is to promote more organized information sharing and hold coordination meetings to achieve this. A good example is the Stop TB Partnership which is a network of international organizations, countries, donors from the public and private sectors, governmental and nongovernmental organizations, and individuals, that have expressed an interest in working together to achieve their shared goal.

Bearing in mind the above considerations, the principal actors in the early stages of health research for developed and developing countries are governments as funders, and medical research councils (or equivalents) as the responsible entities for the execution of research programmes, either directly or through funding third parties.

Spending by developed country governments on health R&D varies widely. In the United States, health R&D spending represents well over 0.2% of GDP. By contrast in Europe, average spending is only 0.05% of GDP. The overall OECD average is about 0.1% of GDP. In developing countries, average health-related R&D expenditure is much lower (30).

It is in the interest of all countries to promote health research that addresses the health needs of developing countries and to set specific and measurable targets in this regard.

2.1 Governments of developed countries should reflect adequately this objective in their research policies. In particular, they should seek to define explicit strategies for R&D and devote a growing proportion of their total health R&D funding to the health needs of developing countries, with an emphasis on upstream and translational research.

2.2 Developing countries should establish, implement or strengthen a national programme for health research including best practices for execution and management of research, with appropriate political support, and long-term funding.

It is right that governments should take responsibility for setting research priorities. However our review of needs suggests a number of areas that may deserve higher priority in the thinking of research councils and governments.

2.3 Government and funder attention should be paid to upstream research that enables and supports the acquisition of new knowledge and technologies that will facilitate the development of new products, including drugs, vaccines and diagnostic tests to tackle the health problems of developing countries. Attention should also be paid to the current inadequacy of the research tools available in these fields of research. These include techniques to understand new pathways to discovery, better ways to use bioinformatics, more suitable animal models and other disease-specific technologies.

2.4 When addressing the health needs of people in developing countries, it is important to seek innovative ways of combating Type I diseases, as well as Type II and Type III diseases. Governments and funders need to assign higher priority to combating the rapidly growing impact of Type I diseases in developing countries, and, through innovation, to finding affordable and technologically appropriate means for their diagnosis, prevention and treatment.

2.5 Actions should be taken by WHO to find ways to make compound libraries more accessible to identify potential compounds to address diseases affecting developing countries.

2.6 WHO should bring together academics, small and large companies in pharmaceuticals and biotechnology, governments in the form of aid donors or medical research councils, foundations, public–private partnerships and patient and civil society groups for a standing forum to enable more organized sharing of information and greater coordination between the various players.

POLICY PROPOSALS: INTELLECTUAL PROPERTY

This report seeks to identify means to promote innovation for diseases that are prevalent in developing countries. Several intellectual property issues are relevant to the discovery phase, such as the appropriation of upstream scientific results, patenting policies by universities and research institutions, protection of databases and the

recognition of and compensation for traditional knowledge eventually used to develop new medicines. This chapter only deals with the two former issues.

RESEARCH TOOLS AND PLATFORM TECHNOLOGIES

In our own consultations, we have also found that more research is required to develop research tools necessary to facilitate innovation. For instance, there is a widespread demand for better animal models that replicate more closely how a disease being investigated affects humans. We have also been made aware of concern regarding potential restrictions in access to research tools. The following is the classic statement of the case that the protection by intellectual property rights of research tools may constitute a problem:

... the recent proliferation of intellectual property rights in biomedical research suggests a different tragedy, an “anticommons” in which people underuse scarce resources because too many owners can block each other. Privatization of biomedical research must be more carefully deployed to sustain both upstream research and downstream product development. Otherwise, more intellectual property rights may lead paradoxically to fewer useful products for improving human health (31).

In developed countries the evidence to date, which mainly comes from the United States, suggests that researchers in both the public and private sector have found various ways of coping with the new environment. Working solutions include licensing, inventing around patents, infringement (often informally invoking a research exemption), developing and using public tools, and challenging patents in court. Changes in the institutional environment, such as the tightening of gene patenting rules introduced by the United States Patent and Trademark Office, and guidelines produced by the NIH to encourage good patenting and licensing practices, appear to have further reduced the threat of breakdown and access restrictions, although the environment remains uncertain. It is clear, however, that these various working solutions involve costs in terms of either time or money or both (32). A recent study in the United States of researchers in academia, government and non-profit organizations suggests that difficulties in gaining access to materials (e.g. data or cell lines) may have more significant implications for the conduct of research than patenting itself (33).

Furthermore, another recent report by the United States National Academies of Sciences on this subject reached the following conclusion:

The committee found that the number of projects abandoned or delayed as a result of difficulties in technology access is reported to be small, as is the number of occasions in which investigators revise their protocols to avoid intellectual property issues or in which they pay high costs to obtain intellectual property. Thus, for the time being, it appears that access to patented inventions or information inputs into biomedical research rarely imposes a significant burden for biomedical researchers. For a number of reasons, however, the committee concluded that the patent landscape, which already is becoming complicated in areas such as gene expression and protein–protein interactions, could become considerably more complex and burdensome over time (34).

Accordingly the committee made recommendations which addressed “an increasingly problematic environment for research in genomics and proteomics as more knowledge is created, more patent applications are filed, and more restrictions are placed on the availability of and access to information and resources” (34).

A special case is that of genetic diagnostic tests, which may be used either clinically or in the course of further research. They, therefore, have a dual nature, both as a final product, and as a discovery tool. A survey of over 100 laboratories in the United States concluded that patenting and licensing practices in this field had had a negative impact on clinical use and the development of further genetic tests. The authors did not express a view about whether patents in this area were critical to the development of genetic tests in the first place (35).

A Swiss survey identified obstacles to research deriving from patent protection. Respondents favoured the creation of an exception for clinical use of genetic tests or some means of non-exclusive compulsory licensing on reasonable terms (36).

The evidence above relates to mainstream research of potential commercial value. It is likely that transaction costs will weigh more heavily on those working with limited resources on projects on diseases particularly affecting developing countries. One notable case is that of the Malaria Vaccine Initiative, pursued by the not-for-profit nongovernmental organization Program for Appropriate Technology in Health (PATH). The programme seeks to develop a vaccine for malaria but is in the process of confronting over 20 partially overlapping patents related to the antigen MSP-1, spending considerable time and money in the enterprise (37). A representative of this organization noted:

Why does the IP landscape for MSP-1 not sort itself out through traditional channels such as technology transfer and the courts? Developers who want assurance of the rights to use MSP-1 would have to obtain licenses from no less than eight organizations. Though theoretically possible, a licensing transaction of this type would take years, require significant staff time, and cost hundreds of thousands of dollars in attorney fees. While companies routinely make such efforts on behalf of commercial products, the economics of malaria vaccines make developers more reluctant to invest in such cumbersome technology acquisition (38).

However, our studies did not reveal other comparably complex cases among public–private partnerships in other fields of research relevant to developing countries (39). Some public–private partnerships say that their philanthropic mandates can be useful in encouraging companies to license their intellectual property more easily, and more cheaply, than would be likely in a commercial exchange. It is, therefore, difficult to draw generally valid conclusions from the evidence available.

There is also very little empirical evidence about the impact of research tool patents in the biomedical field in developing countries themselves. More experience and empirical research is required. The impact of such patents may be more significant than in developed countries, as research institutions or companies in developing countries generally lack the legal and negotiating capacity to engage in complex negotiations, and the organizational flexibility and funds to pay licence fees, if required by patent holders. A survey conducted for us of 103 Indian firms revealed

that among 13 variables that could determine the abandonment of R&D projects by the Indian pharmaceutical industry, restricted access to patented upstream technologies because of contractual difficulties was likely to have the biggest impact on a firm's decision to abandon such projects (40).

Possible approaches used or considered to address this issue include the following:

- changes in patenting policies, or guidelines intended to promote more appropriate behaviour by participants in the system;
- patent pools to facilitate access to needed technologies;
- research exemptions in patent law to reduce the risk of infringement in R&D;
- compulsory licensing to allow access to upstream technologies.

Changes in patenting policies

Countries may adopt different approaches to patenting. On the one hand, the TRIPS agreement in Article 27.1 obliges countries to grant patents across all fields of technology provided that they are new, involve an inventive step (or are non-obvious) and are capable of industrial application (or useful). On the other hand, it allows various exclusions from patentability such as discoveries or genes which do not meet these criteria. Plants and animals may be excluded from patentability, except for microorganisms, and non-biological and microbiological processes. The agreement does not specify how countries should define what an "invention" is, or how the criteria of patentability (i.e. novelty, an inventive step or non-obviousness, and utility or industrial applicability) should be interpreted. The desirability of restricting patentability of genetic discoveries in this way will need to be assessed according to the circumstances of each country. For instance, countries that are mainly users of gene-based research tools patented abroad might promote the use of such tools by limiting their patentability. Other countries, with more advanced capacities in genomics, might favour a less stringent interpretation of patentability. If patents are granted, they can limit the scope of the claims to what has actually been invented. Patenting policy in this field should aim to facilitate research and development of health-care products.

One example of institutional adaptation to the changing technical environment was the announcement in 2001 by the United States Patent and Trademark Office of new guidelines on expressed sequence tags (short pieces of DNA that help to identify when particular genes are being expressed in cells). These guidelines tighten the specifications regarding what constitutes "utility",⁹ and provide guidance to patent examiners about how to apply the utility criterion to biotechnological inventions (41). In such cases, patentability can be established only if the patent application discloses a *specific, substantial* and *credible* utility. It is intended that this new standard will prevent patents being granted on inventions for which only a speculative application is disclosed. The introduction of these tighter criteria may be one reason, among others, why patent applications in this area have declined recently.

⁹ "Utility" in the United States refers to the criterion for patentability which broadly means that the invention should demonstrate some potential use. The criterion in most other countries is demonstration of "industrial applicability."

The EC Directive of 1998 on the legal protection of biotechnological inventions has not been implemented in a similar way in all the European Union. Unlike most other countries, France and Germany have introduced rules that limit the scope of patent protection for human gene sequences to the specific use disclosed in the patent application, thus excluding protection for future, as yet undiscovered, uses. This is because broad protection may disadvantage those wishing to build on the invention, while narrower claims may facilitate their downstream use. Another question is whether subsequent patenting of a new use should be allowed or not (42).

Countries may also consider guidelines or other means to encourage or mandate patenting and licensing policies that promote innovation. In 2004, in the United States NIH introduced draft guidelines (“best practices”) on the patenting and licensing of genetic inventions funded by NIH grants. On patenting, the guidelines said it should be considered whether:

...significant further research and development by the private sector is required to bring the invention to practical and commercial application. Intellectual property protection should be sought when it is clear that private sector investment will be necessary to develop and make the invention widely available. By contrast, when significant further research and development investment is not required, such as with many research material and research tool technologies, best practices dictate that patent protection rarely should be sought (43).

On licensing, they provided a more extensive set of principles supporting non-exclusive licensing as a general rule. Where exclusive licensing might be necessary to promote further development, the guidelines suggest that care should be taken to license only in the specific area the licensee is working in, to avoid blocking off other areas of research that may use the same technology. In addition, they said consideration should be given to including specific provisions to protect further research and public health. For instance, a licence could reserve the right for the invention to be used in non-profit research organizations for either research or educational uses (43).

Governments may choose whether or not to allow the patenting of genetic material.

2.7 Countries should seek through patenting and licensing policies to maximize the availability of innovations, including research tools and platform technologies, for the development of products of relevance to public health, particularly to conditions prevalent in developing countries. Public funding bodies should introduce policies for sensible patenting and licensing practices for technologies arising from their funding to promote downstream innovation in health-care products.

Patent pools

In 2000, a report by the United States Patent and Trademark Office on patent pools and biotechnology patents concluded that “The use of patent pools in the biotechnology field could serve the interests of both the public and private industry, a win-win situation” (44). Among the benefits cited for this approach to licensing

were: efficiency in obtaining rights to patented technology through “one stop” licensing mechanisms; the distribution of risks associated with research and development; and the elimination of “blocking” patents or “stacking” licences, and the consequent encouragement of cooperative efforts. Patent pools, therefore, could be most useful for technologies particularly relevant to developing countries, because the lack of strong market incentives may enable agreements that would otherwise be more difficult to engineer. Low-margin research directed towards problems of poor people might be promoted. Patent pools have also been proposed for the development of vaccines, given the large number of products owned by different entities and, consequently, the complexity of identifying, tracking and obtaining licences for patented technologies.

Patent pools have been established in the consumer electronics industry, specifically in relation to the establishment of industry standards. The biotechnology industry, however, is very different from the electronics industry. An OECD report noted:

However, the pharmaceutical biotechnology industry may be fundamentally different from the electronics sector. It is not an industry in which defining standards is important, and assuring interoperability of technologies is not very important, especially not in the development of therapeutics. A company’s worth is tightly tied to its intellectual property and fosters a ‘bunker mentality’. There are likely to be disagreements among partners over the value of the different patents in a pool, and dominant players may not have a strong incentive to join the pool. If a limited field of application and essential patents can be defined, the patent pool model is worthy of consideration in biotechnology...The suitability of the patent pool for biotechnology patents certainly requires further study, as does the role of government in promoting them (45).

One specific example of where a patent pool in a particular field might be possible in biotechnology is in relation to the SARS vaccine. Following the outbreak of SARS in 2003 many research institutes, mainly in the public sector, rushed to sequence the SARS genome and apply for patents. A proposal by several of the parties is that a patent pool should be developed to promote the development of a treatment or vaccine (46).

2.8 Patent pools of upstream technologies may be useful in some circumstances to promote innovation relevant to developing countries. WHO and WIPO should consider playing a bigger role in promoting such arrangements, particularly to address diseases that disproportionately affect developing countries.

Research exemptions

The TRIPS agreement allows the use of limited exemptions under Article 30, which has a possible application to the research tool issue as well as others:

Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the

legitimate interests of the patent owner, taking account of the legitimate interests of third parties.

In most of Europe, exemptions exist for acts done privately for purposes which are non-commercial, and for experimentation on the subject matter of the invention, even for commercial purposes.

In the United States, by contrast, there are no equivalent statutory exemptions, even for non-commercial or research uses. In the past, however, the courts have generally recognized some scope for “making or using of a patented invention merely for experimental purposes, without any intent to derive profits or practical advantage...” In 2002, this exception was narrowly interpreted in the case of *Madey v. Duke University*. The Court essentially said that, since the “business” of Duke University was research and teaching, there was no exemption from infringement, as the use of the patented invention was in furtherance of that “business”. The profit or non-profit status of the user was not a critical factor for the Court (47). Although not part of the judgement, the implication was that, as universities were now enthusiastic users of patents and licences, and litigated to enforce their patent rights, it would be inconsistent for them to seek to retain similar exemptions in their own activities (18).

Thus there is a broad spectrum of ways in which the research exceptions allowed under the TRIPS agreement are implemented in different countries, and how these are interpreted by courts. The essential point, in this context, is how to ensure that follow-on research that may be important to human health is not inhibited. The appropriate scope of the research exception must be considered in this light.

There is an active debate, particularly in the United States, about the appropriate scope of any research exception. In 2004, the United States National Academies of Science (NAS) published a report on the United States patent system which recommended the introduction of a formal research exemption in the United States for non-commercial purposes (48). This issue featured strongly in consultations for a successor report on DNA and protein patents (49). The American Intellectual Property Law Association (AIPLA) has endorsed the need for a research exemption, on the grounds that its absence in the United States was a hindrance to the progress of science and could drive certain kinds of experimentation abroad (50).

2.9 Developing countries need to consider in their own legislation what form of research exemption might be appropriate in their own circumstances to foster health-related research and innovation.

Compulsory licensing

In most countries, the law allows governments to issue compulsory licences on a number of grounds, including in circumstances where the development of a research field of importance to public health could be inhibited by the actions of particular patentees. For example, in the United Kingdom there are extensive powers in the Patent Act that, although rarely used, can remedy such situations. Section 48A (1) of the Act, for instance, covers:

refusal of the proprietor of the patent to grant a licence or licences on reasonable terms...the exploitation...of any other patented invention which involves an important technical advance of considerable economic significance in relation to the invention for which the patent concerned was granted is prevented or hindered (51).

Similar provisions exist in many other countries. In the United States, the Patent Act does not provide for compulsory licensing as such, but there are similar so-called march-in rights, only where federal funding of an invention is involved (Section 203) (52). The Swiss Federal Institute of Intellectual Property found in a survey of biotechnology companies and research institutes that "survey participants, and in particular research institutes, would welcome a compulsory licensing regulation in those cases where abusive monopoly positions are apparent" (53).

2.10 Countries should provide in their legislation powers to use compulsory licensing, in accordance with the TRIPS agreement, where this power might be useful as one of the means available to promote, inter alia, research that is directly relevant to the specific health problems of developing countries.

PUBLIC SECTOR AND UNIVERSITY PATENTING

As noted above, the 1980 Bayh–Dole Act in the United States permitted universities to patent inventions based on federally funded research on the premise that this would facilitate the commercialization of research, and hasten innovation. Subsequently, most of the developed world has pursued similar policies. In the more technologically advanced developing countries there is also considerable evidence of such patenting activity. For instance, India's Council of Scientific and Industrial Research has long pursued a policy of patenting inventions, and China has, in the past few years, positively encouraged patenting by its research institutes and universities.

This phenomenon has raised a general debate in the United States and other developed countries as to whether the application of a system designed to stimulate private sector R&D activity and commercialization could appropriately be applied to the public and university sectors (54). A classic case of how this would operate would be where a university discovers a potential drug but has neither the skill nor the resources to take it through the clinical trials process and bring it to market. In that case, an exclusive licence in favour of a pharmaceutical company may promote the development process. Without exclusive access to the technology, the company might not be prepared to take the risk of investing the resources necessary to develop the drug into a marketable product. For example, in 1985 Yale University received a patent for its d4T discovery, for the treatment of the AIDS virus. A few years later, the University granted an exclusive licence to Bristol-Myers Squibb to use this intellectual property in the development of Zerit®. In 1994, almost ten years after obtaining the patent, Zerit® was approved by the FDA for the treatment of HIV and AIDS infection.

An opposing point of view contends that the interests of technology transfer and commercial application would most often be best served by the widest possible dissemination of knowledge through publication. For many technologies, particularly upstream ones which are far from being a potential end product, conferring an

exclusive licence may have the effect of restricting the dissemination and use of that technology, and higher final product prices in the absence of competition. The "pure theory" of Bayh–Dole is that its principal benefit would occur through exclusive rather than non-exclusive licensing, in practice more than half of licences issued by universities in the United States are non-exclusive (55). Although disclosure of an invention in a patent allows others access to information that might otherwise not have been published, seeking a patent may also cause a delay in publication of research. All the evidence also suggests that, on average, the net income from patenting and licensing activities in United States universities makes a very small contribution to overall research funding. However, a handful of institutions have done well from the relatively small number of inventions that turn out to be commercially valuable (56).

Many institutions have a policy of undertaking research for the public good. For instance, the international network of agricultural research centres (the Consultative Group on International Agricultural Research) has a policy on intellectual property, with the underlying principle to "take every possible measure to facilitate access to research products for the public benefit, in particular in developing countries", while recognizing also that there will be exceptional circumstances when taking out patents property could be necessary to pursue its objectives (57).

From our point of view, the issue of providing patents on publicly-funded research needs to be examined from the following angles:

- How should developing countries, particularly those where the public sector is the principal reservoir of innovative capacity, frame their intellectual property policies with respect to public sector R&D? Can they learn anything from developed country experience?
- In developed countries such as the United States, does the practice of public sector patenting have implications for research on the specific health problems of developing countries? If it does, what policy implications are there?

Developing countries

Developing countries, even those with a relatively well developed scientific and medical infrastructure, face very different circumstances from those in the United States and other developed countries. Although most developed countries have tried to emulate Bayh–Dole policies in different ways (58), the success of such policies in the United States owes much to institutional arrangements specific to that country and is based on its unique higher education system and history of interactions between universities and businesses (69).

An emphasis on patenting and licensing as the chief means by which technology transfer takes place, as compared to publication and open knowledge sharing, may have negative implications for research in the area of public health as well as others (69). Since revenue prospects will be greater for products which will have a developed country market, this may further distort the allocation of research funding away from the specific public health problems of developing countries. Therefore,

care must be taken to ensure that research priorities, particularly those that could directly benefit poor people, are not distorted by the quest for larger licensing income.

2.11 Developing countries should ensure that their universities and public research organizations maintain research priorities in line with their public health needs and public policy goals, in particular the need for innovative research of benefit to the health problems of their populations. This should not exclude support of health-related research which meets their industrial or export objectives and that could contribute to improved public health in other countries.

Developed countries

Because most health-related R&D is conducted in developed countries, it is important to know how the intellectual property rules in developed countries might affect R&D relevant to the health problems of developing countries. In the absence of an effective research exemption in the United States, as discussed above, universities and technology managers have discussed creative ways in which further research, particularly on diseases affecting developing countries, can be facilitated.

For instance, one prominent United States university (Stanford) has suggested wording on the following lines as a standard means of establishing freedom for universities, public sector research organizations or, indeed, organizations such as public-private partnerships to be able to use particular technologies which are patented and then licensed out by a non-profit institute.

(Non-profit) retains the right, on behalf of **itself and all other non-profit academic research institutions**, to practice the Licensed Patent and use Technology for any purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patent against any such institution. (Non-profit) and any such other institution has the right to publish any information included in the Technology or a Licensed Patent (59).

It needs to be recognized, however, that additional conditions not standard in licensing agreements, such as the exclusion provided above, may act as a disincentive to some potential licensees. Nevertheless, we support the principle of access and, as noted above, universities and public research organizations may also draw on guidelines such as those provided by NIH to facilitate further innovation.

There are a number of examples where universities have licensed technologies on favourable terms to non-profit enterprises. In one example, Yale gave a licence to the non-profit pharmaceutical company OneWorld Health to develop novel azoles for the treatment of Chagas disease (60). The University of California at Berkeley has also provided a royalty-free co-exclusive licence to the same organization and a university biotechnology offshoot to develop a promising technology for the production of artemisinin-based malaria treatments. The TB Alliance has also negotiated deals with Johns Hopkins University and the University of Illinois, among others (61).

Universities have had an important role in the development and patenting of compounds (as well as tests, devices and tools), mainly supported with government funds, which have become best-selling drugs and products. For example, Yale University publishes periodically its pharmaceutical pipeline. In April 2005, this consisted of 28 separate entities, top of the list being Zerit® (62). Florida State University took out a patent on a method for making an anti-cancer drug which was subsequently licensed to Bristol-Myers Squibb to produce Taxol (63). In 2005, Gilead Sciences paid US\$ 525 million to Emory University to buy out future royalties owed to Emory arising from its patent on another antiretroviral. A study quoted by NIH suggests that of the 21 drugs with the highest therapeutic impact introduced between 1965 and 1992, public research was instrumental in the case of 15 of them. In the case of the others (e.g. AZT or flucanazole) NIH had a significant funding role in early research or trials (64).

The question here is whether universities in the developed world should have a responsibility to ensure as far as possible that their patenting and licensing policies not only facilitate R&D relevant to developing countries, but also access to drugs in developing countries. For example, in the case of Zerit®, there were protests in 2000/2001 led by students at Yale, supported by nongovernmental organizations such as Médecins Sans Frontières, demanding that the university should act to allow the import of lower cost generic versions of Zerit® in South Africa. Because the university had granted an exclusive licence to Bristol-Myers Squibb, it was unable to influence the situation in South Africa. In the end, Bristol-Myers Squibb itself took action to reduce its South African prices, and promised not to prosecute any generic producer (65).

These experiences have led some to consider what specific measures might be appropriate in university patenting and licensing policies to facilitate access to new medical technologies in developing countries. For instance, a pressure group called Universities Allied for Access to Essential Medicines is asking universities:

- (1) to adopt licensing language that facilitates access in low and middle income countries to medicines and health technologies originating in university research; and
- (2) to measure the success of technology transfer activities by the degree to which they facilitate global access; and
- (3) to promote research on diseases which principally impact the global poor (commonly referred to as neglected diseases, given the failure of market forces to stimulate research and development) and to find ways to work with non-profits that seek to develop medicines for those diseases (66).

Another body has been formed called Technology Managers for Global Health, as a subgroup within the influential Association of University Technology Managers in the United States, to press for similar sorts of arrangements (67). A project under the aegis of the American Association for the Advancement of Science, "Science and Intellectual Property in the Public Interest", is considering similar issues – including the possibility of so-called "humanitarian licensing" as a means to facilitate access to new technologies and medicines (68).

2.12 Public research institutions and universities in developed countries should seriously consider initiatives designed to ensure that access to R&D outputs relevant to the health concerns of developing countries and to products derived therefrom, are facilitated through appropriate licensing policies and practices.

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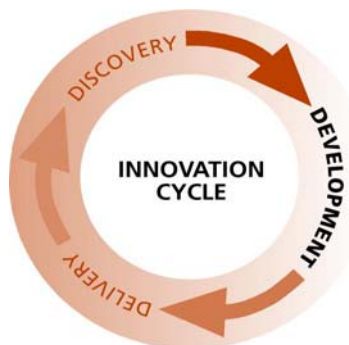
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CHAPTER 3

THE LONG ROAD FROM DISCOVERY TO DEVELOPMENT

INTRODUCTION

Although one of the most challenging aspects of drug discovery is identifying candidate compounds, the most expensive part is the process of taking the candidate through all the required stages of pre-clinical and clinical research and the regulatory process. In developed countries, the rapidly rising costs of health care, including supplies of medicines, are a matter of intense public concern. In developing countries, and even in some developed systems, the cost of medicines, often not available through public health-care systems, can be a matter of life and death.



Various estimates of drug development costs and their rapid escalation have been made, although there are many questions about the representativeness of the samples used, giving rise to controversies about the implications of the results. For instance, a recent study suggested that in the 1990s drug development costs rose by over 7% per annum in real terms. Moreover, while pre-clinical costs increased by 56% over the period, the clinical trials phase increased by 349%, so that clinical trials and beyond accounted for nearly 60% of R&D costs (1). More recent estimates suggest even higher amounts (2). As noted above, some dispute these figures on methodological grounds, as well as the implication that they support higher intellectual property protection for pharmaceutical companies to induce more innovation in the face of higher cost (3). It is generally agreed, however, that the average costs of product development for diseases that mainly affect developing countries are likely to be much lower than average industry costs (4).

Whatever the exact figure, there is certainly good evidence that quite rapidly rising expenditure on R&D has not yet had the desired result. Thus, while R&D spending by pharmaceutical companies based in the United States doubled between 1995 and 2002, the number of new molecular entities approved by the United States Food and Drug Administration (FDA) has not risen between the first half of the 1990s and the first half of this decade (Table 3.1). Annual figures have shown a decline since the mid-1990s from a peak of 53 in 1996 to a low of 17 in 2002, although approvals recovered to 31 by 2004 (Figure 3.1) (5, 6).

There is not the expected acceleration in products reaching patients which optimists predicted five years ago. The data also suggest (Table 3.1) that, while the number of new molecular entities approved each year is broadly the same as in the early 1990s, the proportion regarded by the FDA as potentially significant therapeutic advances over existing drugs (which are given "priority review" status) has tended to decline.

Similarly, the proportion of all new approvals in that category has declined from 26% to 19% since the early 1990s.

Table 3.1 New drug approvals by the United States Food and Drug Administration, 1990-1994 and 2000-2004				
	Priority review approvals (a)			
	NMEs	Others	Total	NMEs (%)
1990 - 1994	63	29	92	69
2000 - 2004	49	31	80	61
	Standard review approvals (b)			
	NMEs	Others	Total	NMEs (%)
1990 - 1994	63	195	258	24
2000 - 2004	71	276	347	20
	Total approvals			
	Priority NMEs	Standard NMEs	Total NMEs	Priority (%)
1990 - 1994	63	63	126	50
2000 - 2004	49	71	120	41
	Total approvals			
	Priority Review	Standard Review	Total	Priority (%)
1990 - 1994	92	258	350	26
2000 - 2004	80	347	427	19
	Total approvals			
	Total NMEs	Total Others	Total	NMEs (%)
1990 - 1994	126	224	350	36
2000 - 2004	120	307	427	28

NMEs, new molecular entities.

(a) Significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease.

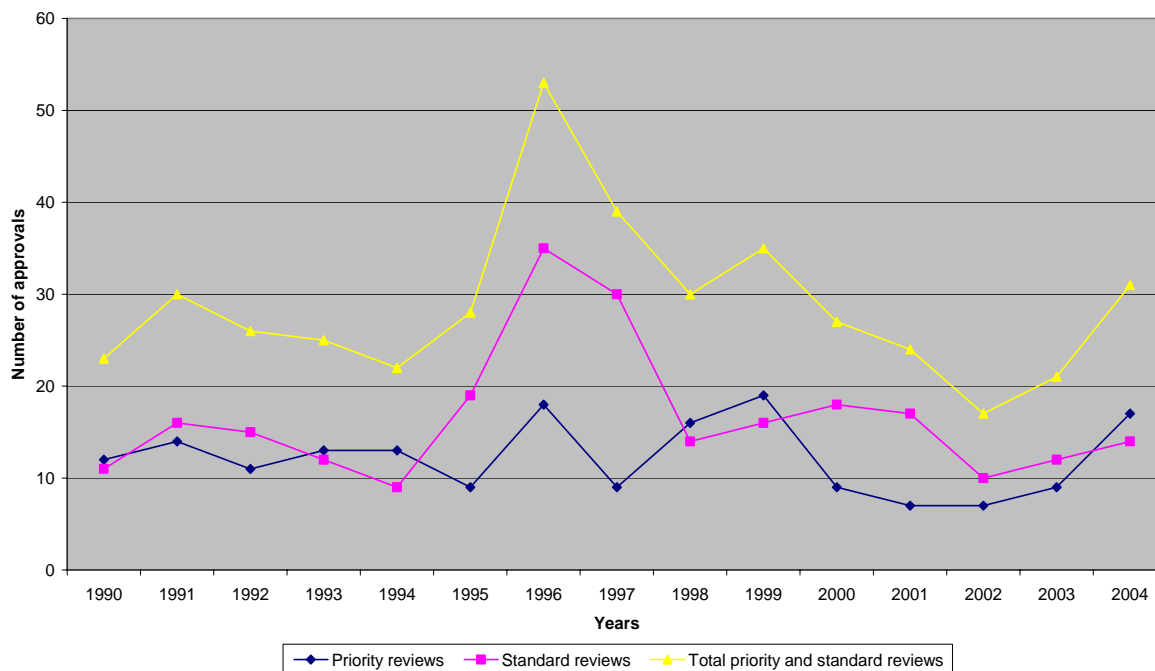
(b) The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

Source: reference (6).

A report for the EU in 2004 concluded that there was a fall in innovative productivity:

...global R&D expenditure over the past decade has shown a strong upward trend...The 'crisis' therefore is that the number of new products has not increased whilst the overall level of resources being invested has risen dramatically (7).

Figure 3.1 New drug approvals by the United States Food and Drug Administration, 1990 - 2004



See notes to Table 3.1.

Source: reference (6).

There are two major sources of explanation for these trends: scientific and technical, on the one hand, and economic, policy and institutional on the other. Looking at the range of activities from optimization of a lead compound through to regulatory review of the safety, efficacy and quality of a new product, there are a number of key issues that require careful consideration.

SCIENTIFIC AND TECHNICAL ISSUES

The explanation offered by the FDA for these trends is that the applied sciences for product development have failed to keep pace with the tremendous advances in the basic sciences, which were noted in Chapter 2 (8). In the view of the FDA, the following are the main deficiencies in the process of development:

- The difficulties of predicting success for a product at each stage of the innovation cycle: for instance, it is estimated that a new compound entering Phase I testing has only an 8% chance of reaching the market compared to an historical success rate of 14% (2).
- The traditional tools used to assess product safety and efficacy, such as animal models or in vitro screening, have not changed in decades, and are not always good predictors of responses in humans. Thus, later failures are not predicted early on in the development phase (and presumably some potential successes may be eliminated).

- Scientific understanding of the pathophysiology of disease, as opposed to a broad understanding of responsible genes or proteins, is deficient, resulting in a lack of ability to correlate early markers of efficacy or safety with outcomes.
- The process of scaling up from a laboratory concept to a medical product that can be mass produced may be a bottleneck in the product development process.

The FDA, therefore, recommends efforts to develop tools that can more reliably and efficiently determine the safety and efficacy of a new medical product. For example, with more knowledge, it might be possible to replace animal testing by reactions at the level of the gene or protein. There may also be much greater scope at this stage for using computer modelling in predictive toxicology. The FDA notes that some commentators believe the extensive use of "in silico" (i.e. computer-based) technologies could reduce drug development costs by 50%.

In general, if it were possible to associate various health or safety outcomes with predictive biomarkers, this could save vast amounts of time and money at various stages of the development process. Biomarkers or surrogate end-points in clinical evaluation can accelerate and shorten the clinical trials phase. For example, in the case of antiretrovirals, the approval by the FDA of CD4 cell counts and viral load as surrogate markers was a major reason for the rapid introduction of these life-saving drugs (as compared to expensive and time consuming trials assessing morbidity and mortality data). Other biomarkers that could be critical include, but are not limited to:

- biomarkers of the genetic basis of a disease, particularly targets for potential therapeutic or vaccine development;
- biomarkers of potential toxicity to candidate compounds;
- biomarkers (probably using pharmacogenetics) to identify “non-responding” and “toxic response” patients.

The FDA and other regulatory authorities have favoured the concept of model-based drug development, using pharmaco-statistical methods. In fact, cars and aeroplanes are now predominantly developed and tested using computer-based systems, which has revolutionized the product development process. The challenge is to bring about a comparable revolution in the far more complex arena of developing products for human health. To do so there has to be further investment in population genomics to understand the genetic basis of disease, the development of biomarkers and surrogate end-points, and the general development and standardization of biological, statistical and bioinformatics methods for identifying characteristics of safety and efficacy.

As noted in Chapter 2, the NIH has launched the Roadmap Initiative, which seeks to overhaul the methodology of basic research and to restructure clinical research:

Ideally, basic research discoveries are quickly transformed into drugs, treatments, or methods for prevention. [There is a]... need to develop new partnerships of research with organized patient communities, community-based health care providers, and academic researchers... This vision will require new paradigms in how clinical research information is recorded, new

standards for clinical research protocols, modern information technology platforms for research, new models of cooperation between NIH and patient advocates, and new strategies to re-energize our clinical research workforce (9).

Finally, the specific techniques used in regulation need to be assessed. The search for biomarkers and surrogate end-points partly reflects the increasing burden of clinical trials and the significant increase in trial sizes required by regulators. Some have, therefore, urged the consideration of alternatives to randomized controlled trials (RCTs) as the "gold standard". While recognizing the value of this methodology, which is why it has become the "gold standard", they encourage the development of alternatives that might be cheaper and smarter and less costly than current methods, without sacrificing standards of safety. One commentator wrote:

The international community should embark on collaborative methodological research to critically evaluate alternatives. This requires an experimental approach, rather than just a theoretical analysis, with formal comparisons of the results of studies comparing novel and traditional (RCT) designs. Some possibilities...have...recently been advanced. They include various forms of sequential, adaptive, decision based and risk-based designs, as well as Bayesian techniques. We should even reexamine old heresies such as observational studies, including historical controlled trials, and confirm or refute the circumstances under which they might be appropriate (10).

These scientific and technical issues in product development are general ones, not specific to diseases that disproportionately affect developing countries. It is recognized, however, that there may be specific issues where the disease, or characteristics of the disease, are peculiar to a developing country setting. For example, several of the technologies needed in developing countries are for prevention (such as vaccines, vaginal microbicides and contraceptives). To demonstrate a statistically significant effect, larger numbers of people are required in clinical trials than is the case with treatments. Moreover, ethical considerations dictate that the "control" group should use the best method currently available, not a placebo; for example, a condom in the case of microbicides rather than a gel with no active ingredients. This increases further the numbers required and the complexity and cost of the trial. There is also the need for a long follow-up period, and the ethical obligation of having to offer treatment to those in whom the intervention fails and who develop the disease.

The central question is whether new methods and models can be devised that will benefit the R&D process across the board. For certain diseases there will always be specific tools of high priority. In addition, some research on Type II and Type III diseases can lead to an exploration of potential new, generalized approaches to determining the safety, efficacy and quality of new therapies. The TB Alliance provides one example: new methodologies in how to assess the clinical safety and efficacy of combination products are being investigated with regulators.

3.1 Governments and the appropriate national authorities and funders should assign a higher priority to research on the development of new animal models, biomarkers, surrogate end-points and new models for assessing safety

and efficacy, which would increase the efficiency of product development. They should also work with their counterparts in developing countries to formulate a mechanism to help identify research priorities in this area for Type II and Type III diseases particularly relevant to developing countries, and provide funding for this R&D.

THE INSTITUTIONAL FRAMEWORK

As emphasized in Chapter 1, the landscape of product discovery and development has changed enormously in the past two decades. We do not wish to reiterate the nature and consequence of these general changes, but rather to focus on the specific changes in the field of the Commission's interest. A pioneering effort was the establishment of initiatives based in WHO, to promote the development of products for treatment and prevention, specifically for developing countries (see Box 3.1).

Box 3.1 WHO-based research programmes

Special Programme for Research and Training in Tropical Diseases (TDR)

TDR is an independent global programme of scientific collaboration. It was established in 1975 and is sponsored by UNICEF, UNDP, World Bank and WHO. It aims to coordinate, support and influence global efforts to combat a portfolio of major diseases of poor and disadvantaged people. Its budget for 2004–2005 was just less than US\$ 100 million. TDR focuses on neglected infectious diseases that disproportionately affect poor and marginalized populations. Its disease portfolio includes: African trypanosomiasis, dengue, leishmaniasis, malaria, schistosomiasis, tuberculosis, Chagas disease, leprosy, lymphatic filariasis and onchocerciasis.

TDR aims to improve existing and develop new methods for preventing, diagnosing, treating and controlling neglected infectious diseases, which are relevant, suitable and affordable by developing endemic countries, which can be readily integrated into the health services of these countries, and which focus on the problems of poor people. TDR also seeks to strengthen the capacity of developing endemic countries to undertake the research required for developing and implementing these new and improved disease control approaches. TDR has produced many products and outcomes, including being a key participant in the genetic transformation of a mosquito that is unable to transmit malaria. In 2002, TDR played an essential part in bringing a new oral treatment for visceral leishmaniasis called miltefosine to registration. Every year 2.4 million DALYs are lost because of visceral leishmaniasis.

Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

HRP was established in 1972, sponsored by UNDP, UNFPA, World Bank and WHO, and is the main instrument within the United Nations system for research in human reproduction, bringing together policy-makers, scientists, health-care providers, clinicians, consumers and community representatives to identify and address priorities for research to improve sexual and reproductive health. HRP's current budget is about US\$ 23.7 million.

HRP has been crucial in the development and promotion of family planning clinics, preventing unsafe abortion, improving maternal and perinatal health, and controlling

sexually transmitted infections and reproductive tract infections. In 2004 several research projects to help develop effective interventions in maternal and perinatal health were completed. Also new software was developed for the analysis of menstrual bleeding patterns and for centralized data management. A multi-country study in East and Southern Africa on the dual risk of unintended pregnancy and HIV indicated that the use of condoms was most likely related to the risks of HIV than a desire to regulate fertility. HRP has also been central to the development of once-a-month injectable contraceptives and the use of levonorgestrel emergency contraceptives.

Initiative for Vaccine Research (IVR)

The WHO Initiative for Vaccine Research was created to guide, provide vision, support and facilitate the development, clinical evaluation and worldwide access to safe, effective and affordable vaccines against infectious diseases especially in developing countries. Through its efforts IVR hopes to create a world in which all people at risk are protected against vaccine-preventable diseases. At present IVR is supporting many new vaccines, including eight new vaccines for tuberculosis that are at Phase I of development, one new vaccine for HIV/AIDS that is at Phase III and three that are at Phase II of development. They are also supporting four new vaccines for malaria at stage II of development.

Source: references (11–21).

Three major changes of note have taken place in the past decade:

- A few companies have set up dedicated R&D units devoted to diseases that particularly affect developing countries. These are: GlaxoSmithKline's Drug Discovery Unit in Tres Cantos, Spain, concentrating on malaria and TB; AstraZeneca's research facility in Bangalore, India, focusing on TB; and the Novartis Institute for Tropical Diseases in Singapore, targeting TB and dengue fever.
- Foundations, including the Rockefeller and Bill and Melinda Gates Foundations, have ploughed funds into this field on an unprecedented scale.
- As a result of the interest of foundations, industry and WHO, among others, public–private partnerships for product development for developing countries have been founded across several disease areas to look for new treatments, vaccines and diagnostics (see Box 3.2).

Box 3.2 Public–private partnerships for product development

Although public–private partnerships have existed in different forms for several decades, in the past ten years a significant number have arisen that focus specifically on the development of products to tackle diseases that mainly affect developing countries.

These arose largely as a result of initiatives on the part of individuals in companies, foundations, nongovernmental organizations and WHO. The first of the recent wave of these public–private partnerships was the International AIDS Vaccine Initiative (IAVI), founded in 1996. They include the following:

HIV/AIDS

International AIDS Vaccine Initiative (IAVI)
International Partnership for Microbicides (IPM)
South African AIDS Vaccine Initiative (SAAVI)

Malaria

European Malaria Vaccine Initiative (EMVI)
Malaria Vaccine Initiative (MVI)
Medicines for Malaria Venture (MMV)

Tuberculosis

Aeras Global Tuberculosis Vaccine Foundation (Aeras)
Foundation for Innovative New Diagnostics (FIND)
Global Alliance for TB Drug Development (TB Alliance)

Other "neglected infectious diseases"

Drugs for Neglected Diseases Initiative (DNDi)

In addition, the Institute for OneWorld Health, a non-profit pharmaceutical company, develops new, affordable medicines for infectious diseases that disproportionately affect people in the developing world, including visceral leishmaniasis, malaria, diarrhoea and Chagas disease. has developed an extensive portfolio of

Common characteristics of these public–private partnerships include:

- they use some private sector approaches to address R&D challenges;
- they target one or more "neglected diseases";
- they use, or intend to use, variants of the multi-candidate/portfolio management approach;
- their primary objective is public health rather than a commercial goal;
- their principal funders are foundations rather than governments.

Source: reference (22).

THE PUBLIC AND PRIVATE SECTORS AND PARTNERSHIPS

Because public–private partnerships bring together public sector funders and researchers, as well as private sector researchers and support in-kind from the private sector, they are an appropriate focus for a discussion of issues in developing country research, although this does not signify that they are the only important actors. Importantly, public–private partnerships provide the drive and scientific and technical leadership to promote coherent programmes of R&D in their area of speciality in the public and private sectors, which they can plan, coordinate, fund and actively manage (see Boxes 3.3, 3.4 and 3.5). Some, like IAVI and Aeras, also conduct in-house research (23). In addition, they have an important role in identifying pathways, and overcoming bottlenecks, in order to get products to those in need of them in developing countries.

A recent study of the portfolios of five public–private partnerships and of a sample of the pharmaceutical industry, identified 63 new drug projects for neglected diseases (including the tropical diseases, malaria and TB) (24). Of these 63 products, 16 were being developed by industry alone and 47 under the auspices of public–private partnerships. As of 2004, 18 of these drugs were in clinical trials, including nine at Phase III or beyond. This contrasts with the much-quoted figure of only 13 drugs of this kind approved between 1975 and 1999 (25). The significant finding was that one quarter came from the pharmaceutical industry working alone, one quarter from the industry together with public–private partnerships, and the balance from public–private partnerships working with a diversity of small firms, developing country firms, academics and the public sector, as well as two products from TDR.

Box 3.3 A diversity of partners

The possibilities for new creative partnerships are demonstrated by the number and diversity of the organizations currently working on an HIV/AIDS vaccine in collaboration with IAVI. These include: Advanced BioScience Laboratories, Inc.; Aaron Diamond AIDS Research Center; AlphaVax; Armed Forces Research Institute of Medical Sciences, Thailand; Agence Nationale de Recherche sur le SIDA; AVANT Immunotherapeutics, Inc.; Australian Vaccine Consortium; Aventis Pasteur; Biovector SA; Chiron Corporation; Epimmune Inc.; Excell Biotech; FIT Biotech; GenVec; GlaxoSmithKline; HIV Vaccine Trials Network; Impfstoffwerk Dessau Tornau GmbH; Istituto Superiore di Sanità, Italy; Kenyan AIDS Vaccine Initiative; Merck; Ministry of Health of Thailand; United Kingdom Medical Research Council; National Institute Allergy and Infectious Diseases, United States; Pediatric AIDS Clinical Trials Group, United States; South African AIDS Vaccine Initiative; St Jude’s Childrens Hospital, United States; Targeted Genetics; Therion Biologics Corporation; University of Massachusetts Medical School; University of New South Wales; Uganda Virus Research Institute; VaxGen; Vical Inc.; Vaccine Research Center, United States; Walter Reed Army Institute of Research, United States; Wyeth.

Source: reference (26).

Moreover, public–private partnerships represent a new opportunity for large pharmaceutical companies to re-focus their research directed at developing countries. Rather than pursue fully-fledged R&D programmes which are unlikely to meet companies’ economic and financial criteria, companies can set up relatively low cost R&D programmes (as in the cases of GlaxoSmithKline, Novartis and AstraZeneca cited above) by focusing on early stage R&D in the expectation that the expensive clinical trials phase, and some of the early stage research, may be subsidized by a public–private partnership or other public or non-profit funding. Such programmes may also benefit from tax deductions or other fiscal measures and can be justified on the grounds of corporate social responsibility. They also offer the possibility of spin-offs for more commercial research programmes. As one of us noted:

It is likely that as these collaborative endeavours progress we shall find homologies within the biochemical structure of various infectious micro-organisms that could form the basis of new targets for drug discovery or for

establishing the utility of new/existing drugs to treat multiple infections (i.e. “Broad spectrum” anti-infective medicines) (27).

Essentially, therefore, large pharmaceutical companies regard their “neglected disease” R&D as no-profit no-loss operations, which nevertheless meet a number of company objectives. It should be noted that the case of R&D on HIV/AIDS is different. There is also a commercial motivation for the development of antiretrovirals, based principally on the developed country market. Even HIV vaccine R&D has considerable commercial potential despite high scientific risks. For instance, there are currently estimated to be 127 products in the pipeline to tackle HIV/AIDS, in addition to the 27 already marketed and the 26 more expected to be marketed by 2015 (29).

Box 3.4 Global Alliance for TB Drug Development

The TB Alliance is the only non-profit drug developer focused exclusively on obtaining a better, affordable cure for tuberculosis, which kills someone every 15 seconds. Its aim is to replace today’s complex, multidrug regimen, which lasts six to eight months, with a superior regimen, preferably in a fixed-dose combination that is limited to only two months or less.

With the support of the Bill and Melinda Gates Foundation and the Rockefeller Foundation, the TB Alliance was formed in late 2000 by the international community to bridge the R&D gap for tuberculosis drugs. It works with diverse partners, including: biotechnology and pharmaceutical companies, such as Chiron and GlaxoSmithKline; academic laboratories, such as the University of Illinois–Chicago; and public research institutes, such as the Korean Research Institute for Chemical Technology. All partners commit to the TB Alliance’s “AAA” strategy, which ensures that any resulting product be priced affordably, adopted by health-care practitioners and made accessible to those in need.

In its search for the most effective antibiotics, the TB Alliance prioritizes drug candidates that could shorten treatment, be effective against multidrug-resistant strains, treat HIV-TB co-infection and, ultimately, improve the treatment of latent infection. With eight discovery programmes and two compounds in clinical trials, the TB Alliance’s pipeline holds the potential for new regimens which could cut treatment time in half and be available within five years.

Leveraging this pipeline, the TB Alliance has designed a new paradigm that will allow for the creation of breakthrough treatments. New regimens will be based on optimal combinations of new drugs that attack multiple targets of the TB bacterium. Rather than replace each of the four current TB drugs individually, this novel strategy will advance candidates to Phase I and then, with approval of regulatory agencies, test combinations of successful candidates.

Source: reference (28).

Small companies, biotechnology companies, contract research organizations and firms in developing countries have commercial imperatives different from those of large pharmaceutical companies. These imperatives vary according to circumstances, but the evidence suggests that the smaller incentives which they may be offered, in the form of contracts or otherwise, can make commercial sense to them despite being of little interest to the larger players. That is why public–private partnerships form alliances with these entities and capitalize on the opportunities each offers to the

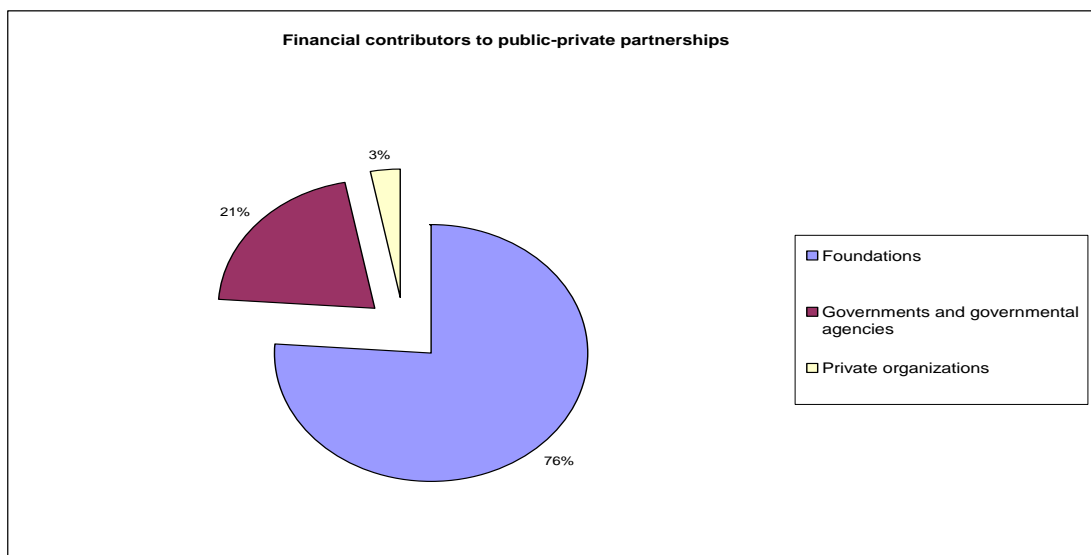
other. In the more homogeneous industry structure of the past, this would not have been possible, as many of those entities did not exist and pharmaceutical companies had a stronger position in the innovation process. Now, in this field, public–private partnerships are performing the service of integrating inputs from different parts of a far more diverse industry (24).

Current funding arrangements

A crucial question relating to the activities of public–private partnerships and other entities involved in this area of R&D is the sustainability of their funding. Because R&D is a long-term process, it requires that all participants have some degree of assurance and protection from risk. In the large pharmaceutical sector, risk is accepted in return for the probability that it will be rewarded across a research portfolio by a proportion of products earning large returns, or at least a spectrum of returns, which more than outweigh the cost of failures. In the case of research directed principally at the health problems of developing countries, this calculation cannot apply. Different mechanisms need to be devised to provide a suitable enabling environment for long-term R&D addressed to the health problems of developing countries.

In background research for the Commission, 24 public–private partnerships were identified which engage in product development (30). Over US\$ 1 billion has been contributed to these 24 partnerships to date. Of that total, approximately US\$ 900 million has been contributed by private foundations, US\$ 244 million by governments and governmental agencies, and US\$ 36 million by private entities (see Figure 3.2).

Figure 3.2 Public–private partnership funding: sources by type of financial contributor



Source: reproduced, with permission, from reference (30).

The Bill and Melinda Gates Foundation is the largest single contributor with more than 60% of the total. Foundations as a whole have contributed three quarters of the total. The Bill and Melinda Gates Foundation alone funds 17 of the 24 public–private partnerships, and it is the single funding source for nine organizations. Governments and government agencies have contributed only about one fifth, of which USAID has contributed 35%. Other governmental funders, among others, include Ireland, the Netherlands, Switzerland and the United Kingdom. The private sector (other than the pharmaceutical industry, which provides support in kind) contributes a very small amount.

Box 3.5 The Drugs for Neglected Diseases Initiative

The Drugs for Neglected Diseases Initiative (DNDi) is the first non-profit organization concentrating primarily on neglected diseases, mainly human African trypanosomiasis (sleeping sickness), leishmaniasis and Chagas disease. It also includes malaria in its portfolio.

DNDi was launched as an initiative of Médecins Sans Frontières in 1999, recognizing the scarcity of effective drugs for these neglected diseases and thus the need to create an entity focusing on them. DNDi was incorporated as a legal entity in 2003.

DNDi is a form of public–private partnership that works through a collaborative approach, linking scientists in developing and developed countries and building regional networks that gather information and actively advocate for drugs for neglected diseases. In order to cut costs, it takes advantage of existing R&D capacity and complements it with additional expertise as needed.

In particular, it seeks to mobilize the public sector in developing countries to conduct R&D on neglected diseases. Its founders include Brazil’s Oswaldo Cruz Foundation, the Indian Council of Medical Research, the Malaysian Ministry of Health, the Kenya Medical Research Institute, and the Pasteur Institute.

DNDi is building a “needs-driven” portfolio based on the medical needs of neglected and most neglected patients rather than potential for profit. It currently has nine projects in its portfolio at different stages of development. It plans to spend around US\$ 250 million over the next 12 years to develop six or seven new drugs.

Source: reference (31).

This distribution of funding support for public–private partnerships is highly unusual in the degree to which the partnerships depend on private not-for-profit funding, the relatively small role played by governments and the dominance of one particular funder. For instance, foundations played a catalytic role in setting up a comparable research network in agricultural R&D for developing countries, the Consultative Group on International Agricultural Research, in 1971. However, about two thirds of the annual funding for this network, currently over US\$ 400 million, is now provided by developed country governments. In addition, the World Bank, which houses the secretariat of the network, contributes US\$ 50 million. Other funders, which include foundations and United Nations organizations such as the Food and Agriculture Organization (FAO), play a minor but valuable part in its diversified funding support (32).

Funding requirements

Estimates of future funding needs are necessarily inexact because of uncertainties about actual costs for each stage of research, attrition rates and the number of products entering development in a fast-moving scene.

In contrast to the cost figures cited at the beginning of this chapter, the estimates for public-private partnership products tend to be much lower. One estimation on behalf of the TB Alliance suggested that Phase I to Phase III clinical testing might cost US\$ 26.6 million for each potential tuberculosis drug tested. After including imputed interest expenses and the cost of failed drug candidates, the final cost of clinical trials is estimated at between US\$ 76 and US\$ 115 million. Based on an estimate that discovery phase costs would add another US\$ 40 to US\$ 125 million yields a total per-drug R&D cost of between US\$ 115 and US\$ 240 million. This is very much less than the equivalent estimates for industry previously cited. These orders of magnitude are supported by other calculations (22). Reasons for this difference include the opportunity to pick potential product candidates from a wide range of sources, in-kind support from the industry, and use of lower cost researchers and clinical trial sites in developing countries.

With regard to attrition rates in the development process, of the 63 products in development studied in the research cited, fewer than ten – on the basis of overall industry statistics – are likely to gain marketing approval. Some argue that the success rate for public-private partnerships is likely to be better than the industry average because the selection process is often based on later stage compounds, and the pipeline attrition is not based on low profit margins considerations. Conversely, because public-private partnerships tend to seek breakthrough products rather than incremental innovation as compared to industry, the attrition rate may well be higher in the longer term, particularly once the "low hanging fruit" has been picked. Because of the selection criteria, and the absence of purely commercial considerations, it is reasonable to think the attrition rate for public-private partnerships may be systematically different from that of industry as a whole.

Regarding numbers of products in development, the 63 products mentioned above do not include the pipelines of public-private partnerships and others looking for vaccines for HIV/AIDS, malaria and TB, or seeking to test microbicides to protect against HIV/AIDS. For instance, there are currently 35 ongoing trials at different stages for HIV/AIDS vaccines and the MVI has 10 ongoing trials.

Overall, although R&D costs in the neglected disease area may be lower than estimates for industry, rates of failure at some stage of the development process may not. Since early stage research is relatively cheap, but late stage and clinical development rather expensive, the youth of the public-private partnerships portfolio means that current funding is inadequate to take all current products through clinical trials and to marketing approval, or to failure at some point in the process. We deal here with the funding of clinical trials, but an equal concern is the availability of infrastructure, particularly in Africa, to conduct clinical trials on an increasing number of potential products.

Inadequate funding obliges sponsors and funders of R&D to take very difficult decisions relating to the likelihood of failure or success at different stages of the development process. Indeed, projects may need to be terminated even if they have the potential for success.

Many governmental funders find public–private partnerships difficult to fit into their traditional funding categories. Public–private partnerships are not governments, nongovernmental organizations or public sector entities. They have a multiplicity of governance arrangements which seek to be inclusive of all the stakeholders involved, but are nevertheless staffed predominantly by former industry personnel, and are, for the most part, entrepreneurial in outlook. Their work necessarily involves a high degree of autonomy and freedom, to make alliances and strike deals (through licensing or contracts) to pursue their objectives. This requires a degree of flexibility and restraint on the part of the donor. Correspondingly it might mean that more donors would consider funding public–private partnerships, and other entities in the field, if systems were in place that provided some independent mechanism for monitoring and evaluation, for collective use by donors in assessing the impact of their funding.

A 2004 estimate, comparing estimated needs with pledged funding for a sample of public–private partnerships, suggested a financing shortfall of between US\$ 1.2 billion and US\$ 2.2 billion up to 2007, or between US\$ 400 million and US\$ 700 million annually. Apart from the size of the funding gap, which may be debatable, a further constraint is the discrepancy between the long-term nature of the R&D process and the relatively short-term nature of funding pledges. Lack of certainty of continuing funding inhibits long-term planning by public–private partnerships. There may be a temptation to seek to do things more cheaply but not necessarily cost-effectively; promising research projects may be delayed and relationships with partners may be damaged because of a short-term approach (22).

Public–private partnerships are a new, effective and important means of pursuing R&D relevant to the health needs of developing countries. They offer the promise of developing products cost-effectively, making use of the diversity of new players in the field of biomedical research. However, this promise will not be fulfilled unless their financing is enhanced and put on a sustained footing.

3.2 To enhance the sustainability of public–private partnerships:

- **Current donors should sustain and increase their funding for R&D to tackle the health problems of developing countries.**
- **More donors, particularly governments, should contribute to increase funding and to help protect public–private partnerships and other R&D sponsors from changes in policy by any major donor.**
- **Funders should commit funds over longer timeframes.**
- **Public–private partnerships need to continue to demonstrate that they are using their money wisely, that they have transparent and efficient mechanisms for accountability, that they coordinate and collaborate, and that they continue regularly to monitor and evaluate their activities.**

- **The pharmaceutical industry should continue to cooperate with public–private partnerships and increase contributions to their activities.**
- **Research institutions in developing countries should be increasingly involved in executing research and trials.**

3.3 WHO should initiate a process to devise mechanisms that ensure the sustainability and effectiveness of public–private partnerships by attracting new donors, both from governments and the private sector, and also to promote wider participation of research institutions from developing countries. However, governments cannot passively rely on what these partnerships could eventually deliver; there is a need for a stronger commitment on their part for an articulated and sustainable effort to address the research gaps identified in this report.

INSTITUTIONAL CHALLENGES

The process of product development can be affected by a wide variety of economic, social and political forces. One obvious example is product liability. The number of large pharmaceutical companies involved in vaccine production has decreased to a handful in the past 30 years. One reason for this, among others, is that vaccines are designed to be given to very large numbers of people (particularly children) who are not ill. The risk of adverse reactions and of potentially very large financial costs for compensation is a very real one and companies may consider the risks too high.

Political factors can also exert great influence. Drugs for women's reproductive health have often been at the centre of political and ideological controversy, thereby influencing the willingness of companies to be involved in product development. Very few pharmaceutical companies are still active in the field of contraceptive R&D. The first antiprogesterin drug was marketed in 1988 for use in medical induction of abortion. No pharmaceutical company has ventured to invest in the development of a new generation of follow-up drugs, based on novel compounds, despite their promising indications in other health fields (33).

In respect of R&D relevant to the health needs of developing countries, particular challenges at the development stage include the regulatory process and the closely related subject of clinical trial capacity.

Regulation and clinical trials

Regulation plays an important role in the development of new medicines, vaccines and diagnostics, setting standards for clinical research and providing a scientific assessment of product safety, efficacy and quality. Importantly, regulators make the critical decisions on market approval and oversee the impact of a product once marketed. Actions taken by regulatory authorities, or not taken by them, can facilitate or hinder product development and delivery.

The reality is that regulatory capacity in most developing countries remains extremely weak. A meeting of public–private partnerships personnel and other experts in 2004 reached the conclusions in Box 3.6.

With so many more products in development today that are specifically related to the health needs of people in developing countries, a principal regulatory concern is the capacity for executing clinical trials in those very settings, particularly in Africa. There has been some developed country input into building this capacity, including through the efforts of organizations such as the Swiss Tropical Institute (see Box 3.7), the United Kingdom Medical Research Council and others. The problems of mounting clinical trials differ between products (e.g. treatments, vaccines, microbicides and contraceptive devices), whether they are registration or post-registration trials, and include difficulties in recruiting participants. Perhaps the most common problem is the lack of infrastructure in terms of health facilities, clinicians, technicians and the management of clinical data. Research organizations such as public-private partnerships will increasingly need to find ways to address this bottleneck, but doing so is outside the mandate of any individual entity and requires a coordinated effort by governments and international organizations.

Box 3.6 Issues in regulation and clinical trials

Effective clinical trials require physical sites, ethical review capacity and the appropriate regulatory bodies to oversee their conduct, and ultimately approve the product for use. In sub-Saharan Africa, where many of the products will need to be tested, there is a shortage of all three. Bridging this gap will require scientific and regulatory leadership as well as significant investment.

- *Trial sites.* With more than 300 products for neglected diseases in development globally, there is not the trial capacity to support the current pipeline. In response, many groups are independently investing in trial site capacity (e.g. the European and Developing Countries Clinical Trials Partnership). Given the high cost of such investment, there may be benefits from increased coordination in this area.
- *Regulatory capacity.* In many of the countries where trials could be conducted, there is limited local regulatory capacity to provide approval for such trials and for successful products. While trials can be run under the guidelines of other recognized regulatory bodies (e.g. the United States Food and Drug Administration), the absence of such capacity is one of the reasons why many industry players choose not to run trials in these countries.
- *Ethical review capabilities.* Credible research cannot be conducted anywhere without two review capabilities: the ability to gain informed consent; and the presence of effective ethical review committees. Although committees are being established, they are often of poor quality because of limited training and lack of awareness of international standards. In cases where researchers work with an international review board, the board may not be sufficiently sensitive to issues raised by the local culture (e.g. the need for consultations with families and communities). Local researchers need to be trained so that they can play a role in determining the nature and type of ethical guidelines to be used in international collaborative research.

Source: reference (22).

One current initiative is the European and Developing Countries Clinical Trials Partnership, which began in 2003. This partnership has the objective of accelerating clinical development of products to fight HIV/AIDS, TB and malaria, with a particular focus on sub-Saharan Africa. Activities include the coordination of the efforts of EU member states, and strengthening capacity in developing countries. There is, however, a very great need in this area, and further efforts are required to build the necessary infrastructure.

Apart from infrastructure and the requisite skills entailed, clinical trials research in developing countries raises a host of difficult practical and ethical regulatory issues which also need attention. These include obtaining informed consent in different cultural environments, lack of capacity in local ethical review committees, and the treatment of trial participants after a trial is completed (e.g. when a successful treatment is not available subsequently through public health services). In the absence of strong local input, externally sponsored trials run the risk of being insensitive to local cultural mores, and socioeconomic factors. These difficult issues are engaging the attention of a number of international bodies, such as the World Medical Association (35).

Box 3.7 Swiss Tropical Institute and clinical trials

The increasing number of regulations and the international harmonization of good clinical practice by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have, according to the Swiss Tropical Institute (STI), taken clinical trials "beyond the needs and possibilities of developing countries". In STI's view, ways have to be found in each individual project of how best to reconcile the requirements of drug registration authorities with local laws and restrictions. Particular questions concerning the ethics of the conduct of clinical trials in developing countries have to be resolved in line with international standards, as well as with the cultural background of the respective country and population. The technical installations of the facilities and the training level of the personnel in countries with limited resources often do not match the requirements for the conduct of registration clinical trials according to international standards. Therefore, such projects usually involve considerable logistic and training efforts. Last but not least, the conduct of clinical trials on tropical diseases requires a profound medical and biological understanding of the illness and the confounding factors to allow competent planning of a trial.

A current bottleneck in product development identified by STI is the lack of sites in relation to the products in the pipeline: more sites are needed, and that means clinical research infrastructure is needed. STI is proud of its contribution to the development of this capacity in Africa through its long-term commitment to building relationships and investing in human resource and infrastructural development. For example, STI instituted a field station of its own at Ifakara in a remote part of the United Republic of Tanzania in 1957 which, by 1991, had become a fully-fledged centre attached to the Tanzanian National Institute for Medical Research. STI attributes the success of this institution-building effort to the following:

- (i) the long-term partnership between the executing agency in the developed country and the partners in the developing country;
- (ii) the support of this partnership by a long-term commitment of the major funding partners;
- (iii) the concept that local priorities form the basis of all activities;
- (iv) the linking of research and training to public health action.

The last two elements are considered to be crucial for the centre's multidisciplinary approach to health research and the support of public health in the United Republic of Tanzania and in eastern and southern Africa.

STI has taken a lead in conducting clinical trials of a promising compound (DB 289) to treat the first stage of African trypanosomiasis. Limited drugs are available for treatment and no vaccine currently exists. In addition, STI conducted Phase IIA (proof of concept) clinical trials in Angola and the Democratic Republic of the Congo to assess the efficacy of a much needed oral treatment for African trypanosomiasis. STI continued its testing efforts and is currently conducting Phase IIB trials in the Democratic Republic of the Congo with 350 subjects. STI has committed itself to planning, organizing and carrying out all Phase II and III clinical trials necessary for the clinical assessment of the compound.

Source: reference (34).

Many countries have extremely limited local regulatory capacity and cannot provide an effective oversight role. While trials can be conducted according to the rules of developed country regulatory authorities such as the United States FDA, these are not necessarily the most appropriate or acceptable locally. For example, judgements about market approval should appropriately reflect local circumstances: there is an important distinction between scientific assessment (i.e. factual analysis of efficacy, safety and quality) and coming to an informed judgement of a particular product, based on weighing the factual analysis of the risks and benefits appropriately in the light of local health needs.

The European Medicines Evaluation Agency (EMA) and individual regulatory authorities in the EU have – in coordination with WHO – set up a mechanism to provide a scientific assessment of products destined for a third country (36). Under this mechanism, it would be up to developing countries to make their own risk–benefit and market authorization decisions. This highlights a key public health issue where different regulatory actions may be justified according to differing country circumstances. Risks of side-effects may loom large in developed countries, because they are large in relation to mortality and morbidity caused by the condition itself; but that risk assessment may be reversed in developing countries, where the disease burden is large compared to any risk of side-effects (see Box 3.8).

Box 3.8 The story of rotavirus vaccines

In the United States, there are 50 000 – 60 000 hospital admissions and 20 – 40 deaths (one child in 500 000) annually as a result of severe diarrhoea caused by rotavirus. In 1998, the first rotavirus vaccine, Rotashield produced by Wyeth, was approved by the United States FDA for the prevention of the most common form of diarrhoea in children worldwide. However, reporting of side-effects, before and after marketing approval, determined that Rotashield caused intussusception (when one portion of the bowel slides into the next, creating an obstruction in the bowel) in an unacceptably large number of children (estimated to be 1 in 10 000 vaccinated). As a result, the company withdrew the product from the United States market in 1999.

The NIH's latest estimates are that about 600 000 children die worldwide each year from severe rotavirus diarrhoea. When compared to the 20–40 deaths each year in the United States, and accounting for population differences, the risk of death resulting from rotavirus in developing countries is several thousand times greater than in the United States. This should mean that the ratio of benefits to risks is very much higher in a typical developing country than in the United States. Nevertheless when, in February 2000, WHO held expert consultations on the issue, paediatricians and public health leaders from developing countries were not convinced that there was good evidence for allowing Rotashield in developing

countries, in part because there had been no trials in developing countries. Moreover, these experts acknowledged that it would be politically difficult to introduce and use a product that had been withdrawn from use in the United States.

The experience with Rotashield has profoundly affected subsequent development of rotavirus vaccines. GlaxoSmithKline and Merck had vaccines under development at the time of the withdrawal of the Wyeth product. Both decided to proceed after careful consideration and encouragement from public health agencies. In addition, there are vaccines in development by companies in China, India and Indonesia. Positive influences included a decision by the Global Alliance for Vaccines and Immunization (GAVI) in 2002 to give priority to the development and introduction of rotavirus vaccines, and large donations to GAVI for the purchase of vaccines, including from the Bill and Melinda Gates Foundation.

A less positive consequence is the need for very large Phase III trial sizes, involving well over 60 000 subjects in each case, to determine the risk of low probability side-effects. GlaxoSmithKline has taken the unusual route of first getting marketing approval in Mexico, then in other Latin American countries and in Europe. Significantly, it has chosen not to seek approval in the United States at this stage, although it has not ruled out seeking such approval.

There remain important unanswered questions about rotavirus and the new vaccines coming on line. Outside Latin America, very few trials have been done in the developing world. But a trial of one vaccine, in the Gambia and Rwanda, failed to demonstrate efficacy. There is a concern that the impact in terms of immune response may be much less in Asia or Africa than in the developed world. Other concerns include the likely cost, and the ability to pay for the vaccines.

Sources: references (37–39).

Improving the regulatory process is not easy but many developing countries are recognizing the importance of doing so. India announced this year that it will modernize its regulatory apparatus by creating an independent agency modelled on the United States FDA. Similar efforts are taking place in many other countries, including China, Brazil, Singapore and Thailand. The visits of the Commission to Brazil, India and South Africa provided a clear picture of the importance of good regulatory systems, and the efforts being made to enhance them

3.4 Further efforts should be made to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards. WHO has a role to play, in collaboration with interested parties, in an exploration of new initiatives that might be undertaken to achieve this goal.

This issue is discussed further in Chapter 5.

INCENTIVES TO DEVELOP NEW PRODUCTS

In light of the above analysis and recommendations, we have examined existing incentives for investing in product development, as well as the many schemes put to the Commission to address the lack of innovation relevant to developing countries and the lack of access. Some schemes focus on one or the other of these, while others seek to cover both aspects. We have also considered how far the implementation of the TRIPS agreement might promote innovation relevant to developing countries.

Many of the proposals were presented as submissions to the Commission and are available on our web site, along with a number of critiques of these proposals (40). There were also some interesting exchanges in our online discussion forum (41).

These proposals need to be assessed according to a number of criteria: economic efficiency relative to other possible schemes; political feasibility; complementarity with existing mechanisms; and long-term sustainability. In the end, policy-makers need to decide, based on their own country circumstances.

THE TRIPS AGREEMENT

The TRIPS agreement, by extending minimum standards of intellectual property protection globally, is theoretically one form of incentive for innovation in developed and developing countries. While developing countries (excluding least developed countries) with little technological and innovative capacity are bearing the cost of implementing the TRIPS agreement, there are no documented cases of positive impact on innovation in the medical field as yet. If there is to be an impact it will be in those developing countries that already have a promising science and technology base.

Because it is fairly well documented, including through our own studies, we have looked principally at the experience of India since 1995. This has particular interest because India, after 1970, introduced a regime where pharmaceutical products were not patentable, although processes for producing them were. Under the terms of TRIPS, countries such as India were allowed to retain such regimes until 2005 when patent protection in accordance with the provisions of TRIPS had to be introduced.

We have examined whether the extension of implementation of the TRIPS agreement to countries such as India will have an impact on innovation for diseases that particularly affect developing countries. India is a good case study as it is now a major producer of pharmaceutical products (and some vaccines), with a very large population affected by many of the diseases that are common in developing countries.

India took advantage of the transitional period until 2005 offered under the TRIPS agreement before it had to introduce product protection on pharmaceuticals (and chemicals). Such legislation was introduced as from 1 January 2005, a fact known for more than a decade, following India's signature of the TRIPS agreement in 1994. The post-1970 patent regime and the transitional period without product patent protection permitted India to develop a thriving pharmaceutical industry, supplying pharmaceutical products domestically and globally (including low-cost active pharmaceutical ingredients). This development created conditions for some of the companies in the industry to initiate investment in R&D.

The central question concerns the impact this transitional period had on R&D and innovation in the industrial sector. The evidence suggests that industry R&D increased very modestly from 1990 to 2000, rising from just over 1% of sales to about 2%, with total investment of US\$ 73.6 million in 2000. Since 2000, there has been a very rapid increase in pharmaceutical R&D. By 2003/2004, the combined investment of 12 of the leading companies was estimated to be US\$ 230 million annually, representing nearly 8% of turnover (42).

Much of the impetus for this growth derives from the markets in the developed world, not the impending introduction of patent protection in India. For instance, Ranbaxy, one of India's leading companies, aims to increase the share of its revenues from the developed world from 20% in 2000 (when worldwide sales were US\$ 475 million) to 70% in 2007 (when sales are projected at US\$ 2 billion) (43). Other companies have similar growth objectives, focusing on building on their strengths by launching generic versions of big-selling drugs in the United States and other developed country markets, including challenging patents where necessary. In 2003, India was granted 72 pharmaceutical patents in the United States. Although this is a small proportion of the total, it makes India the eleventh largest foreign source of United States patents in that category (44).

There is also a new emphasis in the plans of some Indian companies on new drug discovery. In another of India's leading companies, Dr Reddy's, expenditure on new drug discovery increased from US\$ 9 million in 2001/2002 to US\$ 17 million in 2003/2004, accounting for 37% of its total R&D budget (45). The numbers are still small but there is an unmistakable and rapid trend towards more expenditure on new drug discoveries, alongside investment in developing existing technologies, including adapting them to the Indian market.

Nevertheless, the great majority of new molecules under development in the private sector in India are designed to target Type I diseases which have good market potential (42). A survey we commissioned compared the R&D plans of Indian companies in 1998 with those in 2004. It found that, in 2004, 10% of all R&D (US\$ 21 million of US\$ 203 million in the firms surveyed) was aimed at diseases principally affecting developing countries (a list including malaria but not TB or HIV/AIDS) (46). In the 1998 survey, the equivalent figure was 16% (47). These figures nevertheless do not capture R&D on Type I diseases (e.g. diabetes), which are also of particular relevance to developing countries.

Where development of drugs for Type II and Type III diseases is occurring, there is normally significant involvement by the public sector or philanthropic funding. For example, Ranbaxy is collaborating with the Medicines for Malaria Venture, a public-private partnership, on the development of a synthetic antimalarial drug (48). Another Indian company, Lupin, has a new anti-TB drug in clinical trials; development of the drug has been 40% financed by the government and has received significant support from Indian public sector research institutes (49). In the case of vaccines, Indian private sector manufacturers have become major suppliers of low-cost vaccines to international public sector purchasers such as UNICEF. At the same time there are also new investments by the private sector such as AstraZeneca's TB research facility in Bangalore. When announcing this investment in 2003, the CEO of AstraZeneca noted that "We are investing in India because of its vibrant science and because we anticipate the adoption of meaningful intellectual property rights and total abidance to the Patent regime in 2005" (50).

The conclusion of our studies is that whatever incentives for R&D the availability of product patents for pharmaceuticals may create in India, local companies are likely to focus on products that offer the most lucrative opportunities, which are in developed country markets, whereas the new products that the Indian population most needs are likely to be less lucrative. The Indian market, because of its numerical size, offers

more incentives for R&D than is the case in most smaller developing countries; nevertheless, the global market remains far more important for medicines, diagnostics and vaccines. There has been a rapid growth in research relationships with multinational companies, partly fuelled by the latter's desire to exploit India's strengths in chemistry and cost advantages, and also by the need of Indian companies to collaborate in areas where they are weak, for instance in biology, or to meet regulatory requirements, and to bear the cost of doing so in the developed world.

One reason for this finding is that India's public sector spending on health care is very low by international standards, about 1% of national income. About 80% of India's health-care services are financed privately, by out-of-pocket funds rather than insurance schemes, which have very small coverage. Even so, total spending on health care (about 4.5% of national income) is also below the average for low and middle income countries. In both the public and private sectors, the preponderance of expenditures is on staffing, infrastructure and services; expenditure on medicines is a relatively small part of total health-care costs. Thus, although the potential market for medicines is very large, actual expenditure is much smaller than might be expected (51).

There is no evidence that the implementation of the TRIPS agreement in developing countries will significantly boost R&D in pharmaceuticals on Type II, and particularly Type III diseases. Insufficient market incentives are the decisive factor.

SPECIAL INCENTIVES TO SPUR PRODUCT DEVELOPMENT

There are a number of proposals which have been made that reflect a serious concern about shortcomings in the current system, in particular inadequate incentives for innovation relevant to health needs of developing countries and the need to promote access to new products in these countries. There are a selection of existing schemes and new proposals which rely on the provision of monopolies, additional exclusivities, or other forms of market-based rewards, to stimulate the development of new products for diseases mainly affecting developing countries.

Orphan drug schemes

In orphan drug schemes, there is an offer of limited additional market exclusivity (along with other tax and funding benefits) to promote the development of drugs to treat diseases that affect relatively few people (less than 200 000 in the United States). The United States Orphan Drug Act of 1983¹⁰ resulted in more than 1238 orphan drug designations from the United States FDA as of May 2003, of which 238 had received marketing approval. This is a 10-fold increase on the rate of development of orphan drugs before the Orphan Drug Act. Some have proposed a number of modifications to orphan drug legislation in the United States or Europe to provide a greater stimulus for diseases mainly affecting developing countries (52). The pharmaceutical industry has suggested the idea of tropical diseases drug legislation, based principally on the package of orphan drug incentives (53).

¹⁰Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa - ee (1998)).

Although some question its cost-effectiveness, the Orphan Drug Act in the United States is widely regarded as successful in the development of new drugs or new indications of existing drugs. Its impact relies on the fact that a small market in the United States may still be a lucrative one, particularly as the grant of exclusivity allows prices to be set according to what the market will bear. But for a disease that mainly affects developing countries, the grant of exclusivity in the United States (or other developed country) does not address the absence of a market. For example, drugs for most tropical diseases, which have a small market in the United States, currently qualify under the existing United States legislation, but this has not generated substantial new investment by the private sector in innovation for these diseases. Of the 238 products receiving marketing approval, only 12 were targeted at tropical diseases (52). Any proposal of this nature, therefore, also needs to address the absence of a paying market, and affordability.

Tax credits

An element of orphan drug schemes is the provision of tax credits. For instance, in the United States there is a 50% tax credit on clinical trials. The main incentive is, nevertheless, the offer of exclusivity. Some governments, such as that of the United Kingdom, have introduced specific additional tax credits to boost research on, for instance, HIV/AIDS, TB and malaria. The evidence is mixed on the effectiveness of tax credits in boosting R&D on diseases where the market is uncertain, although there is evidence that general tax credits have an impact on market-driven R&D (54). At the extreme, if no market exists, even a 100% tax relief would have no stimulating effect. Moreover, tax credits cannot work in the absence of profits, and this may particularly reduce their impact in the biotechnology sector where many firms work at a loss.

Scheme for transferable intellectual property rights

The proposal for transferable intellectual property rights (TIPRs) seeks to overcome the lack of a market by allowing the reward for innovation to come from a patent extension on an unrelated product in a developed country market. Thus, a company that develops a drug for a notified disease may be rewarded by an extension of the patent term on an existing product (e.g. a “blockbuster” drug).

The mechanism would introduce a new distortion in developed country markets. Patients, or more likely governments and insurers paying on their behalf, would be denied the benefits of generic entry for a period of months or years. In effect, for most countries, patients, ministries of health and private insurers are being asked to pay the reward. Moreover, our consultations have revealed that the bulk of the pharmaceutical industry is firmly opposed to the scheme.

Transferable fast-track review scheme

A variation on the TIPR proposal is to spur private sector involvement in the development of treatments for neglected diseases by offering companies fast-track regulatory review status on a product with a substantial potential market in the developed world. This would be a variation on current procedures of regulatory authorities, which allow fast-tracking for products that meet certain criteria of

potential therapeutic benefit. This proposal might allow entry to the market a year or two earlier than otherwise possible. In one version, this scheme is operated simply as an auction and thus becomes a way of raising money which can then be spent as desired on R&D in the public or private sectors (55). The proposal under review suggests spending this money on a programme to support public-private partnership links with industry. A possible advantage of this plan over TIPRs is that it does not involve an extension of the patent term. A disadvantage is the potential to distort regulatory priorities as a result of incorporating financial considerations alongside therapeutic criteria in decisions on fast-tracking.

Reward systems

The central idea in the proposals for reward systems is that patents on products would be bought out, or replaced altogether, by governmental payments in relation to a calculation of the incremental therapeutic value of the product. By this means, it is argued, priorities for innovation could be more closely related to public health priorities, and the product could then be made available at production costs, excluding those of R&D. This could have the important effect that, while the incentive for innovation is retained, the loss in economic efficiency through the distorting effect of patents on prices is avoided (56, 57). Moreover, proponents claim that there could be big savings in advertising and marketing expenses, which are a large component of pharmaceutical industry costs (58).

Others see drawbacks in these proposals. A sponsor must choose the amount of a reward based on an estimate of a product's therapeutic value over and above an existing product, the basis of which must necessarily be indicative. Measuring this value, in advance of extensive use by patients, is problematic, and involves an element of judgement. This opens the door to the possibility of paying more for an innovation than would be the case under a patent regime, or an amount insufficient to stimulate innovation, or to rewarding a product which then could be withdrawn from the market when unforeseen side-effects are discovered. Moreover, while some see merit in this proposal because it would penalize new products with a small therapeutic advantage, others see this as a disincentive to incremental innovation (59).

A variation on these comprehensive proposals is to introduce a reward scheme specifically targeted at products to meet the needs of developing countries. The intention would not be to supplant patents, but to supplement them by offering a reward for products to tackle diseases that affect developing country populations where, because market incentives are deficient, patents are not an effective incentive. Thus, the implementing authority could set a high value on products that would have a correspondingly high public health impact in these countries (60). Such a proposal would, of course, require fewer resources for implementation than a general scheme.

A different approach is provided by the advance purchase commitment proposal, which seeks to mimic the market by guaranteeing the purchase at a future date of, for example, a new vaccine in a pre-established quantity and price. The vaccine would have to meet specific criteria for efficacy. The same principle could also apply to treatments, or indeed diagnostics. The intention is to replicate the potential rewards of a minor blockbuster drug as an incentive to induce companies to invest in R&D

(61). In addition, commitments would be built into the contractual arrangements to oblige a price reduction once the guarantee expired.

A very active debate on this subject was conducted on our electronic forum, with inputs from both proponents of this approach and its critics (41). A central issue was whether this mechanism is likely to be effective in stimulating R&D on products, such as vaccines for HIV/AIDS or TB, where the science is difficult, the risk high and the reward uncertain and far into the future. Much will depend on whether the promise made to purchase a product under such a scheme will provide a credible incentive equivalent to that which the market provides for "mainstream" products. However, where current research is only at the discovery stage, or the disease is not being addressed at all by the private sector, this may not be the case. In addition, the practical feasibility of the scheme was questioned in various ways on grounds similar to those noted above in relation to the practical implementation of prizes based on incremental therapeutic value (62).

In addition to those that have created specific facilities, a few of the multinational companies (e.g. Johnson & Johnson, Otsuka, and Bayer) have decided to devote resources specifically to developing country diseases. These are areas where there are difficult scientific issues (as in, for example, any of the vaccine projects for HIV/AIDS, malaria and TB) and where the effective demand is low. Whatever incentives are offered by governments (and any long-term commitment by governments must carry some risk), they are unlikely to outweigh the opportunity costs of deploying scientists in more potentially remunerative areas. The prospect of stimulating a larger R&D effort by pharmaceutical companies for products which have high scientific and market risks, and low potential profitability, seems unlikely.

There may well be benefits in advance purchase commitments that specifically seek to bring potential product candidates with a strong possibility of success through the last stages of clinical trials to market approval and delivery, which is one of the principal constraints noted above. This pull strategy would be an appropriate complement to push mechanisms, mentioned elsewhere, which bring into being products of potential value, but where additional costs and risks need to be borne to bring products to market.

There is important value in an explicit commitment from donors to provide the necessary additional funding needed by developing countries to introduce newly developed products of public health importance. This will encourage parties already engaged in the process of developing such products or those who have hit on a possible new lead compound.

The Governments of France, Italy, Spain, Sweden and the United Kingdom have recently agreed to provide additional funding to GAVI in the amount of US\$ 4 billion over the next decade, using the mechanisms of the International Finance Facility (IFF) proposed for purchasing vaccines and accelerating their introduction (63). Current funding would be found by the sale of bonds backed by an intergovernmental guarantee of repayment from overseas aid budgets. This allows spending to be brought forward at a cost to future budgets of interest and capital repayments, and other costs associated with this mechanism. The objective would be to increase vaccine supply and promote affordability by offering manufacturers secured financing

(such as an advance purchase commitment) for priority vaccines for the public sector market in developing countries. This would help stimulate new private sector investment and greater competition, leading to a more rapid reduction in vaccine prices in the longer term (64).

There is a very large gap in the ability to get products which have demonstrated possible efficacy through the stages from development to delivery (e.g. from Phase II to market approval and then to people). We support the concept underlying this attempt to combine enhanced and sustainable funding for both the purchase of existing vaccines and the faster and cheaper delivery of vaccines in development. Nevertheless, advance purchase commitments are unlikely to be practical or effective in stimulating early stage research.

3.5 Governments should continue to develop forms of advance purchase schemes which may contribute to moving later stage vaccines, medicines and diagnostics as quickly as possible through development to delivery.

Medical R&D treaty

We have evaluated a proposal – signed by 162 people from academia, government, politics and civil society – for a global medical R&D treaty (65). We have consulted widely, and requested the view of a number of senior scholars.

The basic idea behind the proposed treaty is that governments would commit themselves to spending a certain proportion of national income on medical R&D in a number of ways. The proposal seeks to introduce more eclectic and innovative means of financing R&D, underpinned by a global commitment by governments, embodied in a treaty, to spend agreed proportions of national income on medical R&D:

The treaty proposal recognizes the importance of ensuring sustainable sources of finance for innovation, including R&D for neglected diseases and other public health priorities, and it provides opportunities to experiment with new and promising mechanisms to finance R&D, such as prize funds, competitive intermediators, compensatory liability regimes, or open collaborative projects such as the Human Genome Project...

A trade framework that only relies upon high prices to bolster medical R&D investments anticipates and accepts the rationing of new medical innovations, does nothing to address the global need for public sector R&D investments, is ineffective at driving investments into important priority research projects, and when taken to extremes, is subject to a number of well-known anticompetitive practices and abuses. Policy makers need a new framework that has the flexibility to promote both innovation and access, and which is consistent with efforts to protect consumers and control costs (65).

The proposal recognizes the importance of ensuring sustainable sources of finance for innovation, including R&D for neglected diseases and other public health priorities, and it provides opportunities to experiment with innovative mechanisms to finance R&D. It seeks to address the fundamental policy dilemmas in promoting innovation and access relevant to public health, and has initiated a useful debate.

However, it is still unclear to many people how the proposal would work in practice. Many comments emphasized that the proposal was set out in a broad-brush fashion, making it difficult to assess, without further information and analysis, how various legal, financial, technical and institutional issues could be addressed, as well as genuine concerns about political and practical feasibility (66).

3.6 Recognizing the need for an international mechanism to increase global coordination and funding of medical R&D, the sponsors of the medical R&D treaty proposal should undertake further work to develop these ideas so that governments and policy-makers may make an informed decision.

Open source approaches

“Open source” refers to the method of innovation pursued by computer programmers all over the world who have collaborated to produce new software products. Open source software has developed a more or less proven research model, based on a general public licence which makes modifications of a software programme freely available for others to use or develop (67). The important aspect of this approach is that it mobilizes innovative effort from a range of developers at little cost (68). This business model has been adopted by some commercial companies (e.g. IBM), and is increasingly being used by governments as the basis for computer networks. Commercial suppliers of this type of software make a profit by providing backup services, systems support and related hardware, with a potential competitive advantage compared to the providers of commercially developed software.

It has been suggested that this particular model of innovation may be replicable in some types of biomedical research, particularly as computational models using genetic information become more important as part of the product development process (as proposed in the United States FDA Critical Path analysis). For example, it has been proposed that open source in biomedicine would involve volunteers from the public or private sector working on existing databases to identify promising targets and drug candidates, which would then be tested in “real” laboratories. One practical issue is how far “in silico” research can further the R&D process, the availability of supporting databases, some of which would be subject to companies' control, and other resources that might be necessary. It is also pointed out that incentives are very different in software development as compared to biomedical research (69). Open source models may not be so relevant to biomedical research because there may be no advantage from a network effect or first mover advantage, as is the case with software.

Whatever the practicalities, there would be great merit in mobilizing scientists to address the health problems of developing countries, where this kind of interactive work is possible. The motives for participation could be a combination of professional development, a desire to contribute to better health, and the possibility of peer-reviewed publications. A prize programme could also be considered.

3.7 Practical initiatives that would motivate more scientists to contribute to this field through “open source” methods should be supported.

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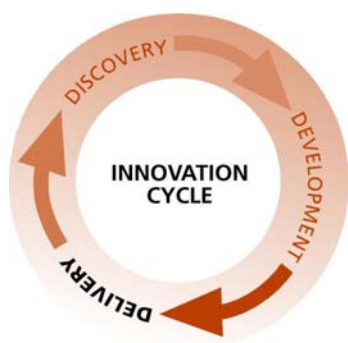
CHAPTER 4

DELIVERY: GETTING PRODUCTS TO PATIENTS

INTRODUCTION

However successful efforts might be to develop new products to address the public health problems of developing countries, they will be of no value if they cannot be made available and accessible to those who need them. The World Health Assembly in 2002 adopted a resolution on ensuring accessibility of essential medicines which called upon WHO among other things:

"to pursue all diplomatic and political opportunities aimed at overcoming barriers to access to essential medicines, collaborating with Member States in order to make these medicines accessible and affordable to the people who need them" (1).

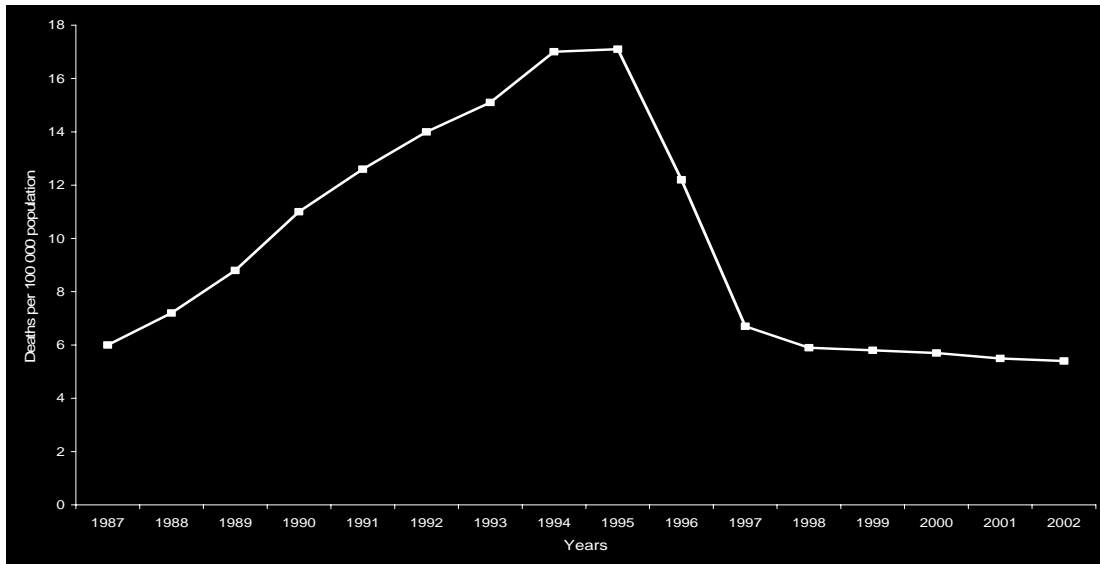


The consciousness of the world of this issue was heightened by the emergence of the HIV/AIDS pandemic in the 1980s, and the discovery of effective treatments in the mid-1990s. This led to the mobilization of people infected by HIV/AIDS on an unprecedented scale, in both developed and developing countries, not just to influence the price of drugs, but also decisions of companies and public authorities on the release and availability of new treatments, and the launch of prevention campaigns.

In the United States the combination of scientific advances leading to the availability of new drugs and public pressure resulted in a dramatic turnaround in mortality from AIDS through treatment and reduced infection (Figure 4.1). AIDS deaths fell from 17 per 100 000 to 5 per 100 000 between 1995 and 1998 (2).

By contrast, in most developing countries the epidemic continued unabated throughout the 1990s, despite the availability of drugs that could have had the same effect on AIDS mortality as in the United States. The cost was too large, the delivery infrastructure inadequate and political commitment sometimes lacking. As a result, AIDS deaths globally continued to rise inexorably (Figure 4.2).

Figure 4.1 Trends in annual age-adjusted^a rate of death attributable to HIV/AIDS, United States, 1987-2002

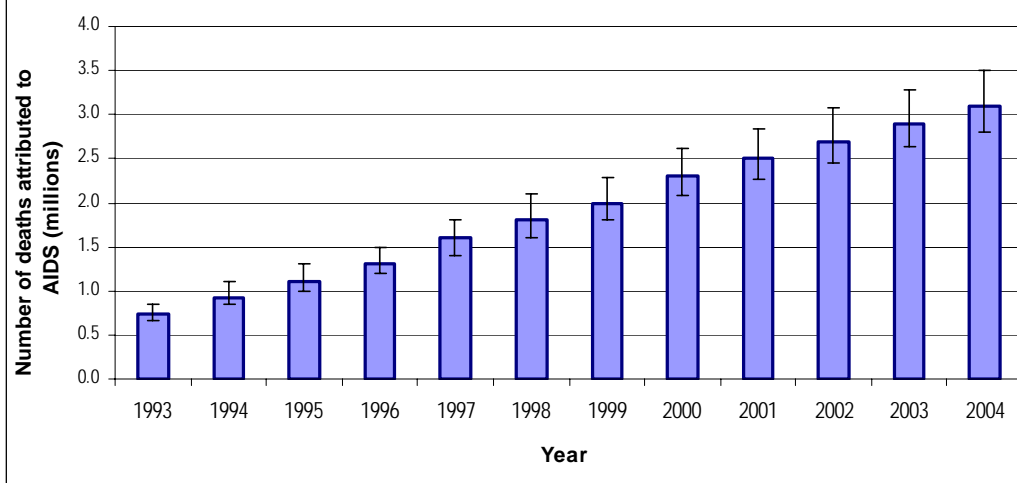


Note: For comparison with data for 1999 and later years, data for 1987 - 1998 were modified to take account of ICD-10 rules instead of ICD-9 rules.

^a Standard: age distribution of United States population in 2000

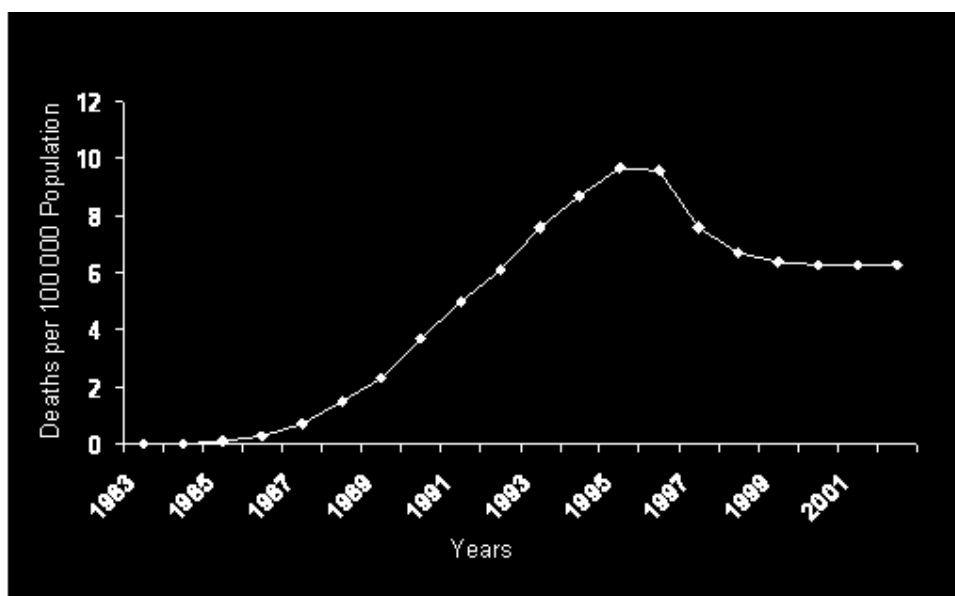
Source: reference (2).

Figure 4.2 Estimated number of adult and child deaths (0-49 years) attributed to AIDS worldwide, 1993-2004.



Source: reference (3).

Figure 4.3 Trend in annual rate of AIDS - related deaths, Brazil, 1983-2002



Source: reference (4).

In Brazil, among few other developing countries, a combination of factors allowed inroads to be made in the escalating numbers of AIDS victims. The Brazilian experience demonstrates what could be done, given political commitment and the resources to put a treatment programme into effect (see Box 4.2).

The case of HIV/AIDS is, however, just one dramatic example. The problem of access to medicines is certainly not limited to antiretrovirals but concerns the whole range of medicines, even when available at the lowest cost in the poorest settings, both for prevention and cure as well as diagnostic tools. For instance, in the case of malaria there is a massive gap in access, with the most effective treatments (artemisinin-based combination therapies) in short supply, and the finance available for their purchase small in relation to need.

"Improving access" has been the rallying cry of those concerned with improving the health of the disadvantaged – a call to the world to turn its attention to the needs of the millions who fail to share in the rewards of scientific innovation. But the conditions for ensuring "access" are multifaceted, ranging from pricing to human and financial resources and the general level of infrastructure.

This chapter examines the factors affecting the introduction of new and existing products into developing countries, without which the benefits of biomedical innovation cannot reach the people who need them.

The schema of availability, accessibility, acceptability and quality set out in Chapter 1 suggests how to frame problems and identify appropriate solutions *given existing social and economic conditions* (5). Addressing these fundamental social and economic conditions is outside of the scope of this Commission (6), but this does not mean that they are unimportant for public health. On the contrary, the economic,

social and environmental determinants of health (such as poverty, malnutrition, poor housing or inadequate sanitation) are critical, and governments can make a large impact by addressing the underlying determinants of poor health through measures to alleviate these conditions. But investments in direct health-care delivery services are also important alongside addressing these fundamental determinants of health status.

The realities of poverty can and should inform proposals about the kinds of products that are needed by poor people in developing countries, relevant to their circumstances. The existence of a medicine, vaccine or other product can only benefit patients when they are able to make use of it.

THE DETERMINANTS OF AVAILABILITY

Innovation is an important determinant of availability at the level of product development but also at that of local communities. For products where a commercial market exists, delivery is not the end of the story. Rather, the experience with the product in real life situations by large numbers of patients provides new information on responses, side-effects and other characteristics, which may form the basis for further incremental, or even more fundamental, innovation. In a commercial setting it is this feedback from the market-place that contributes to a process of continuous improvement and innovation.

Although the experience in the developing country setting may reveal significant deficiencies in the existing treatment regime, the incentive for innovation to improve the regime is lacking. For instance, no new TB drugs have been discovered for about 40 years and the current treatment regime is very lengthy (six months or more), making compliance a big problem, and fuelling the spread of drug-resistant strains. Only in the past few years, as a result of the work of groups such as the TB Alliance, has there been a systematic programme to develop new drugs in combinations which will shorten treatment, improve compliance and combat resistant strains.

In general, there is too little innovation that relates to improving access to diagnosis and treatments in developing countries in ways consistent with their needs and resources. Examples of the kind of innovation that is needed include the development of a simple-to-use and rapid blood test to monitor HIV infection (7) and the recent invention of a low-cost endoscope by a doctor in Viet Nam (8). PATH, a nongovernmental organization, is one of too few organizations that focus on the development of health technologies appropriate to low-resource settings.

The task is therefore to seek conditions under which needed treatments can become available, and an important aspect of creating such conditions is the stimulation of relevant innovation to promote access. Delivery is also about the ability to make existing products available, for which a capacity for efficient local production as well as a capacity to import are important. There is also a need for ongoing adaptive research to make new or improved products better suited to developing country settings.

HEALTH DELIVERY SYSTEMS

The adequacy of national health systems – basic infrastructure, adequate human resources with the requisite skills, functioning primary and secondary health-care delivery systems, among many others – are central to making existing treatments available. Investments in health delivery systems are necessarily hampered by a lack of resources. But the diverse experience of countries and regions at different levels of income shows what can be done if there is a political commitment to improved health. Box 4.1 describes some examples of how governments' investment in the "basics", such as infrastructure and education, as well as delivery, has resulted in notable improvements in health outcomes.

Box 4.1 Cuba and Kerala (India)

Cuba is an example of a lower middle income country that has achieved considerable success in ensuring good health for its people. Life-expectancy at birth in Cuba, 76 years, is closer to that in the United States and United Kingdom, 76 and 77 years respectively, than in Bolivia and Ecuador, 62 and 70 years respectively. Mortality rates for children under 5 years of age in Cuba are close to those achieved in developed countries, and much better than those achieved by other lower middle income Latin American countries. Despite its economic challenges, Cuba's public health picture resembles that of far wealthier nations.

Cuba's public health achievements are derived in large part from its focus on education and on its health-care system. Cuba remains committed to providing free, universal, and mandatory education up to the 12th grade. Cuba's adult literacy rate stands at 96.7%. Cuba's public health system was also designed to limit disparity, and focus on the principles of universality and accessibility. The strong primary health care system, with doctors and nurses living in neighbourhood clinics, was able to provide comprehensive care for the community. Moreover, the integration of primary, secondary and tertiary services, despite economic strain and limited infrastructure, has led to the strong performance of the public health system in Cuba.

Kerala's per capita income is only about a hundredth of that in wealthy countries. Its annual expenditure on health (US\$ 28 per person) is much less than that of the United States (US\$ 3925 per person), and yet its performance with regard to standard health indicators is remarkably similar. Life expectancy at birth in Kerala, 76 years for women and 70 years for men, is close to that in the United States, 80 years for women and 74 years for men. In contrast, life expectancy at birth in India as a whole is 63 years for women and 62 years for men. The infant mortality rate in Kerala, 14 per 1000 live births, is close to that achieved in the United States, 7 per 1000 live births, and much less than for India as a whole, where 68 of every 1000 babies born alive do not survive their first year of life.

A number of different factors have facilitated the public health success that Kerala has achieved. Primary among them are the government's focus on education, on access to primary health care, and strong political and financial commitment towards ensuring public health. Until recently, Kerala allocated a large portion of its state budget, approximately 25%, towards improving its educational system. Kerala has been successful in achieving a high level of female literacy, with 87% of adult women able to read and write. In comparison, only about 55% of adult Indian women are able to read and write. Moreover, more than 97% of Kerala's population has access to health care, facilitated both by the state's strong focus on primary health care facilities and the substantial work of faith-based organizations in the state.

Much like Cuba, Kerala has been able to protect and ensure the health of its people despite facing strong economic challenges.

Source: references (9-11).

In 1978, government and civil society representatives made a historic commitment to "health for all" in the Alma-Ata declaration – with an emphasis on equity and equality, and on the importance of primary health care in achieving this goal. The Declaration defines primary health care as:

...essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination. It forms an integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process (12).

The "health for all" target was set for 2000, and this ambition has clearly not been achieved. However, the conference was nevertheless a defining moment in that heads of State declared that basic health care should be within the reach of even the neediest.

Improved performance in controlling emerging and re-emerging diseases in developing countries is dependent on the quality, equity and efficiency of health systems, which comprise all the organizations, institutions and resources devoted to improving health (13). A health system's vital functions are fourfold:

- **service provision** (including service organization and delivery in the formal and informal sectors);
- **resource generation** (including human resources, physical capital, medical products and supplies);
- **financing** (namely, financial resources available for the health system and mechanisms for its transferral to providers);
- **stewardship** (including setting the direction of health policy, employing data, and exerting influence through regulation).

Potential obstacles to the uptake of existing interventions include prices being too high, lack of financial resources as well as inappropriate financial incentives, inadequate human resources both in terms of quantity and quality, a lack of access to care, health policies that fail to promote cost-effective interventions or that advocate unproven activities, and a failure to provide practitioners with access to appropriate information (14).

While governments are the main actors in the improvement of health systems, others also play important roles: for example, bilateral donors, private foundations,

nongovernmental organizations and other civil society actors, and companies. In their different ways they can be important contributors to various aspects of health systems strengthening, whether through financing and investment, capacity building and training, or monitoring and evaluation.

The way in which the health system is financed has important implications for the ability of patients to gain access to available products and services. Because most health expenditure in developing countries is borne by patients themselves, rather than the State or insurers, this means poor people are either unable to avail themselves of treatments, or face the risk of extreme poverty in order to do so (15). High prices of medicines and user fees create obstacles to access for poor people, and further impoverish those who face medical problems (13). As noted above, the lack of a viable and sustainable market for products, because of the poverty of patients and the absence of an alternative means of payment provided by the State through insurance or otherwise, is a reason for a critical gap in the innovation cycle. There are no simple rules about how countries should finance health care, or about how they should structure or modify other elements of their health systems. For this reason, there is a growing emphasis on the need for health systems research to better inform policy-making on health system reform, including its financing, oversight and management, in a way that is context-specific. The Ministerial Summit on Health Research, held in Mexico in 2004, acknowledged that:

2. Strong national health systems are needed to deliver health care interventions to achieve the health-related MDGs; to address other communicable and noncommunicable diseases, sexual and reproductive health, injuries, violence, and mental ill health; and to improve health and health equity.
3. Research has a crucial but under-recognized part to play in strengthening health systems, improving the equitable distribution of high quality health services, and advancing human development (16).

The World Health Assembly in 2005 mandated a number of follow-up actions to respond to the conclusions of the Summit (17).

The effective management of human and material resources is another critical element in ensuring appropriate health systems. For example, apart from their own efforts to provide resources and manage them effectively, the increasing burden of HIV/AIDS and other resurging diseases has increased the pressure on already overburdened health services with the loss of large numbers of health-care workers, in particular as a result of HIV/AIDS. In fact, in some African countries it is estimated that AIDS causes up to one half of all deaths among employees in the public health sector (18).

People are the most important part of any health system. The health sector is labour intensive and the performance of health systems depends on the availability of qualified and motivated workers. Low income countries are suffering a massive haemorrhage of skilled health-care workers to high income countries, and from rural areas to urban areas (19). More than 23% of nearly 800 000 physicians in the United States received their medical training elsewhere, and two thirds of these in low or lower middle income countries (20). Higher education is one of the principal conduits of permanent migration. The persistent flow of health-care workers out of a country causes shortages of specialist personnel, and represents a huge loss in terms of

investment in their education. For example, more than 70% of physicians trained in Zimbabwe in the 1990s have left their country, as have 60% of Ghanaian physicians trained in the 1980s (21). It has been estimated that sub-Saharan Africa needs an extra one million trained health workers, three times the current number, if the achievement of the Millennium Development Goals is to be a possibility (22, 23). At the same time, massive deficits of health workers in developed countries are projected into the future – in 2020 the United States may be short of 200 000 doctors and 800 000 nurses. Doctors' organizations in developed countries have recognized this problem and called for developed countries to aim for self-sufficiency in their health-care workforce by expanding training.

One way of addressing these problems is to make better use of traditional medicine practitioners, who comprise an important part of health delivery systems in developing countries. A large proportion of the population of developing countries seeks the help of these practitioners as a first option when people fall sick (24). It is estimated that there may be three times as many informal, traditional, community and allied health workers globally as there are "modern" health workers (22). Increasingly, efforts are being made to integrate "modern" and "traditional" medical delivery systems to make the most of the extensive network of traditional practitioners with close links to local communities. Integrating traditional healers into health systems is an important step in many countries towards bridging the distance between sick people, particularly the poor and marginalized, and health services. In South Africa, where a majority of the population consults traditional healers, the government recently adopted the Traditional Health Practitioners Bill, which recognizes and regulates the practice of South Africa's traditional healers (25). Peru has recently announced a similar strategy to integrate the two systems (26). The pursuit of this strategy globally may offer the opportunity to make medical services more available and accessible.

4.1 Governments need to invest appropriately in the health delivery infrastructure, and in financing the purchase of medicines and vaccines through insurance or other means, if existing and new products are to be made available to those in need of them. Political commitment is a prerequisite for bringing about a sustained improvement in the delivery infrastructure and health outcomes. Health systems research to inform policy-making and improve delivery is also important. The integration of traditional medicine networks with formal health services should be encouraged.

4.2 Developing countries should create incentives designed to train and retain health-care workers in employment.

4.3 Developed countries should support developing countries' efforts to improve health delivery systems, inter alia, by increasing the supply of their own trained health-care workers.

THE DETERMINANTS OF ACCEPTABILITY

The determinants of acceptability include quality, which is dependent on effective regulatory arrangements to ensure the safety, efficacy and quality of medical

products. In addition, technologies that may have been developed elsewhere may need to be adapted to make them acceptable locally.

QUALITY

Even when medicines and other products get to sick people, they may not always be of good or adequate quality. Sometimes the best available medicine can have important side-effects, like antiretrovirals, or can even be toxic, like some treatments for African trypanosomiasis and some cancers. Often there are special challenges in developing products of adequate safety and efficacy for pregnant women and children. In these instances, improving quality is a matter of innovation – producing something better, or making improvements to the existing intervention.

The regulatory authorities worldwide have an important part to play in ensuring quality, a concept that we here take to include also safety and efficacy. Even in developed countries, ensuring product quality is a matter of making a probabilistic judgement about the risks and benefits of a new product on the basis of necessarily incomplete information about all possible impacts. While companies are required to provide all information they obtained about potentially dangerous side-effects, and regulators should ensure that they have at their disposal as much data as possible before reaching a decision on marketing approval, information on side-effects may come to light only after the product has been marketed and used by a large population.

The institutional arrangements in developing countries for the approval of medicines differ in many respects from those in place in developed countries. In some cases, developing country authorities examine safety, efficacy and quality of health products within their capacity, while some authorities rely on evidence of prior examination of safety and efficacy done by regulatory authorities in developed countries as a part of their decision to authorize market approval. In many developing countries, however, the regulatory institutions require considerable strengthening, as noted elsewhere in this report. The objective should be for all developing countries to bring all products on the market within the compass of regulation as soon as possible so that patients get products that have appropriate levels of quality.

Exactly how regulatory authorities can do this, or what methods and methodologies are appropriate in regulating different classes of medicine depends on a range of circumstances and case-by-case judgements about risks and benefits. The financial and human resources available to the regulatory authorities can limit their effectiveness to assure the quality of medical products supplied to their patient populations.

In the case of “multisource” pharmaceutical products WHO guidelines state "multisource (generic) drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the originator's product. In addition, reasonable assurance must be provided that they are, as intended, clinically interchangeable with nominally equivalent market products" (27).

Another important issue relates to counterfeit drugs, which are defined by WHO as those:

which [are] deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging (28).

Quality of medicines is a source of great concern worldwide, particularly in many developing countries. Recent reports indicate that the availability of substandard and counterfeit drugs has reached a disturbing proportion in developing countries. Use of poor-quality drugs has serious health consequences and wastes scarce resources. Other human costs of poor-quality medicines include loss of work and income resulting from death, disability, or extended duration of disease. The United States Food and Drug Administration estimates that counterfeits make up more than 10% of the global medicines market and are present in both industrialized and developing countries. It is estimated that up to 25% of the medicines consumed in poor countries are counterfeit or substandard. A World Health Organization survey of counterfeit medicine reports from 20 countries between January 1999 and October 2000 found that 60% of counterfeit medicine cases occurred in poor countries and 40% in industrialized countries (54). The International Conference of Drug Regulatory Authorities (ICDRA) brings together regulators from more than 100 countries and has addressed the topic in several meetings. For example, at the ICDRA meeting in Madrid in 2004, one of the issues discussed was counterfeit medicines. Further work was recommended to create a better international framework to fight counterfeit medicines (29).

There is growing awareness of the problem posed by counterfeit medicines, although the full extent is not well understood because of a lack of data. Lack of political will, corruption and conflict of interest, as well as a demand that exceeds supply, are among several factors underlying the problem. Appropriate and effective regulation, among other things, is an important means of combating counterfeiting. The enforcement of good manufacturing practices, and supply chain management systems, are also essential to protect patients against unsafe medicines (30).

4.4 Governments have an important responsibility to put in place mechanisms to regulate the quality, safety and efficacy of medicines and other products. As a starting point, adherence to good manufacturing practices and effective supply chain management can ensure product quality and will also curb the circulation of counterfeit products.

SUITABILITY OF PRODUCTS FOR USE IN POOR SETTINGS

The goal of achieving as close as possible to universal access to HIV treatment by 2010 was endorsed by G8 leaders in Gleneagles in 2005. Achieving this goal will require a significant new investment of resources and effort in research directed towards scaling up treatment in resource-limited settings, through innovations such as more new formulations of HIV drugs for children and simpler tests to diagnose and monitor patients. A speaker at the International AIDS Society Conference on HIV Pathogenesis and Treatment, held in Rio de Janeiro in 2005, noted:

The list of research questions is long. But if we are going to achieve universal access, we will need to invest in applied research and move new products and

approaches quickly into the field... We have the knowledge to answer many of these questions... I would argue that in no other field are the opportunities to translate evidence into action so great, as they currently are in HIV/AIDS. Not only can researchers have direct impact on policy and practice, they can reduce inequities by helping to make scientific advances available more quickly to the millions of people who need treatment (31).

In a 2004 report, Médecins Sans Frontières made the following comment about one of its largest HIV/AIDS treatment programmes:

The programme of Médecins Sans Frontières (MSF) in Chiradzulu District, Malawi, has demonstrated the value and feasibility of antiretroviral therapy (ART) in a poor rural context. Some 2194 patients were receiving ART in March 2004 and the clinical results were comparable to those found in developed countries. Although the Chiradzulu programme is still evolving and the treatment systems and point of care are still being modified, the project already shows that, when treatment is adapted to local conditions and adequately supported by human and financial resources, comprehensive HIV/AIDS care, can be effectively provided in a rural setting (32).

What is evident from the MSF report is that improvements in "access" (availability, acceptability, accessibility and quality) are possible even in the face of weak infrastructure and poverty, if programmes and tools are properly adapted.

For many human diseases, interventions with a high degree of safety and efficacy exist for their prevention, treatment or management in the conditions of developed countries. But these interventions fail to benefit as many people as they should because they are poorly adapted for use in low-income settings, where there is often an absence of trained staff, reliable sources of electricity, adequate supplies and appropriate equipment – including for the storage and administration of medicines and other products.

For Type I conditions, such as cancer, asthma, cardiovascular disease and diabetes, innovations in treatment regimes can be very expensive, in part because of the scientific complexities in addressing these diseases. Cancer is a prime example of a class of diseases that affect both rich and poor, and whose treatment can be hugely expensive in terms of products and high technology interventions. In developing countries, the shortage of resources makes such approaches to treatment unfeasible for the great majority of sufferers. However other approaches, such as preventive measures in terms of lifestyle (e.g. stopping smoking), or reducing blood pressure (also by pharmaceutical methods) may be relatively much more cost-effective.

For Type II conditions, such as HIV/AIDS, existing treatments, as we have seen, have radically improved the length and quality of life of people living with the infection in industrialized parts of the world; but the same is not the case in sub-Saharan Africa and other parts of the developing world. This is, in part, because of the cost of medicines but it is also because of the difficulties in applying the same diagnostic, monitoring and treatment tools in communities where human, material and financial resources are scarce. Moreover, there is still inadequate knowledge about how to treat conditions, which may be largely confined to the developing world, such as HIV/AIDS in children. Similarly, there is a need for products such as antiretrovirals

or vaccines to be made more robust (for example, heat resistant), and for cheap and simple diagnostic tools (33).

For other Type II conditions, such as malaria or TB, and Type III conditions, such as Buruli ulcer and lymphatic filariasis, the problem is more often that the existing treatment is simply inadequate, in terms of its clinical safety and efficacy – where it exists at all (34). In these cases, fundamental product development is required. Thus, bridging the "acceptability" gap to create interventions better adapted for use in poorer communities can mean introducing relatively minor changes that confer significant clinical benefit (such as combining drugs to improve compliance and to reduce the likelihood of resistance), or developing new products that break entirely new technical ground.

A number of the grant recipients of the Grand Challenges in Global Health initiative are working on the creation of adapted tools, such as single-dose vaccines and needle-free vaccine delivery systems (35). For many diseases, both infectious and otherwise, there is a great need for appropriate diagnostic techniques that are both accurate and low cost. For example, use of robust technology platforms, such as DNA-based polymerase chain reaction, has been an important part of creating adapted diagnostic tests for use in poor communities by initiatives such as the Sustainable Sciences Institute. While programmes for technology transfer and adaptation exist, they need to be expanded and supported to reach a scale that will begin to make an impact beyond the local level (36).

4.5 Policies for biomedical innovation must take account of the fact that health systems in many developing countries remain resource-constrained. Policies must emphasize affordable innovations adapted to the realities of health-care delivery in developing countries, and covering appropriate technologies for the diagnosis, prevention and treatment of both communicable and noncommunicable diseases. Mechanisms for promoting such adaptive research in a systematic way must be improved.

THE DETERMINANTS OF ACCESSIBILITY

There are many determinants of accessibility (and indeed availability) which, in particular circumstances, may override economic and other considerations. Policies can be influenced by legal, political, cultural and religious factors. This applies, for example, to drugs for women's reproductive health (37). Approval of contraceptives has often been delayed. Emergency contraception is still the subject of controversy in some countries. It was only very recently that the medical regimen for induction of abortion was added to the Complementary List of the WHO Model List of Essential Medicines, "where permitted under national law and where culturally acceptable," even though the regimen was first developed and marketed in the 1980s.

However, the determinants of accessibility on which we will concentrate are principally economic. We have described above, at some length, how availability and acceptability are dependent on the state of health-care infrastructure and resources provided by governments. The focus here includes factors affecting the price at which products, whether existing or prospective, can be supplied and the funds available to purchase these products (by patients or by others on behalf of patients) or

to subsidize further their price. Together these determine economic accessibility. The price of medicines and other health products, even when "at cost" in the poorest settings, and the ability to pay for them, are the critical factors in enhancing or hindering access.¹¹

The price of the product involved (such as an antibiotic for TB) may not be directly related to the overall cost of treatment. For instance, a new TB antibiotic may itself cost significantly more than its predecessors but the overall cost of treatment may be much lower because the treatment time is shorter, compliance better and the overall call on ancillary services less. Assessing the cost-effectiveness of different interventions requires taking a long-term view of cost, and not simply counting the dollars required up-front for the purchase of a product. In the case of the Brazilian AIDS programme (see Box 4.2), although the cost of the drugs and administration is high, substantial savings have been estimated, which are likely to exceed the costs of the programme. Apart from direct health benefits (extended life of better quality), direct cost savings include avoided hospitalization and opportunistic infections (such as TB) (38).

Thus products which are more expensive than their possible substitutes can make economic and financial sense as well as improve health, provided the price remains affordable (39). The relevant concept in this case is "opportunity cost". The fact that a given programme might generate savings greater than its costs does not necessarily mean that it is the best use of available health-care resources. Greater health benefits may be generated at lower cost by other forms of intervention.

Nevertheless, the pricing of the product itself is extremely important in developing countries because most medicines are purchased directly by patients, rather than the State or insurers. Just as the price of food in relation to overall income level is an important determinant of food security and poverty, because it looms larger in the budgets of poor people, so also is there an analogous relationship between the ability to secure needed treatments and their price (40).

Box 4.2 Brazil's national HIV/AIDS programme

The median survival for AIDS patients living in Brazil in the 1980s was five months; by 1996, it was nearly five years. These figures reflect developments in drug therapies, which significantly transformed the characterization of AIDS treatment as a chronic illness. They also demonstrate a commitment by the Brazilian government to provide universal access to antiretroviral treatment.

Brazil launched its first government AIDS programme 20 years ago in the state of Sao Paulo, when only four AIDS cases had been reported. Antiretrovirals were first provided via the public health system in the early 1990s. Then, in 1996, highly active antiretroviral therapy (HAART) was institutionalized by a presidential decree guaranteeing free access to essential medications to combat HIV. Financial, human resource and infrastructure challenges meant that the implementation of the programme was subject to progressive realization.

¹¹ For example, WHO estimates that "about 30% of the world's population lacks regular access to essential medicine; in the poorest parts of Africa and Asia this figure runs to over 50%" (55).

Currently, about 140 000 people have access to free treatment provided through government financing. This is possible because of a variety of measures taken by the Brazilian Government. The AIDS treatment programme is rooted in a public health system that, under the new federal Constitution of 1988, mandated free, universal health access. The programme has also enjoyed consistent and strong political support from the very highest level of government. The result has been the passing of regulatory policies and the sustainable allocation of financial resources at the national, state, and local levels.

According to UNAIDS, Brazil's capacity to produce its own AIDS medicines in both the public and private sectors is a key to programme sustainability. As well as making use of its capacity to produce cheaper local versions of brand-name antiretrovirals (for which there were no patents in Brazil), Brazil has also actively used the possibility of compulsory licensing as a negotiating tool to reduce the cost of imported patented antiretrovirals. As their cost represented a significant portion of the Ministry of Health budget, the Brazilian Government announced that compulsory licences would be issued if the supplier companies did not reduce the prices. The ability to manufacture locally, and to estimate the likely cost of local production, adds to the credibility and strength of Brazil's negotiating position with companies. As a result, even as the number of patients needing more expensive and complex treatment has increased, the average cost per patient per year has decreased by two thirds in the past few years, although the few patented drugs, not manufactured locally, still account for a substantial proportion of the overall drug procurement cost.

AIDS nongovernmental organizations have played a major role in advocacy, policy development, and implementation of key activities. Those individuals who manage the programme in the Brazilian Ministry of Health are seen as highly qualified technical and administrative staff. In addition, a strong and active national business council on AIDS has been in place since 1998.

Finally, given the constitutional commitment to universal health coverage, the AIDS programme has saved the Brazilian government money. While the programme cost US\$ 1.8 billion between 1997 and 2003, estimated savings from avoided hospital admissions, ambulatory care and drug costs for opportunistic infections, are US\$ 2 billion, thus resulting in total net direct health-care savings of US\$ 200 million dollars. These ignore indirect economic benefits arising, for instance, from prolonged productive employment.

Sources: references (38, 41).

A number of approaches may be adopted to ensuring that the prices of drugs and other products are as affordable as possible. There are global policies such as differential pricing, or global funding mechanisms to provide subsidized or free drugs or vaccines. There are also a host of national policies that may affect pricing, including taxes and subsidies, competition policy, pricing and reimbursement policies, and intellectual property policy.

INTERNATIONAL PRICING POLICIES

At the heart of debates about the pricing of health-care products internationally is how the burden of R&D costs should be shared between countries with widely varying standards of living, and between richer and poorer people. Therefore, intrinsic to this international dimension are concepts of fairness and equity, as well as economics. Where the financing of R&D is primarily derived from product sales, this requires governments in countries with significant sales to strike a balance between the need to spur innovation, and to make medicines more affordable for patients or government-

financed health-care services. Countries make decisions on the policies they pursue in the light of their own circumstances. For instance, countries with significant pharmaceutical industries (such as Switzerland or the United States) either allow a relatively free market to set prices, or set prices at levels that reward innovation. In other countries, particularly developing countries, prices may be set with affordability in mind. Thus prices for the same products may vary quite substantially between countries in response to differing government policies and market conditions.

Company pricing policies

Thus, although pricing policies are national, they have an international dimension. The term equity pricing has been coined to indicate companies' pricing policy that is "fair, equitable and affordable, even for a poor population and/or the health system that serves them" (42). Some also use the term differential (or tiered) pricing to describe company strategies that help determine the best prices from a commercial point of view in different markets (related, for instance, to ability to pay).

Economic theory suggests that when prices are set according to willingness to pay companies can maximize their profits and at the same time consumer welfare increases. Doing so depends on there being a means of keeping these markets completely separate from each other. Because consumers in rich countries would be prepared and able to pay more than consumers in poorer countries, companies should be able to make more profit by "differential" pricing, than by selling at a uniform global price (where they would lose revenues in rich countries not compensated by gains in poorer countries where most consumers are unable to pay higher prices). By this means, companies can achieve larger profits, inter alia to plough back into R&D, while selling medicines at lower prices in developing countries. That is why benefit is seen in promoting differential pricing as a commercial strategy for companies (43).

The differential pricing approach undertaken by pharmaceutical companies varies significantly in response to price elasticity and other factors. Where they exist, open market prices usually respond to local market conditions. Companies do generally set different prices that take account of market conditions, willingness to pay and local regulations. Companies may be concerned that lower priced drugs in low income nations may be channelled back, one way or the other, to higher income countries, undermining their profits there even if, as is currently the case in most of the developed world, patented products from elsewhere (known as parallel trade – see below) are generally not permitted to be imported. Even if there is no physical leakage of product between different markets, they may be concerned that governments in developed countries, under pressure from drug purchasers, may use prices in low income countries as a reference point for their own price setting or purchasing decisions. Moreover, because incomes are very unequally distributed in most developing countries, companies may find it best for their profitability to concentrate only on high income segments in developing countries, in particular because it is more difficult to apply a differential pricing policy within developing countries than it is between them.

Separate from differential pricing, originator and generic companies also offer discount schemes for particular customers in developing countries (international agencies, governments, companies or nongovernmental organizations). According to

corporate strategies, discounted prices may be offered in countries and sectors which are eligible. Many companies now price certain antiretroviral drugs, malaria treatments, diagnostic tools, and vaccines at lower prices in a selection of developing countries than in developed country markets (see, for example, Box 4.3). Not all medicines or developing countries are covered, and discounts are available only to public, private or non-profit institutions.

Box 4.3 Accelerating Access Initiative

Established in 2000, the Accelerating Access Initiative (AAI) involves seven research-based pharmaceutical companies; Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Roche, and Merck & Co., Inc, and five United Nations partners; UNAIDS, the World Health Organization, World Bank, UNICEF, and the United Nations Population Fund (UNFPA). The AAI combines pharmaceutical industry research knowledge with that of its partners to establish practical, long-term solutions that help to improve access to HIV health care in resource-poor countries.

The AAI companies remain committed to dialogue with all external organizations sharing similar goals to help people living with HIV/AIDS in the poorest countries. AAI members are actively engaged with many groups focused on making meaningful and practical differences on the ground.

In March 2005, a total of 427 000 people living with HIV/AIDS in developing countries were receiving treatment with antiretroviral medicines provided by the AAI companies. The total number of patients receiving treatment from the AAI companies increased by 47% over the previous year, with 130 000 people initiated on treatment during 2004. In Africa alone, 216 000 patients are being treated with medicines supplied by the AAI companies. With an increase in excess of 121% over the previous year, there has been a 23-fold increase in Africa since the establishment of the AAI in May 2000. The estimated number of people on treatment is based on actual quarterly drug supply data from the seven companies.

Source: reference (44)

In the case of discount schemes, most companies that offer discounted prices extend their programmes to all sub-Saharan African countries. Companies, however, take varying approaches in determining which other developing countries to include. Some companies extend their programmes to other least developed countries, as defined by UNCTAD (45–47). Although this definition includes a significant number of countries, most companies exclude from discount schemes countries with large markets, such as Brazil, China and India, where about half the world's poor people live (48), preferring instead to operate differential pricing. There are, however, some schemes run by companies, such as that for an anti-leukaemia drug, which cover these countries. Companies could work towards reducing prices on a more consistent basis for low and lower middle income developing countries (49).

It is also the case that the cost of second-line antiretroviral drugs remains significantly higher than that of older first-line antiretroviral drugs in developing countries. Access to second-line antiretroviral drugs is critical for patients in developing countries who fail to benefit from first-line therapies, and will increasingly be so as resistance develops (48).

Differential and discount pricing will remain important for a wider range of products as a result of rapidly rising rates of noncommunicable disease in developing countries. This could raise a number of challenging issues, in the way that differential pricing of antiretrovirals has done. For noncommunicable diseases, thought needs to be given, by governments and companies, as to how treatments, which are widely available in developed countries, can be made more accessible for patients in developing countries.

Competition brought about by the generics industry has played a significant role in pushing down the prices of off-patent products. Governments should work to create a pro-competitive environment for the marketing of medicines, as competition is in the last instance the key tool to drive prices down and improve access to medicines. Avoiding or dismantling unjustified barriers to the entry of generics is a major responsibility of governments.

Company donation programmes

Pharmaceutical companies have for many years contributed to a large variety of donation programmes, in a number of disease areas and in many parts of the developing world (see Box 4.4). Such programmes are established for philanthropic reasons, to improve a company's public image, and in many countries donations benefit from tax advantages.

In order to estimate the contribution of the industry towards meeting the Millennium Development Goals, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) recently conducted a survey of the contribution of different companies through donations of different kinds over the last five years or so. This survey, which cannot be published for reasons of commercial confidentiality, collects data on 126 company partnerships and finds that in terms of the number of programmes and patients, the ten most significant diseases addressed by industry include elephantiasis, hepatitis, HIV/AIDS, influenza, malaria, polio, river blindness, sleeping sickness, trachoma and tuberculosis.¹²

A recent evaluation in four countries concluded that the tropical drug disease donation programmes provided considerable benefits, and were welcomed by countries (49). Donations are probably best suited to disease eradication programmes because of their time-limited nature, although many have been longstanding (for example Merck's river blindness programme which began in 1987 and has donated over 1 billion doses of ivermectin). Some companies have committed to continue such donations "for as long as it takes to eradicate the disease." In other cases, particularly in the context of chronic diseases, donations are unlikely to be a sustainable means for a private company to address health-care needs more generally. The former chief executive officer of Merck has noted that:

¹² This information comes from an IFPMA press release (7 December 2005). <http://www.ifpma.org/News/NewsReleaseDetail.aspx?nID=4123> Although IFPMA, cannot publish the survey which justifies these data, it is due to have published in March 2006 a document it has commissioned from the London School of Economics with the objective of verifying the unpublished study. Kanavos P, Hockley. T and Rudisill C "The IFPMA Health Partnerships Survey: A critical appraisal" LSE Health & Social Care, London School of Economics & Political Science, London 2006.

Corporations cannot choose to write off the developing world as beyond their business interests. Although philanthropy remains an important role for corporate America, the development of workable, long-term business models is the only real way to ensure that the products and services we generate are truly available to fight global poverty and meet health challenges such as AIDS, malaria and TB (50).

Box 4.4 Selected major corporate donation programmes in developing countries

The African Programme for Onchocerciasis Control (APOC) was launched in the mid-1990s. APOC is based on the distribution of ivermectin. This drug was developed by Merck & Co. in the 1980s and is now donated for riverblindness control. Mectizan is distributed by communities themselves, trained and supported by the river blindness partners, including international agencies, participating country governments, nongovernmental organizations, donor countries, and of course, the communities themselves. APOC was tested and validated on a local basis and has been scaled up by continually launching more projects. From modest beginnings in 1996, it is estimated that by 2007 a total of 65 million people will be reached annually through this programme. The distribution network is also being tested to deliver other interventions.

Under the WHO-sponsored Global Alliance to Eliminate Filariasis, GlaxoSmithKline has agreed to donate all needed supplies of its drug, albendazole, and Merck has similarly agreed to donate ivermectin free of charge until the disease is eliminated. By working together, pooling skills and resources, and working through the national health systems in the affected countries, elimination can be achieved, local capacity installed and developmental potential assured for those whose lives would otherwise be blighted by the disease. In 2003, GlaxoSmithKline donated 94 million albendazole tablets which were supplied to 34 countries and Merck donated nearly 66 million tablets of ivermectin for this programme.

Many other companies are involved in donations of drugs including, for example, the Global Polio Eradication Initiative (Sanofi-Pasteur <http://www.polioeradication.org>), the International Trachoma Initiative (Pfizer <http://www.trachoma.org>) and the Global Alliance for the Elimination of Leprosy (Novartis <http://www.who.int/inf-pr-1999/en/pr99-70.html>). Other programmes include long-term health-care programmes in 49 countries (Bristol-Myers Squibb), and the donation of an antiretroviral drug, nevirapine, for the prevention of mother-to-child transmission of HIV (Boehringer Ingelheim).

Source: references (52, 53, 87, 88)

Public policy

Pricing of products is such a crucial factor in determining access to treatment that governments in many countries, both developed and developing, have introduced a variety of means to regulate prices of both patented and non-patented products. These include direct price regulations, formulae to determine prices at which the state or

insurers will reimburse companies, monitoring and controlling the price of patented and other medicines, and the application of regulation of various kinds. Competition policies are also used.

Central to these is the degree of competition as it may affect the distribution chain. The way price regulation is operated by government can also be influential. Sensitive price control regimes may promote efficient marketing, while others may be counterproductive in deterring necessary investment in the wholesale and retail network on which availability and accessibility may depend. The pricing regime adopted by governments has to be sensitive to the needs of poor consumers and the need to ensure that there are sufficient incentives to make drugs available to them at the best possible prices. Companies' publicity and marketing costs for promoting the use of medicines are often a significant component of the final price. These costs should be subject to limits coherent with public health objectives.

Tariffs and taxes on essential health care are under the direct control of governments – it is important that they also contribute to public health objectives. A recent study, undertaken on behalf of the Commission, examined data on the tariff rates levied and revenue generated by over 150 countries on pharmaceutical products (51). The analysis shows that most countries for which data are available do not levy duties on pharmaceutical products. Furthermore, 90% of countries apply tariff rates of less than 10% on medicines. Pharmaceutical tariffs generate less than 0.1% of gross domestic product in 92% of countries for which data are available. According to the study, factors other than tariffs – such as manufacturer's prices, sales taxes including value-added tax, mark-ups and other charges – are likely to have a greater impact on the price of medicines than tariffs. Thus, in the majority of developing countries the extent to which pharmaceutical tariffs are a barrier to access should not be overestimated. However, the removal of tariffs will not help patients if the benefits of any reductions are absorbed in the supply and distribution chain, for instance by patent owners or importers.

4.6 All companies should adopt transparent and consistent pricing policies, and should work towards reducing prices on a more consistent basis for low and lower middle income developing countries. Products, whether originator's or generic, should be priced equitably, not just in sub-Saharan Africa and least developed countries, but also in low and lower middle income countries where there are a vast number of poor patients.

4.7 For noncommunicable diseases, governments and companies should consider how treatments, which are widely available in developed countries, can be made more accessible for patients in developing countries.

4.8 Continuing consideration needs to be given to the prices of treatments for communicable diseases, particularly of second-line drugs for HIV/AIDS treatment.

4.9 Governments of low and middle income countries where there are both rich and poor patients should formulate their funding and price regulation with a view to providing access to poor people.

4.10 Governments need to prioritize health care in their national agendas and, given the leverage to determine prices that patents confer, should adopt measures to promote competition and ensure that pricing of medicines is consistent with their public health policies. Access to drugs cannot depend on the decisions of private companies but is also a government responsibility.

4.11 Corporate donation programmes can be of great value in a number of fields in collaboration with the actions of governments and nongovernmental organizations. However, addressing health needs in developing countries requires more structured and sustainable actions by governments and other parties to stimulate accessibility to products, while generating new treatments and products adapted to the needs of developing countries.

4.12 Governments should remove any tariffs and taxes on health-care products, where appropriate, in the context of policies to enhance access to medicines. They should also monitor carefully the supply and distribution chain to minimize costs that could adversely influence the prices of medicines.

INTELLECTUAL PROPERTY

Prices and competition

Intellectual property rules are territorial in nature but different international conventions and treaties, such as the WTO TRIPS agreement, lay down agreed minimum standards. The Doha Declaration on the TRIPS Agreement and Public Health (see Box 4.5) stressed the need for the TRIPS agreement to be part of the wider national and international action to address public health problems (paragraph 2), recognized that intellectual property protection is important for the development of new medicines, and also recognized the concerns about its effects on prices (paragraph 3).

A feature of the past few years has been the significant decline in the price of antiretrovirals in developing countries. The costs for typical treatment combinations have fallen from more than US\$ 10 000 per annum in 2000 (valued at export prices) to prices now as low as a few hundred US\$, although there is a great deal of variation in actual prices paid. WHO now regularly publishes information on prices and volumes of transactions in antiretrovirals and other medical products (56). The initial large decline to about US\$ 1000 per annum in 2001 in the prices of brand-name companies arose from reductions under the Accelerating Access Initiative, in large part in response to considerable public pressure from activists and the international community more generally. Further declines to current levels were the result of competition from suppliers of equivalent drugs, principally from India.

A precondition for this potential competitive pressure was that the TRIPS Agreement had no retroactive effects, and allowed countries to retain in the public domain products for which a patent had not been filed before 1 January 1995. This transitional period, which ended in 2005, allowed Indian firms to produce antiretrovirals patented elsewhere and, importantly from the point of view of public health, to produce easier to administer combinations of antiretrovirals, not already available from brand-name companies. These generic copies of patented drugs have

thus come to play a significant part, alongside brand-name products, in the global supply of antiretrovirals in developing countries. Following approval by the United States Food and Drug Administration or the WHO Prequalification Project, a variety of these products can now be used in programmes financed by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the United States President's Emergency Plan for AIDS Relief.

Now that the transition period is over, companies can patent new products in all WTO Members (except least developed countries taking advantage of their transitional period). It is uncertain how this might affect worldwide pricing and the accessibility of new products, and how, in the absence of potential competitive pressure, pricing of the kind that has emerged to date in the antiretroviral market can be sustained.

The Doha Declaration and compulsory licences

The 2001 WTO Doha Declaration on the TRIPS Agreement and Public Health recognized the right of countries under TRIPS to use to the full the flexibility in the agreement to protect public health and to promote access to medicines for all. One of these flexibilities in TRIPS is the ability to issue a compulsory licence as specified in Article 31 (see Box 4.6). Compulsory licensing allows for the use of a patented invention, without the authorization of the patentholder, by a third party e.g. a generic manufacturer. Most national laws also permit the government to make use of patented inventions for public purposes. The TRIPS agreement refers to such use as "public non-commercial use". Compulsory licences can be used for public health reasons in relation to any pharmaceutical product. In the case of a national emergency, other circumstances of extreme urgency, anti-competitive practices and "public non-commercial use", the TRIPS agreement allows the issue of a licence without the requirement, which otherwise applies, for prior negotiations with the patent holder. The Doha Declaration confirmed that WTO Members, while maintaining their commitments in the TRIPS Agreement, reaffirmed the right of WTO members to use, to the full, the provisions in TRIPS which provide flexibility for the purpose of protecting public health, including the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

Countries such as Zambia and Zimbabwe have recently issued compulsory licences and others (such as Malaysia and Indonesia) have applied government use provisions. Other countries have threatened the granting of such licences in order to obtain substantial price reductions, as in the cases of Brazil (see Box 4.2) and South Africa (58).

Countries which have adequate technological and manufacturing capacity may use these mechanisms to lower prices, remedy anti-competitive practices, create a sustainable supply or for other reasons, as determined by national laws. Even if a compulsory licence is not actually issued, the fact that its use may be invoked strengthens a government's negotiating hand. Only a small number of compulsory licences or non-commercial government uses have actually been authorized in developing countries. Companies may view the use of these mechanisms as threatening to their interests. There is very little real evidence, one way or the other,

on how the availability or possible use of compulsory licences will affect willingness or reticence to invest in R&D.

The Doha Declaration recognized that countries with inadequate manufacturing capacities could be handicapped in making effective use of compulsory licensing under the TRIPS agreement, a handicap which could assume added importance after 2005. This handicap arises for a number of reasons but a particular obstacle is that Article 31(f) restricts the scope of a licence to predominantly the domestic market. Consequently, countries needing to import drugs under a compulsory licence could have difficulties in finding supplies since the producing countries would face export limitations. A decision which proposed mechanisms by which such countries would do this was finally agreed in the WTO, on 30 August 2003, in the form of a waiver to Articles (f) and (h) of the TRIPS agreement, and agreement was reached in December 2005 to transpose this into a permanent amendment to the TRIPS agreement.

Since 2003, several developed countries (including Canada, the Netherlands, Norway, Switzerland and the European Union) have moved to change their legislation to permit their producers to act as exporters under the compulsory licence regime agreed in WTO. India's 2005 legislation also implemented the waiver. Several different issues have arisen in drafting these laws, including procedures, coverage of countries and medicines, and regulatory approval, among others.

Generic producers in both developed and developing countries argue that there remain economic and procedural barriers to their participation in these arrangements (59, 60). Although their business models are different, generic companies share with the research-based industry the common motivation of serving the interests of their shareholders. The mechanism will not be used if the financial incentives for participation, taking account of the risks involved, are deemed inadequate. Whether this mechanism is capable of making supplies of lower cost drugs available to developing countries with inadequate manufacturing capacity, remains to be seen. So far no developing country has sought to make use of it.

Box 4.5 Declaration on the TRIPS Agreement and Public Health (Doha Declaration)

Adopted on 14 November 2001

1. We recognize the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics.

2. We stress the need for the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to be part of the wider national and international action to address these problems.

3. We recognize that intellectual property protection is important for the development of new medicines. We also recognize the concerns about its effects on prices.

4. We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all.

In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.

5. Accordingly and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include:

- a) In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles.
- b) Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.
- c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.
- d) The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN and national treatment provisions of Articles 3 and 4.

6. We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.

7. We reaffirm the commitment of developed-country Members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least-developed country Members pursuant to Article 66.2. We also agree that the least-developed country Members will not be obliged, with respect to pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, without prejudice to the right of least-developed country Members to seek other extensions of the transition periods as provided for in Article 66.1 of the TRIPS Agreement. We instruct the Council for TRIPS to take the necessary action to give effect to this pursuant to Article 66.1 of the TRIPS Agreement.

Box 4.6 Agreement on Trade-Related Aspects of Intellectual Property Rights, Article 31

Other Use Without Authorization of the Right Holder

Where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:

- (a) authorization of such use shall be considered on its individual merits;
- (b) such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly;
- (c) the scope and duration of such use shall be limited to the purpose for which it was authorized, and in the case of semi-conductor technology shall only be for public non-commercial use or to remedy a practice determined after judicial or administrative process to be anti-competitive;
- (d) such use shall be non-exclusive;
- (e) such use shall be non-assignable, except with that part of the enterprise or goodwill which enjoys such use;
- (f) any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use;
- (g) authorization for such use shall be liable, subject to adequate protection of the legitimate interests of the persons so authorized, to be terminated if and when the circumstances which led to it cease to exist and are unlikely to recur. The competent authority shall have the authority to review, upon motivated request, the continued existence of these circumstances;
- (h) the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization;
- (i) the legal validity of any decision relating to the authorization of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;
- (j) any decision relating to the remuneration provided in respect of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;
- (k) Members are not obliged to apply the conditions set forth in subparagraphs (b) and (f) where such use is permitted to remedy a practice determined after judicial or administrative process to be anti-competitive. The need to correct anti-competitive practices may be taken into account in determining the amount of remuneration in such cases. Competent authorities shall have the authority to refuse termination of authorization if and when the conditions which led to such authorization are likely to recur;

Note : Article 31 (l) omitted.

4.13 The Doha Declaration clarifies the right of governments to use compulsory licensing as a means of resolving tensions that may arise between public health and intellectual property, and to determine the grounds for using it. Developing countries should provide in their legislation for the use of compulsory licensing provisions, consistent with the TRIPS agreement, as one means to facilitate access to cheaper medicines through import or local production.

4.14 Developed countries, and other countries, with manufacturing and export capacity should take the necessary legislative steps to allow compulsory licensing for export consistent with the TRIPS agreement.

4.15 The WTO decision agreed on 30 August 2003, for countries with inadequate manufacturing capacity, has not yet been used by any importing country. Its effectiveness needs to be kept under review and appropriate changes considered to achieve a workable solution, if necessary.

Company patent policies

Pharmaceutical companies have a role to play in adopting sound patent policies which recognize the circumstances of developing countries. Because pharmaceutical companies regard patent protection as very important to their businesses, and are extremely wary of any perceived threats to the integrity of the patent system, they have on occasion, appeared to react disproportionately to developments which had very little direct impact on them. This was true, as is now admitted by many, in a famous case in South Africa in 2001 when about 40 pharmaceutical companies challenged provisions of South Africa's proposed Medicines Act on the grounds that they violated the country's constitution, including because they were contrary to provisions in the TRIPS agreement which had been enacted in South African law.

Patenting policies of companies generally relate to considerations of market size and the potential for copying. Patents are often not sought or enforced in countries where prospects of sales and profits are very low, or where there is no meaningful judicial patent protection. Low income developing countries are an insignificant contributor to the balance sheet of the companies. In addition, as a result of paragraph seven of the Doha Declaration, least developed countries have been exempted from granting and enforcing pharmaceutical patents until 2016 and, hence, companies would not be able to exercise patent rights in such countries.

Some companies now have global patent policies which seek to address concerns raised about their patenting policies in developing countries. Roche, for instance, explicitly states that it will not file patents for any of its medicines in the 50 countries defined as least developed countries by UNCTAD and has pledged not to file patents on new or investigational HIV medications in least developed countries and in sub-Saharan Africa (46). Similarly, Bristol-Myers Squibb has committed itself to forego infringement action against generic companies for HIV/AIDS medicines in sub-Saharan Africa (61).

Even in circumstances where pharmaceutical companies have retained their patent rights, a few have provided voluntary licences to the generic industry in developing

countries, for the development of essential drugs (46,62,63). For example, GlaxoSmithKline has granted six voluntary licences for the manufacture of antiretrovirals in Africa (five in South Africa and one in Kenya). However, in at least one case, in South Africa, the granting of a voluntary licence followed the determination of anti-competitive practices by the competition authorities, which required licensing to other producers as part of the settlement reached (58).

Roche has also stated that it will publicize the patent status for antimalarials in least developed countries and sub-Saharan Africa. Publicizing patent status in developing countries may facilitate the supply of generics into these markets when no patent protection exists. A number of countries, nongovernmental organizations, and international procurement organizations have expressed concern that the lack of certainty about the patent status of products, and the possibility of infringement action being taken, can inhibit the flow of generic products to developing countries. This problem is complicated by the multiplicity of patents that exist on variants of some products. WHO is currently considering the possibility of creating a database to address this gap in information. A publication on the lines, for instance, of Canada's Patent Register (which lists patents on different drugs compiled by Health Canada) or the United States FDA's Orange Book (which contains similar information on patents supplied to the FDA by companies but not independently assessed) could be very useful to those involved in the procurement of medicines in developing countries.

4.16 Companies should adopt patent and enforcement policies that facilitate greater access to medicines needed in developing countries. In low income countries, they should avoid filing patents, or enforcing them in ways that might inhibit access. Companies are also encouraged to grant voluntary licences in developing countries, where this will facilitate greater access to medicines, in cases where patents do exist on medicines and other products, and to accompany this with technology transfer activities.

4.17 Developing country governments should make available full and reliable information on patents granted. WHO, in cooperation with WIPO and others, should continue to pursue the establishment of a database of information about patents, in order to remove potential barriers to availability and access resulting from uncertainty about the patent status in a country of a given product.

Other patent-related schemes

Other schemes, relating to patents, have been proposed to promote access to medicines. These include:

- a scheme based on patentees making a commitment not to enforce patents in certain low-income developing countries (foreign filing approach) (64);
- patent “buy-outs” in developing countries (65).

These schemes are alternative ways of avoiding patenting in low income countries. The first proposal involves a rather complex (in practice if not in principle) formula for deciding, by disease, which low income countries should escape patents (essentially those countries which collectively account for less than 2% of global

sales). Although it can be implemented by developed countries alone, it will require coordinated action, and changes in patent rules and legislation, to do so.

The patent buy-out proposal also takes advantage of the fact that, because so few sales actually take place in developing countries, and because developing countries make such a small contribution to either profits or the costs of R&D for Type I and II diseases, patents can be purchased from companies by a public authority at relatively low prices.

Both schemes make the assumption that in the absence of patents, despite a small market, generic producers will enter the market and make products available at a lower price than the brand-name producer. But this is not necessarily the case, particularly where there are no generics readily available for importation, because they are patented in potential exporting countries, or there are economies of scale in the production of the relevant active ingredients and formulations. For some products, local production on a small scale may make economic sense and result in more availability and lower prices – in other cases this may not be so (66). This is the type of situation, created by the global extension of pharmaceutical patents through TRIPS, that paragraph 6 of the Doha Declaration instructed the Council for TRIPS to deal with.

It would be much simpler and less expensive if more companies were to make a commitment not to take out patents in low-income developing countries or not to enforce existing patents. Preferably they would also enter into voluntary licensing arrangements, as some companies have already done when local production is feasible and viable. But this requires companies and their shareholders to exhibit an enlightened view of their long-term interests. Relying on companies' decisions alone cannot provide a sufficiently solid and predictable basis for action. The extension of the transitional period for the recognition and enforcement of pharmaceutical patents at least until 2016 for least developed countries, as agreed by the WTO at Doha and subsequently confirmed by the WTO General Council, is an important step forward in that direction.

Access to production technologies and the creation of local manufacturing capacity, at the national or regional level, could provide the most appropriate solution. There is no evidence, however, of any significant move to comply with the obligations that developed countries assumed under Article 66.2 of the TRIPS agreement, nor implementation of paragraph 7 of the Doha Declaration (see Box 4.5).

4.18 Developed countries and the WTO should take action to ensure compliance with the provisions of Article 66.2 of the TRIPS agreement, and to operationalize the transfer of technology for pharmaceutical production in accordance with paragraph 7 of the Doha Declaration on the TRIPS Agreement and Public Health.

Parallel imports

In the context of differential pricing, the rules which countries use concerning the import of patented products produced elsewhere assume some importance. This relates to the principle called “exhaustion” in intellectual property law, which essentially means the exact point in the process of sale where the rights of the patentee become "exhausted". Where the principle of international exhaustion is applied in national law, this is equivalent to allowing what are called parallel imports. In practice, this means a situation, for example, where a wholesaler in Country A makes available to a purchaser in Country B a product patented in both countries, at a lower price than it is available in Country B. If Country B allows parallel imports, then the purchaser could import the product at a lower price than the product is available locally. Thus, in principle, parallel imports are a means to reduce the cost of medicines where there are significant intercountry differences in prices. Whether they actually do so depends on a number of assumptions, in particular that any price reductions obtained are passed on to patients rather than absorbed in the distribution chain.

TRIPS explicitly says that nothing in the agreement “shall be used to address the issue of the exhaustion of intellectual property rights.” This means that countries can choose whether to allow or forbid parallel imports as they think best, without fear of a dispute settlement case being brought in the WTO.

As regards parallel trade between developed countries, taken as a group, and developing countries, taken as a group, there is little doubt that restrictions on parallel imports, which exist in the laws of most developed countries, are beneficial as they help to preserve price differentials through market segmentation that potentially benefit developing countries, and help maintain lower prices in those countries.

The benefits and costs of parallel trade between developing countries, or parallel imports by developing countries from developed countries, require close consideration. Free trade principles would suggest that restrictions on parallel trade should be avoided wherever possible. However, some developing countries have opted to restrict parallel imports for reasons other than public health considerations. Developing countries should be free to benefit from the gains available from international trade.

4.19 The restriction of parallel imports by developed countries is likely to be beneficial for affordability in developing countries. Developing countries should retain the possibilities to benefit from differential pricing, and the ability to seek and parallel import lower priced medicines.

Test data protection and data exclusivity

The purpose of the requirement for data protection under the TRIPS agreement is to ensure that the collection of data which involves considerable investment (e.g. the trials data required for marketing approval) for new chemical entities are protected against unfair commercial use. The relevant article (Article 39.3) says:

Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

Article 39.3, unlike the case of patents, does not require the provision of specific forms of rights. But it does oblige Members to protect undisclosed test or other data against unfair commercial use. It does not create property rights, nor a right to prevent others from relying on the data for the marketing approval of the same product by a third party, or from using the data except where unfair (dishonest) commercial practices are involved.

Thus, the TRIPS agreement does not refer to any period of data protection, nor does it refer to data exclusivity. In some countries, however, such as the United States, a *sui generis* regime was adopted prior to the TRIPS agreement under which, for a period of five years from marketing approval, no other company may seek regulatory approval of an equivalent product based on that data without the approval of the originator company. In the European Union the period has now become up to 10 years, during which generic companies are allowed to develop the product, and may submit an application for authority to market it after eight years. Some developing countries have also adopted this regime in one form or another.

If the patent period has expired, or there is no patent on the product, this *sui generis* data exclusivity may act independently of patent status to delay the entry of any generic companies wishing to enter the market. This is because the regulators cannot use the data in the period of protection to approve a product, even if the product is demonstrated to be bio-equivalent, where required. The only alternative for a generic company would be to repeat clinical trials, which would be costly and wasteful, and would raise ethical issues since it would involve replicating tests in humans to demonstrate what is already known to be effective. These *sui generis* regimes, which provide for data *exclusivity* need to be clearly differentiated from the TRIPS agreement's requirement for data *protection*.

According to its proponents, the claimed benefits of data exclusivity relate, to a great extent, to the additional incentives offered to companies in the long and expensive process of pharmaceutical R&D (67). They note that data exclusivity gives companies an incentive to extend the original use of the product (e.g. to a wider population by age or geography and in new indications for therapeutic use) and provides an additional opportunity for originator companies to recoup their investment where marketing approval occurs late in the patent life, so that the protection afforded extends beyond patent expiry. They also argue that it offers benefits to domestic innovators in developing countries. Further, it is argued that data exclusivity provides an incentive for research to identify new uses for existing unpatented products (e.g. paediatric formulations) and an incentive for originator companies to introduce products into developing countries, which they would not otherwise do because of the possibility of generic competition.

Opponents note that, for developing countries, there are no benefits of data exclusivity, since it would not promote R&D in those countries, and the benefits to the companies themselves will be small because of the limited market potential in most developing countries. It will not add materially to R&D incentives for companies more generally. They argue that its purpose is to allow additional periods of exclusivity for originator products, and it therefore correspondingly delays the onset of generic competition and thus prevents possible reductions in the cost of medicines. Therefore, they argue, the principal result will be added health-care costs. For instance, the United Nations Special Rapporteur on the Right to Health commented on the possible additional health-care costs of the proposed Free Trade Agreement between the United States and Andean Pact countries relating to the introduction of data exclusivity (68).

Particular issues arise from the incorporation of data exclusivity provisions in the increasing number of bilateral and regional trade agreements. Most United States bilateral treaties involve agreement to the five year rule as in the United States. In the Central American Free Trade Agreement, approved in 2005 (69), this applies also to a product approved in another party to the agreement; i.e. marketing approval in Country A deters generic entry in country B for a period of five years. If the originator seeks marketing approval in Country B within five years, there will be a further five years of data protection in Country B from the time of obtaining marketing approval. The Central American Free Trade Agreement also obliges parties to provide extensions to the patent term on the grounds of unreasonable delays in granting a patent (e.g. five years from filing) or unreasonable delays in procuring marketing approval.

In the context of bilateral trade negotiations, many different considerations of national interest come into play, and countries may be obliged to trade off potential gains in one area for potential losses in others. In those circumstances, it is important that the possible public health impact of new intellectual property measures is given full weight in decisions on the best deal to strike.

Several resolutions passed by WHO Member States in 2003 and 2004 have emphasized the importance of the flexibilities in the TRIPS agreement. A resolution of the World Health Assembly in 2004 urged Member States:

...to encourage that bilateral trade agreements take into account the flexibilities contained in the WTO TRIPS Agreement and recognized by the Doha Ministerial Declaration on the TRIPS Agreement and Public Health; (70)

4.20 Developing countries need to decide in the light of their own circumstances, what provisions, consistent with the TRIPS agreement, would benefit public health, weighing the positive effects against the negative effects. A public health justification should be required for data protection rules going beyond what is required by the TRIPS agreement. There is unlikely to be such a justification in markets with a limited ability to pay and little innovative capacity. Thus, developing countries should not impose restrictions for the use of or reliance on such data in ways that would exclude fair competition or impede the use of flexibilities built into TRIPS.

4.21 In bilateral trade negotiations, it is important that governments ensure that ministries of health be properly represented in the negotiation, and that the provisions in the texts respect the principles of the Doha Declaration. Partners should consider carefully any trade-offs they may make in negotiation. Bilateral trade agreements should not seek to incorporate TRIPS-plus protection in ways that may reduce access to medicines in developing countries.

INTERNATIONAL PURCHASING ARRANGEMENTS

Even at the reduced prices for first-line antiretrovirals that are now available in many countries, the size of the HIV/AIDS pandemic and the paucity of resources available to developing countries, means that international assistance to promote accessibility is important. Further, international arrangements for pooled purchasing can generate additional price reductions through enhanced negotiation capacities and economies of scale in production and distribution. Regional approaches to join together to negotiate prices with companies have had mixed success to date for a variety of reasons.¹³

Examples of pooled arrangements include the longstanding purchase of childhood vaccines for the Expanded Programme on Immunization by UNICEF and, more recently, the Global Alliance for Vaccines and Immunization and its associated Vaccine Fund. The WHO-based Global Drug Facility for tuberculosis was created to respond to difficulties experienced by countries in the 1990s in finding and funding stable TB drug supplies, which in turn hindered the expansion of the TB control strategy. A constant and reliable supply of high-quality products means that the WHO-recommended strategy for fighting TB can be expanded by governments.

Global procurement schemes and the encouragement of local production of vaccines can have a powerful effect on pricing. For example, it was more than two decades after the invention of the hepatitis B vaccine in the early 1980s before a combination of factors, including increased funding of international procurement (offering opportunities for economies of scale) and price reductions resulting from competition between many developing country suppliers, made it significantly more available and affordable in developing countries. Prices fell from some US\$ 18 a dose or more on launch to as low as US\$ 0.30 in this decade (71).

Other schemes do not operate on a pooled basis but provide grants to individual countries to purchase, among other things, medicines and other products. Thus the Global Fund to Fight AIDS, Tuberculosis and Malaria provides finance to countries for prevention and treatment programmes, but the procurement of supplies is left in the hands of grant recipients. The opportunities for greater leverage in achieving economies of scale and lower prices, in cooperation with suppliers, may not be fully exploited. In contrast, UNICEF and the Vaccine Fund operate a pooled procurement strategy which allows for greater leverage over suppliers.

¹³ For example, in June 2003, the Pan American Health Organization (PAHO) announced the completion of price negotiations between mainly generic companies and 10 Latin American countries – Argentina, Bolivia, Chile, Colombia, Ecuador, Mexico, Paraguay, Peru, Uruguay, and Venezuela, although the long-term effectiveness of this arrangement is unclear.

In fact the number of major vaccine companies has declined massively in recent years, there being only a few global companies now conducting R&D in this important area for health. Long-term procurement strategies are necessary that recognize the need both to stimulate the introduction of new products required by developing countries, and to encourage lower prices in the longer term, as well as enhanced competition. A recent report to the Board of the Global Alliance for Vaccines and Immunization proposed the following principle:

The focus of a long-term procurement strategy should be to support the development of the market for new products by offering introductory prices that reward innovation and achieve lower prices over time by encouraging the entry of multiple qualified suppliers (72).

Such an approach could also incorporate, or indeed have the nature of, advance purchase contracts to encourage the development and bringing to market of promising vaccine or drug candidates.

A perennial problem in this field is the disparity between the estimates of demand for vaccines or treatments, based on public health need, and the effective demand for these products in terms of the actual funds available for purchasing them. This makes it a very uncertain environment for manufacturers, particularly where scaling-up production requires costly investments. In those circumstances it becomes essential to seek better ways of making realistic projections of demand in the years ahead, and of introducing a greater certainty that such demand will actually come to fruition. Again, advance purchase contracts offer this possibility.

Governments in a position to do so should increase their support for the coordinated purchase of products for prevention and treatment by the Global Alliance for Vaccines and Immunization, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and multilateral mechanisms for different products.

4.22 Governments and concerned international organizations should promote new purchasing mechanisms to stimulate the supply of affordable new products and to enhance the number of suppliers in order to provide a more competitive environment.

POLICIES TO PROMOTE COMPETITION

A number of government policies exist to promote competition in order to make markets work better for consumers; these include regulatory measures designed to promote competition, or other means to achieve similar ends. It needs to be recognized that the application of such measures, in the way this is done in developed countries, is difficult for many developing countries at their stage of institutional development.

There is potential tension between policies to promote industrial development, for example in the pharmaceutical industry, and promoting public health in developing and developed countries. Careful thought needs to be given as to how these tensions are resolved in policy terms to achieve an appropriate balance.

Governments have a number of policy levers by which they may make markets for health-care products more competitive; i.e. promoting a competitive environment in supply and distribution of products to achieve higher efficiency, lower prices and higher consumer welfare. In the United States, the Federal Trade Commission has played an important role in seeking to balance intellectual property and competition policy in the interests of consumers (73,74).

Sophisticated policy measures have been designed to promote competition and punish anti-competitive behaviour. For example, antitrust policies have traditionally been used to oblige merging companies to dispose of some of their intellectual property to avoid excessive market power. There are also policy measures, such as compulsory licensing, which can be used to remedy anti-competitive behaviour (57).

Effective competition policies are also important in developing countries. But they face various challenges, as many developing countries have no competition laws, or the existing regimes are not adequately implemented. It is beyond the scope of this report to consider the wider aspects of competition policy. Nevertheless there are a number of specific measures that developing countries can take in respect of health-care products.

4.23 Developing countries should adopt or effectively implement competition policies and apply the pro-competitive measures allowed under the TRIPS agreement in order to prevent or remedy anti-competitive practices related to the use of medicinal patents.

FACILITATING THE ENTRY OF GENERIC COMPETITION ON PATENT EXPIRY

Facilitating the entry of generic competition after the expiry of a patent is one means of potentially bringing down the price of health-care products. Countries can employ a number of intellectual property measures or exceptions, consistent with the TRIPS agreement, to promote rapid market entry of generic products after patents on products expire. One measure of importance is a provision that exists in most countries' legislation (commonly known as the "early working" exception) which allows prospective generic producers to make use of a patented product within the patent period for the purposes of obtaining regulatory approval of their product as soon as the patent expires. The "early working" exception¹⁴ constitutes jointly, with parallel imports and compulsory licences, one of the flexibilities that the TRIPS agreement permits, with an aim to get a balance between private and public interests, as set out in articles 7 and 8 of the agreement.

This policy has been used very successfully in the United States and other jurisdictions to facilitate generic entry as soon as the patent expires. It has recently

¹⁴ The report of the Canada – Patent Protection Of Pharmaceutical Products WTO Panel found that Canada's patent law (Section 55.2(1)), to allow early working for the purpose of obtaining marketing approval for pharmaceutical products, was not inconsistent with TRIPS, but that Section 55.2(2), allowing the manufacture and storage of articles intended for sale after the date on which the term of the patent expires, was not consistent with TRIPS (86).

been introduced in the European Union. In the United States the generic share of the market (by volume of prescriptions) has risen from 19% to over 50% since this legislation was introduced in 1984 as part of the Hatch–Waxman Act. Evidence from the United States shows that, especially where there are several generic producers (and hence competition), this will result in very substantial price declines on patent expiry (75). But this outcome may depend on the size of the market (76). In developing countries where markets are small, this mechanism may work less effectively to reduce prices significantly and it needs, hence, to be supplemented by other measures, including those to promote generic competition and regulate prices.

In some countries, companies (both the originator and generic producers) may differentiate their off-patent original or generic products through branding and promotion to obtain higher prices. Whereas consumers may prefer a more expensive brand-name food product to an equivalent and cheaper supermarket own-label, for rational or irrational reasons, there is no reason to purchase a medicine accordingly if both the brand and generic have been properly approved by the health authority for marketing. Several developed countries have introduced policies that allow doctors to prescribe medicines by generic names, or for pharmacists to substitute approved generics for brand-name drugs prescribed by doctors. One answer to this problem is appropriate legislation in relation to prescribing, and the education of pharmacists, doctors and patients in the availability of brand-name and generic products and their pricing (77).

4.24 Countries should provide in national legislation for measures to encourage generic entry on patent expiry, such as the "early working" exception, and more generally policies that support greater competition between generics, whether branded or not, as an effective way to enhance access by improving affordability. Restrictions should not be placed on the use of generic names.

4.25 Developing countries should adopt or effectively implement competition policies in order to prevent or remedy anti-competitive practices related to the use of medicinal patents, including the use of pro-competitive measures available under intellectual property law.

4.26 Bilateral trade agreements should not seek to incorporate TRIPS-plus protection in ways that may reduce access to medicines in developing countries.

INCREMENTAL INNOVATION

Incremental innovation can play an important part in the development of improved products that address public health needs. For instance, improving safety, simplifying the delivery of a drug or vaccine, or improving the efficiency with which it can be manufactured, can have an important impact on clinical outcomes or affordability and acceptability. Many of the modifications needed to align existing interventions more closely with the needs of poorer populations are likely to be of the incremental variety. Moreover, because patients do not respond identically to the same product, slight variations among products can result in considerable therapeutic benefit for particular groups of patients. It has also been argued that incremental innovation, which relies on small successive improvements, is the very basis for real therapeutic advance in the pharmaceutical industry, as it is in other industries.

The first drug developed in a particular class (e.g. antibiotics or antiretrovirals), often referred to as a “breakthrough” drug, does not usually prove to be, in the longer term, the best in its class. For instance, improvements in the efficacy of antibiotics, such as penicillin, have been made by changing the salt or ester of the originally discovered molecule. Such changes have also contributed to new antibiotics to combat the problem of resistance to the older drugs. In the case of HIV/AIDS, resistance developed rapidly to the original drug AZT. Small changes in the chemical structure of this family of antiretroviral compounds has resulted in the availability of more than 20 new drugs which, when used in combination, are pivotal to the prevention of progression to full-blown AIDS (78).

The development of new dosage forms of an original product by delaying or sustaining the release of the drug from a capsule or tablet has resulted in many new treatments that reduce side-effects or increase compliance. A particularly good example in this context is the development by Ranbaxy in India of a sustained release formulation of the antibacterial drug ciprofloxacin which was available originally from Bayer of Germany.

Many of the modifications needed to align existing interventions more closely with the needs of poorer populations are likely to be of the incremental variety. For example, the use of combination products in the treatment of infectious diseases such as malaria, HIV/AIDS and tuberculosis is an essential strategy for therapeutic success. Simplifying the delivery of a vaccine by using innovative devices means that it has become easier and cheaper to carry out mass inoculation schemes.

Incremental innovation, by improving the efficiency with which a drug can be manufactured, may reduce the cost of production and so have an important impact on affordability and acceptability.

Such incremental innovations may or may not be patentable, depending whether or not they include an inventive step.

On the other hand, there are studies which find that many new medicines offer little or no improvement over existing medicines. For instance, in a recent Canadian study, the conclusion was that in British Columbia, 80% of the increase in drug expenditure between 1996 and 2003 was explained by the use of new, patented drugs that did not offer substantial improvements over less expensive alternatives available before 1990 (79, 80).

Though difficult to discern from incremental innovation in practice, so-called “evergreening” is importantly different. As usually understood, “evergreening” occurs when, in the absence of any apparent additional therapeutic benefits, patent-holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term. President Bush, in 2002, provided a working definition while announcing reforms in response to a Federal Trade Commission (FTC) report (73) on delays to the entry of generic products onto the market:

The FTC...discovered that some brand name drug manufacturers may have manipulated the law to delay the approval of competing generic drugs. When a drug patent is about to expire, one method some companies use is to file a

brand new patent based on a minor feature, such as the color of the pill bottle or a specific combination of ingredients unrelated to the drug's effectiveness ... In the meantime, the lower-cost generic drug is shut out of the market ... This is not how Congress intended the law to work. Today, I'm taking action to close the loopholes, to promote fair competition and to reduce the cost of prescription drugs in America ... These steps we take today will not undermine patent protection. Instead, we are enforcing the original intent of a good law. Our message to brand name manufacturers is clear: you deserve the fair rewards of your research and development; you do not have the right to keep generic drugs off the market for frivolous reasons (81).

Evergreening can occur in a number of ways but typically, as noted by President Bush, it arises when companies file and obtain patents, subsequent to the original patent, on other aspects of the same compound or reformulations of the original compound in ways that might be regarded as of no incremental therapeutic value, but which are nevertheless patentable. For instance, strategies include a similar but different dosage form such as capsules rather than tablets, salts, esters, or crystals (polymorphs) of the same product or other changes dependent on the ingenuity of the formulators and the lawyers. These types of strategies occur in almost all jurisdictions, especially for lucrative products (see Box 4.7) (82, 83).

Box 4.7 Evergreening in the United States

In December 1992, the United States Food and Drug Administration (FDA) approved Paxil (paroxetine hydrochloride) for the treatment of depression and associated conditions. At the time of the approval, the original patent for paroxetine (4 007 196) had expired. GlaxoSmithKline (GSK) listed with the FDA a patent for paroxetine hydrochloride hemihydrate (4 721 723), which was the form approved by the FDA and marketed by GSK.

On 31 March 1998, Apotex Corporation filed with the FDA an application for paroxetine hydrochloride anhydrate, a different form of the paroxetine hydrochloride molecule. Apotex certified, as required by FDA procedures, that it did not infringe GSK's then only patent listed with the FDA. GSK brought an infringement suit against Apotex, which automatically resulted in a 30-month stay on FDA approval of the generic version, because Apotex's version would contain some of the patented hemihydrate. Subsequently, GSK listed with the FDA nine more patents on the product, including patents on new uses, different forms of paroxetine hydrochloride, and GSK's commercial formulation, and pursued four additional infringement suits. The infringement suits resulted in five overlapping 30-months stays, which prohibited the FDA from approving Apotex's application for over 65 months. In only one year of the second stay, GSK received over one billion US dollars in net sales of Paxil.

On 4 March 2003, a federal judge for the United States District Court for the Northern District of Illinois ruled that the GSK patent for paroxetine hydrochloride hemihydrate (4 721 723) was valid but not infringed by Apotex's product. While the judge found it likely that Apotex's product would contain some hemihydrate, he ruled that GSK did not demonstrate that hemihydrate would be present in sufficient amounts to substantiate infringement, and so Apotex's product did not fall within the scope of the claim. GSK proceeded to appeal the ruling.

The last 30-month stay on FDA approval expired on 19 September 2003. Subsequently, Apotex, with protection under the district court ruling, began marketing its lower-cost paroxetine hydrochloride generic in September 2003, five and a half years after filing its application with the FDA. Further litigation took place in 2004 and 2005 on the appeal. In the end, the appeal court reversed the district court decision on all counts: it now held that the Apotex product fell within the scope of GSK's claim but that the claim was invalid.

Source: references (73, 85).

Where there is a linkage between the patent system and the procedures for approving new drugs (for example, in Canada and the United States), the policy issues take a particular form. In the United States, for instance, the Federal Trade Commission catalogued a number of instances where generic entry was delayed by up to five years by successive stays of up to 30 months on the entry of a generic competitor (see Box 4.7). These stays were provided automatically under the United States law if a brand-holder challenged the generic company for infringement, until the changes announced by President Bush reduced this to one stay only.

These linkage arrangements are essentially supplementary to the patent system. But they alter the way in which the patent system operates for pharmaceutical products.¹⁵ Nevertheless, the final decisions on patent validity and infringement cases lie with the courts. This means that any change to tackle evergreening at its roots requires measures to reduce the likelihood of such patents being granted or, if granted, of being upheld in the courts.

While, as previously stated, some forms of incremental innovation might be important in terms of patient benefit, faced with the reality of the TRIPS agreement, developing countries need to consider how their own patent laws may deal with this issue. Patents on minor developments are used, often aggressively, by some patent holders to delay or block generic competition. Small and medium-sized generic firms in developing countries, in particular, are generally unable to sustain costly and lengthy legal challenges, and opt to avoid fields where litigation may arise. The outcome may be the reduction or suppression of competition and, in some cases higher prices for patients.

Countries can adopt legislation and examination guidelines requiring a level of inventiveness that would prevent evergreening patents from being granted. The TRIPS agreement gives freedom to WTO Members to determine the hurdle required for the inventive step. In its 2005 Patent Act, India sought to make the following unpatentable:

(d) the mere discovery of a new form 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.

Explanation.—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of

¹⁵ Consequently, in both Canada and the United States, there remain provisions whereby a brand-name company can trigger a stay of generic entry, irrespective of the merits of the claim of the generic company to be non-infringing (which only the courts can decide). Thus these types of rules provide, in effect, for additional periods of exclusivity, offered by the regulatory authority, rather than the patent system.

isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy (84).

The intention here is to rule out from patentability variations on a known drug, by treating them all as the same substance, except where it can be demonstrated that a drug has superior efficacy. In that sense, the legislation is trying to make a distinction in law between evergreening (where there are no additional therapeutic benefits) and incremental innovations (where there are).

A fundamental practical issue is that at the time of patenting, very little may be known about efficacy or other characteristics, particularly incremental, relative to the parent drug. Moreover, given the variability of the current skills set of patent examiners, it is difficult to rely on consistent and appropriate decisions on efficacy claims, particularly when patent applications routinely precede clinical trials which would, inter alia, determine efficacy and other product characteristics. There is a case for patent authorities to consult health authorities in the examination process, to help determine whether patentability criteria are met.¹⁶

Thus, demarcating the line between incremental innovations that confer real clinical improvements, therapeutic advantages or manufacturing improvements, and those that offer no therapeutic benefits is not an easy task. But it is crucial to avoid patents being used as barriers to legitimate competition.

4.27 Governments should take action to avoid barriers to legitimate competition by considering developing guidelines for patent examiners on how properly to implement patentability criteria and, if appropriate, consider changes to national patent legislation.

¹⁶ As, for example, is done in Brazil.

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CHAPTER 5

FOSTERING INNOVATION IN DEVELOPING COUNTRIES

INTRODUCTION

In the longer term, the development of innovative capacity for health research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies. The determinants of that capacity in developing countries are many. Each country has a unique set of political, economic and social institutions, which means there is no single recipe for advance. Nevertheless it is possible that lessons can be learnt from those countries which have made significant progress in this area.

In recent years, developing countries have demonstrated that they have much to offer the world in promoting health research generally, and in meeting their own health-care priorities. The most scientifically and technologically advanced developing countries (sometimes known as innovative developing countries) are becoming significant contributors to biomedical R&D. They are becoming more integrated into global biomedical research networks, particularly as their advantages in terms of their ability to undertake high quality research at very competitive costs are recognized. This applies in terms of R&D aimed at developed country markets, but also offers the possibility of making progress in addressing the needs of developing countries. As one editorial in 2005 noted:

There are even more reasons for optimism. Firstly, many countries affected by neglected diseases, such as Brazil, Egypt, and India, now have the infrastructure to conduct their own neglected-disease research...they are now reaping the benefits of decades of investment in education, health research infrastructure, and manufacturing capacity. These countries can begin controlling their endemic tropical diseases themselves by developing their own treatments and vaccines with only modest technical or financial assistance from more developed countries (1).

The achievements of developing countries have been very considerable. Cuba developed the first meningitis B vaccine. Recombinant hepatitis B vaccines were developed in Cuba, India and the Republic of Korea. Chinese scientists played a leading role in the discovery of the antimalarial properties of artemisinin and subsequently in the development of derivatives and combinations which led to a joint venture with the pharmaceutical company, Novartis, to develop Coartem, one of the leading artemisinin-based combination therapies (ACTs) for malaria. More examples are provided in Table 5.1 (2-5).

Apart from growing capacity in R&D, some developing countries now have expertise in production, which can have a powerful effect on quantities of products available and on prices. Developing country producers are now responsible for meeting over 60% of the demand arising from UNICEF's vaccine procurement for its Expanded

Programme on Immunization. In India, hepatitis B vaccine was available at US\$ 11 per dose as recently as 1997 from a multinational company, but the entry of an Indian firm has helped reduce the price to US\$ 0.40 per dose.

Table 5.1 Biomedical innovations in developing countries

Sector	Product	Application	Source
Vaccines	Recombinant hepatitis B surface antigen	Hepatitis B	Instituto Nutantan (Brazil)
	Recombinant live oral vaccine	Shigella dysentery	Lanzhou Institute (China)
	Synthetic <i>Haemophilus influenzae</i> type	Pneumonia/meningitis	Heber Biotec (Cuba)
	Purified capsular polysaccharide Vi	Typhoid	Bharat Biotech (India)
Therapeutics	Human recombinant insulin	Diabetes	Biobras/NovoNordisk (Brazil)
	Recombinant streptokinase	Cardiovascular	Tonghua Herbal Link (China)
	Recombinant interferon- α	Viral infections	Heber Biotec (Cuba)
	Recombinant human interferon α -2b	Cancer	Shantha Biotechnics (India)
Diagnostics	Recombinant antigens	Chagas disease	Bio-Manguinhos (FIOCRUZ) (Brazil)
	Enzyme-linked Immuno-absorbent assays	Hepatitis C	Shanghai Huaguan Biochip (China)
	Miniaturized enzyme-linked Immuno-absorbent assay kits	AIDS	Tecnosuma Internacional (Cuba)
	Immunoblot assays using recombinant HIV-1 antigens	HIV-1/HIV-2	J. Mitra (India)

Source: reference (2).

Apart from growing scientific and technological expertise, developing countries have a massive indigenous resource in the form of traditional medicine – both the knowledge accumulated over centuries about the medical properties of natural products, as well as unique systems for diagnosis and treatment, which have a different paradigm from “modern” medicine as it has developed in the western world. This resource is more widely used than modern medicines in most developing countries. Probably more people in developing countries have consulted a traditional medicine practitioner than they have a doctor. The possibilities exist for making better use of traditional medicine, by making traditional remedies more widely available, and by applying this knowledge to accelerate the development of new treatments. The development of artemisinin-based combination therapies is one example of this. Many other drugs in use today are derived from natural products, such as the anti-cancer drug, Taxol, based on the Pacific yew tree, *Taxus brevifolia*.

In this chapter we address the issues that are relevant to the building of capacity in developing countries, in an attempt to answer the following questions.

- What are the common policies that have promoted the development of capacities for health innovation?

- What can be done to increase the contribution of developing countries to addressing their own and global needs for new diagnostics, and preventive and curative treatments?
- How can the potential of traditional medicine be tapped? What policies will promote innovation based on traditional medicine, and also ensure a fair share of the benefits from that innovation?

Box 5.1 Innovation at FIOCRUZ

Fundação Oswaldo Cruz (FIOCRUZ) is a Brazilian public research organization that encompasses the innovation spectrum from basic to applied research. The organization engages in development, design and production, as well as the promotion of higher education and training. FIOCRUZ has 15 institutes including two research hospitals and two manufacturing plants. It has about 800 employees with PhDs in subjects such as public health, biomedicine, health biotechnology and genetic engineering.

FIOCRUZ is the largest producer of vaccines in Brazil and the world's largest producer and exporter of yellow fever vaccine. In 2001, FIOCRUZ became the largest vaccine manufacturing centre in all of Latin America. The plant in Manguinhos can process 180 million doses of vaccines annually, and can produce a range of vaccines for yellow fever, smallpox, tuberculosis, typhoid fever, measles, diphtheria, pertussis and tetanus (DPT), and meningitis for both the Brazilian and international markets.

In 1985, the Brazilian Ministry of Health started the National Programme for Self-Sufficiency in Immunobiologicals with the specific purpose of strengthening the vaccine industry and establishing a process for national production. Since 1986, the Brazilian Government has invested US\$ 150 million on modernization of public laboratories producing serums and vaccines.

Even with FIOCRUZ's strong research capabilities, it was a technology transfer from Smith-Kline Beecham (later GlaxoSmithKline) to the Manguinhos plant which played a significant role, not only in strengthening FIOCRUZ capacity to produce a pneumonia and meningitis vaccine (Hib), but also propelled the organization into becoming a major vaccine manufacturing centre. FIOCRUZ used the acquisition of foreign technologies to revamp product lines, engage in increasingly complex activities, and finally, realize indigenous manufacturing capacity.

FIOCRUZ continues to demonstrate how government institutions and policies can leverage outside expertise to enhance the domestic system of innovation in an effort to address public health needs. In April 2003, FIOCRUZ and GlaxoSmithKline signed another technology transfer agreement. Over five years, FIOCRUZ will produce 100 million doses of mumps, measles and rubella (MMR) vaccine to vaccinate children in Brazil.

Source: references (6, 7).

THE DEVELOPMENT OF INNOVATIVE CAPACITY

The development of innovative capacity requires an array of interlocking policies, including in the spheres of education, intellectual property and technology transfer.

DIMENSIONS

In our analysis we have made use of a typology (see Figure 5.1) which describes and characterizes the innovative capabilities of developing countries at different stages of development.

Figure 5.1 Typology of innovative capability

	Low	High
High Economic strength	I	II
Low	III	IV

Source: reference (8).

In the top right quadrant are developed nations. They have a highly developed indigenous science and technology capacity, and high incomes. In contrast, in the lower left quadrant, there are low income developing countries, including in sub-Saharan Africa, where indigenous capacity as well as economic development is low. In the top left quadrant are countries which, largely as a result of their natural resources, have attained high incomes (such as the oil rich Middle East countries). But they do not have any significant indigenous science and technology capacity. Countries in the lower right quadrant have high indigenous science and technology capacity but relatively low incomes. And several examples have been given above (see also Boxes 5.1 and 5.2).

Not all countries see the development of innovative capacity as a current priority. Rather they consider the focus should be on addressing poverty, poor education, infrastructure and health facilities, and the capacity for generic production. Only relatively few developing countries currently have the capability of developing a genuinely innovative capacity. In other countries, the proper emphasis may be on other areas relevant to the improvement of public health and the development of the capacity to apply locally health technologies developed elsewhere. In this respect, each country needs to decide on its own priorities.

The positions of developing nations in this diagram are not static. Different countries at different times have occupied different positions. For instance, 50 years ago, the Republic of Korea belonged to the lower left quadrant. But it has now moved diagonally upwards to attain the status of an OECD country, through sustained investment in education and scientific and technological development, including biomedical research.

Box 5.2 Biotechnology in Cuba: innovation from within

The primary focus of Cuba's health biotechnology research has been on developing products, rather than basic research. Vaccines have become a speciality. The meningitis B vaccine

developed in the 1980s was the first in the world against this strain of meningitis. The current research portfolio includes a recombinant Dengue vaccine, one for cholera and another as cancer therapy.

Cuban health biotechnology has reached its current level of sophistication because of the vision, leadership and commitment of its political leaders. Government-led integration and administration of the health system and biotechnology sector has promoted the adoption of cost-effective treatment options and encouraged collaboration between basic and clinical researchers. However, government-funded science means that effort is not an academic pursuit and individual interests are subservient to goals being set according to the social priorities rather than the search for profit.

Public research institutions are the core of the sector and they often have commercial branches involved in manufacturing products. Many of them are concentrated in the West Havana Scientific Pole: a cluster of research, higher education and hospital facilities that were linked in the early 1990s so as to encourage closer integration of science, education and health. They are involved in basic research, through development, production, quality control and commercialization of the end-products. Knowledge sharing among and within the research institutions is also an important feature of the Cuban system.

One centre of excellence is the Pedro Kouri Institute of Tropical Medicine which is currently working on a new cholera and AIDS vaccine. Paul Farmer, professor of medical anthropology at Harvard Medical School, noted that "... it is respected throughout Latin America and beyond. With a comparatively tiny budget - less than that, say, of a single large research hospital at Harvard - {it} has conducted important basic science research, helped develop novel vaccines, trained thousands of researchers from Cuba and from around the world, and developed ties with researchers in the United States, too."

Cuba's comprehensive education system and its universities have played a key role in training experts for health biotechnology. But international links have also played a crucial role in building expertise in the sector. Cubans are also involved in collaborations with private sector firms around the world. Through these linkages, Cubans have gained access to markets, capital and commercialization expertise.

Source: adapted from references (9–11).

THE POLICY FRAMEWORK

As noted previously, a key factor in developing policies is to recognize the importance of innovation systems, the interconnectedness of the innovation process, and the need to link together the activities of different players in the public and private sectors. Networks and collaboration, both domestically and internationally, are critical to making progress, as is the proper balance between investments in science and technology.

In many developing countries significant investments in higher education, and science and technology capacity, have not borne the expected fruit because of isolation from the wider domestic economy, and indeed from the global economy. The linkages have been absent and so these investments have not perceptibly contributed to innovation, or to attaining economic and social objectives. This may be the case, for example, in many countries in sub-Saharan Africa or even in Latin America (12).

For instance, the Brazilian Minister of Science and Technology, Eduardo Campos, noted in 2004:

Brazilians get lost between basic research and its transformation into technology, between academic life and the manufacturing system (13).

Frustration and lack of opportunity, rather than just material gain, have been important reasons why talented scientists have emigrated to developed countries. For instance, countries such as China and India have provided large resources of human capital to developed countries, in particular the United States, through students undergoing advanced education and then contributing to R&D and to the application of new technologies in the developed world. To a considerable degree, developed countries have benefited from this migration through the influx of fresh talent from around the globe. But now a considerable number of mature and skilled scientists and technologists are returning to their home countries, as the domestic opportunities for applying their expertise have improved, in particular in the private sector.

This illustrates two points. First, it takes time to develop a set of policies and the necessary critical mass to allow a country to reach a point of take-off in science and technology development. Although interconnectedness is important, it cannot be created overnight. It is necessary to start somewhere, and it is not possible to put all the pieces of the jigsaw together at once. In addition, the right configuration of wider political and economic forces is required, if such policies are to be introduced. Brazil, China, Cuba and India in their very different ways illustrate the importance of these wider policies, but also how very diverse political and economic conditions can be consistent with the development of scientific and technological capacity.

Countries that have developed innovative capacity, or are on the way to doing so, have most often relied on learning from abroad. In the biomedical field, India is the classic example of a country that has begun to develop innovative capacity, but on the basis of a long period where it developed skills in the reverse engineering of products (i.e. developing ways to produce a known product), drawing in particular on the expertise in chemistry developed in the public sector (Box 5.3). In general, through importing technology, countries can develop the skills to understand how technologies work, how to use and adapt them to meet their own circumstances, and also how to make incremental improvements. Normally this is the first stage of technological development that most developing countries have undergone in recent times – an essential learning process.

Box 5.3 Product development in India

A total of 2.4 million disability-adjusted life years (DALYs) are lost each year to leishmaniasis, a disease transmitted by the phlebotomine sandfly, from which 350 million people are at risk. One clinical and often fatal form of leishmaniasis, visceral leishmaniasis, affects 500 000 people annually and occurs predominantly in just five countries: Bangladesh, Brazil, India, Nepal and Sudan. If visceral leishmaniasis is left untreated, an individual has a near 100% mortality rate within one to four months of infection. Current treatment for visceral leishmaniasis requires hospitalization and daily injections with drugs. Further complicated by increasing resistance, the current treatment puts tremendous strains on resource-poor areas. Thus, there is a public health need to produce an affordable, oral treatment that can withstand resistance.

One promising drug is miltefosine. In 1988, researchers reported that miltefosine demonstrated anti-leishmaniasis activity after parenteral use in mice. Miltefosine was originally invented as an anti-cancer agent by ASTA Medica, a German pharmaceutical company, and since 2001, had been developed by Zentaris AG, its biotechnology spin-off, in conjunction with the Max-Planck-Institut in Göttingen and the Universitätsklinik in Göttingen. However, miltefosine was abandoned after Phase II clinical trials, being less effective than another anti-cancer candidate.

In 1995, ASTA Medica/Zentaris signed an agreement with the Special Programme for Research and Training in Tropical Diseases (TDR) for the clinical development of miltefosine as an oral treatment for visceral leishmaniasis. TDR, in close collaboration with ASTA Medica/Zentaris and researchers in India, planned and co-sponsored Phase II and Phase III clinical trials evaluating the safety and efficacy of miltefosine in Indian patients including children aged two years and older, who are especially susceptible to contracting visceral leishmaniasis. The studies reported that the final cure rate of oral miltefosine was approximately 94%.

Phase IV trials are currently being conducted in collaboration with Indian regulatory authorities and the Indian Council for Medical Research. Indian investigators were heavily involved in all clinical development. Thus upon registration of the drug in 2002, the Indian authorities were able to promptly execute Phase IV studies and determine the necessary steps for implementation of miltefosine treatment in national health policy. Another consequence was that participation by the Rajendra Memorial Institute of Medical Science in Patna in the clinical trials resulted in the institute being recognized as a centre of excellence for undertaking clinical studies.

Source: references (14–18).

A recent study reviewed in detail the development of the biotechnology industry in seven developing countries (2). Its conclusions for each country, and the lessons learned, were diverse and are reproduced in Table 5.2. But it identified some common characteristics:

- All the case studies noted the **importance of political will** – what governments do in terms of a range of policies and the overall framework is very important to the outcome. This applies also, as we have seen, in developed countries where the promotion of the "knowledge society" has become a political mantra.
- **Individual leadership is important.** In each of the developing countries studied a few individuals tend to stand out as architects of change as a result of their dynamism and vision. Governments need to identify such people and support them.
- Niche areas, or **areas of specialization, may be important.** Thus in several countries vaccines, particularly recombinant ones, have been an important opportunity because of public health benefits and relatively accessible technology. Other countries may specialize in reverse engineering or incremental innovation, or bioinformatics.
- As noted above, in each country **the importance of close linkages between the different players** was emphasized. For instance Cuba has been

successful, despite very limited resources, by encouraging collaboration and resource sharing between its institutes, and in Brazil the public sector has also successfully collaborated, for example in genome sequencing. But in several countries, poor linkages between universities and industry slowed innovation. One common policy is the promotion of geographical clusters; these have proven successful in both biotechnology and other industries.

- Where the private sector is weak, **measures need to be put in place to stimulate enterprise creation**. In itself this may encompass a number of different policies, such as encouraging spin-offs from universities, fostering appropriate sources of financing (from government or by encouraging private suppliers of capital such as venture funds). Encouraging the return of émigrés is another way to stimulate enterprise creation.
- **Weak intellectual property regimes in the past facilitated technological learning** for all the countries studied. The policy environment which facilitated this (e.g. the absence of product patents in India, or weak intellectual property protection in the first decades of technology development in Egypt and the Republic of Korea) has now changed for most developing countries as a result of the TRIPS agreement. That is one reason why, in countries such as China and India, intellectual property protection and enforcement have become controversial issues.

Table 5.2 Fostering innovation: lessons learned in developing countries

<p><u>Brazil</u></p> <ul style="list-style-type: none"> • Focus on developing a strong science capacity • Promote linkages and exploit existing strengths in disparate fields • Exploit local biodiversity for health • Gain access to key actors <p><u>China</u></p> <ul style="list-style-type: none"> • Provide long-term government support • Attract expatriate professionals • Ensure that biotechnology development goes hand-in-hand with regulation • Leverage large population base <p><u>Cuba</u></p> <ul style="list-style-type: none"> • Ensure long-term governmental vision and policy coherence • Promote domestic integration to spur innovation • Capitalize on international linkages • Tap into national pride 	<p><u>Egypt</u></p> <ul style="list-style-type: none"> • Focus on health needs • Gain access to key actors • Take advantage of international linkages <p><u>India</u></p> <ul style="list-style-type: none"> • Leverage strengths when cultivating linkages • Meet international standards • Use competitive advantage • Pay attention to regulatory environment <p><u>Republic of Korea</u></p> <ul style="list-style-type: none"> • Create a mix of small and large firms • Exploit existing competitive advantages • Go global <p><u>South Africa</u></p> <ul style="list-style-type: none"> • Focus in government policy on public health needs • Exploit both indigenous knowledge and science-based innovations • Develop local R&D infrastructure for self-reliance
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Source: reference (2).

Thus it is perhaps unwise to generalize about the policies that might be necessary for developing countries to generate innovative capacity. Some developing countries have developed such capacity, but by diverse means in very different political, social and economic contexts. There is no blueprint. Moreover, most attention is paid to the relatively few developing countries that have made significant progress. Making such progress is more problematic for those countries where the preconditions for the development of innovative capacity have yet to be put in place. But for these countries too, attaining a minimum level of capacity in the understanding and use of foreign technologies should be a necessity:

... vector and water borne disease, AIDS, inadequate prenatal and maternal/child healthcare and other deficiencies continue to create a tremendous burden in the developing countries. Countries will be unable to correctly identify public health needs and choose cost-effective packages of health services if they lack science and technology capacity (19).

POLICY OPTIONS

There are many possible policies relevant to the development of innovative capacity but we focus here on a few of the most important.

Education

Underpinning all subsequent progress, the starting point for capacity development has to be public investment in education, including at the critical tertiary level. This was pre-eminently the case in East Asian countries. In the Republic of Korea, the illiteracy rate dropped from 78% in 1945 to virtually nothing in 1980. Meanwhile university enrolment grew from under 40 000 in 1953 to 1.15 million in 1994 (52). In other countries, education has expanded rapidly but without the same impact on innovative capacity, partly because the tertiary sector was accorded low priority, not least because of donor country policies favouring, in particular, primary education. In India, while the overall record in improving education (e.g. as measured by illiteracy rates) has been modest by comparison with countries such as the Republic of Korea, there are centres of excellence in the medical sciences, in chemistry and biology, and in technology more generally. The Indian Institutes of Technology are world class organizations. The Commission for Africa recommended in 2004 a massive infusion of donor resources to develop a network of centres of excellence in science and technology, including African institutes of technology and the biosciences (20).

Concerns about the brain drain should be put in context. In some cases such emigration may be positively beneficial in the long term, as reverse flows occur at a later stage as has happened in the Republic of Korea, and is now happening in China and India. Such returnees bring with them skills, technologies and international networks which are a necessity. But this investment in skilled emigration is not always rewarded in this way. Most developing countries continue effectively to subsidize developed countries through trained expatriates. Many developed countries, in particular the United States, have depended in recent years on foreign immigration, including from many developing countries, to fill gaps in their need for scientific and technological manpower and to promote continued economic growth. Their concern

is now that, as the demand for such personnel rises in other countries, they will be unable to sustain and enhance their own capacity.

5.1 A prerequisite for developing innovative capacity is investment in the human resources and the knowledge base, especially the development of tertiary education. Governments must make this investment, and donors should support them.

Promoting networks

Technological learning occurs in many ways. It is about absorbing knowledge from elsewhere in ways that subsequently allow the learner to make productive use of that knowledge.

Domestic and international networks are critical in the sharing of information and new knowledge, and the building of capacity in developing countries. These might include North–South partnerships such as those promoted by the medical research councils in the developed world (e.g. the Swiss Tropical Institute or the Wellcome Trust promote several collaborative research networks in countries such as the Gambia, Thailand, Uganda and the United Republic of Tanzania). Many other specific examples exist – for example, the collaboration between the Universities of Havana and Ottawa in developing and patenting the first human vaccine with a synthetic antigen (for *Haemophilus influenzae* type b). Collaboration between the International AIDS Vaccine Initiative, the Indian Council of Medical Research and a United States biotechnology firm (Therion Biologics), has resulted in the transfer of significant technology and know-how from the United States company to India. Informal networks, for example those brought back by returning émigrés may be extremely important.

South–South networks have often been neglected in the past but may become especially useful now that world class expertise exists in some developing countries. For instance, the Technology Network for HIV/AIDS, announced during the 2004 Bangkok meeting on HIV/AIDS, includes Brazil, China, Nigeria, the Russian Federation, Thailand and Ukraine (and will possibly include India and South Africa in the near future). The Network is intending to support research and South–South technology transfer on antiretroviral drugs and drug formulations, and the development of an HIV vaccine. The Developing Country Vaccine Manufacturers' Association was established in 2000 with the aim of providing a consistent and sustainable supply of high quality vaccines at an affordable price to developing countries. Public–private partnerships too have helped to establish partnerships between different players in developing and developed countries.

5.2 The formation of effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal, is an important element in building innovative capacity. Developed and developing countries should seek to intensify collaborations which will help build capacity in developing countries.

The role of the public sector

Intellectual property rights, in particular patents, may impinge upon the transfer of technology in a number of ways. As we have noted, weak intellectual property rights may facilitate learning in the early stages of development and some countries have used this, as in the case of India, to generate capacities in pharmaceutical R&D and then in biotechnology.

Now, all of the developing countries with significant R&D capacity have TRIPS-consistent frameworks. In these circumstances, technology needs to be used or acquired through licensing, or patents have to be invented around. Participants in the public and private sectors have to understand what this means for acquiring technologies needed from others, and what it means for the technologies they may produce. The skills and knowledge with respect to intellectual property that have developed over time within bodies such as the United States National Institutes of Health are lacking in those countries.

Some of the most important impediments to the effective management of the growing body of developing country knowledge, particularly in the public sector, are the limited institutional resources in the form of skilled staff that can deal with intellectual property issues. There are diverse activities that the management of intellectual property entails, including negotiation of agreements on material transfer, confidentiality, and product development, not to mention expertise in patenting. As noted in earlier chapters, issues that are currently matters of debate in developed countries (e.g. the patenting of research tools, the use of patenting by the public sector or the cost of litigation) will also become increasingly important in developing countries. Thus the recommendations made in earlier chapters are also relevant in this context.

But the main point that needs to be emphasized here is the need to build the required institutional framework (e.g. patent office, administrative and court procedures) and the requisite skill set.

...a research organization's IP management team needs to include or draw on individuals with skills in business strategy or business development, marketing, law, science and medicine, production, and finance. The utilization of these various skill sets is standard operating procedure in the private sector, while many public sector organizations do not take advantage of these resources thereby hobbling their efforts (21).

Assistance that might be offered by developed countries could include:

...training in IP management, technical assistance to developing country public sector research and development organizations, dissemination of relevant information, and conduct of policy relevant research (21).

Technical assistance provided from outside needs to be neutral in the way it provides advice on how developing countries can use the intellectual property system to develop their innovative capacity. Not all developing countries find the advice they

receive on this issue from established providers of technical assistance is well adapted to their particular needs (22).

5.3 WHO, WIPO and other concerned organizations should work together to strengthen education and training on the management of intellectual property in the biomedical field, fully taking into account the needs of recipient countries and their public health policies.

Technology transfer in production

A factor in technology transfer in the area of production is the relative lack of experience and skill of developing country enterprises to conclude adequate legal arrangements to acquire the necessary technology. Other issues include the limited capacity of domestic firms to operate further up the value chain, and a lack of capacity to adapt acquired technology to local needs. Firms that own production technologies may be reluctant to transfer them, as they prefer to concentrate production in a few sites with large economies of scale, or are not interested in helping the emergence of future competitors. In fact, the transfer of technology to developing countries for manufacturing medicines and, particularly, active ingredients, is scant or nonexistent.

As for production capacity, it is important to realize that manufacturing pharmaceutical products (which include active ingredients, formulations or finished dosage forms and biologics) entails many processes. Some general production categories can be listed as: chemical synthesis; fermentation; extraction; and formulation and packaging. Some developing countries have established a reliable manufacturing capacity for the formulation of medicines. Few developing countries have, however, the capacity to produce the active ingredients required in pharmaceuticals, in part because economies of scale are more important for active ingredients than for formulations. For instance, Brazil and Thailand rely on imported active ingredients, and even producers such as India or China need to import those they do not produce. There may be special challenges, particularly for smaller, less scientifically advanced countries, in developing local production (23). These might include the following.

- Making local production viable requires a clean environment, water supply, a reliable power supply and the availability of skilled technicians.
- For many countries, technical expertise, raw materials, and production and laboratory equipment need to be imported, so that the overall costs and security of supply need to be weighed against the price, availability and security of imports.

Developing a local manufacturing capacity nevertheless has many advantages, such as employment of local technicians and professionals, savings of foreign currency, ability to respond to health emergencies, and better knowledge of local conditions for storage and distribution. Moreover many countries, particularly the more scientifically advanced, have positive advantages as low-cost producers of high quality products. For example, India has more manufacturing plants meeting the

standards of the United States Food and Drug Administration than any other country outside the United States. Box 5.4 provides a number of reasons why.

These cost advantages are another reason why countries such as India are attractive to foreign companies as a source of active ingredients, and a location for manufacture directly or under licence. Voluntary licensing offers one possible route for extending the availability and affordability of drugs particularly needed in developing countries.

One approach to facilitating technology transfer – provided that technology owners are willing to part with it – is to enhance the capacity of developing countries to receive and use these complex technologies. Several initiatives have been considered for technology transfer. For example, the technology transfer model for the Meningitis Vaccine Project and the Program for Appropriate Technology in Health has targeted a meningococcal conjugate vaccine for Africa (24). The approach followed was technology transfer, from an established manufacturer in an industrialized country, to a manufacturer in a developing country. We have previously noted such examples in Kenya and South Africa.

The TRIPS agreement provides that developed countries shall provide incentives to their enterprises and institutions to promote and encourage the transfer of technology to least developed countries (article 66.2). This provision was re-emphasized in the Doha Declaration. Although developed countries regularly submit reports to the WTO on these measures, the practical impact of this part of the TRIPS agreement is negligible.

Box 5.4 Cost advantages of Indian firms

Indian firms have lower costs – estimated to be one eighth (in R&D) to one fifth (in manufacturing) compared to firms in developed countries.

The following factors are the basis for this cost advantage.

- **Fixed asset cost.** The cost of building a new manufacturing facility complying with international regulatory norms is about one quarter of the cost of setting up a similar facility in Europe or the United States. Civil construction is US\$ 90 - US\$ 130 per square metre versus US\$ 800 in the United States. Material costs (e.g. of reactors, vessels and other equipment) may also be lower.
- **Cheaper labour.** The cost of an Indian-based laboratory analyst or chemist is one fifth to one eighth of the cost in the United States. Higher level Indian scientists are well trained yet earn about a third of their counterparts in the developed world. Finally, plant employees cost US\$ 120 - US\$ 150 per month.
- **Chemistry or process expertise and development costs.** More than three decades of reverse engineering "on-patent" drugs (process engineering) has made Indian companies extremely proficient in speeding generic drug development, therefore more productive per unit of cost. Lower development costs result in lower regulatory filing costs, and this, combined with the increasing admissibility of Indian bio-equivalence studies to the United States Food and Drug Administration puts India at an advantage. On the manufacturing side, continuous process improvement has also resulted in a highly efficient cost structure for India's bulk production of active ingredients.

- ***Clinical study costs.*** A large population of patients not on other treatments facilitates rapid trial recruitment into large clinical studies. Cost per patient enrolled is approximately one tenth of the cost in the United States. However, neither Indian companies nor international companies have leveraged this cost advantage in any material sense – Indian companies because of nascent drug discovery research, and multinational pharmaceutical companies because of concerns over intellectual property confidentiality.

Source: reference (25).

5.4 Developed countries, and pharmaceutical companies (including generic producers), should take measures to promote the transfer of technology and local production of pharmaceuticals in developing countries, wherever this makes economic sense and promotes the availability, accessibility, affordability and security of supply of needed products.

5.5 Developed countries should comply with their obligations under article 66.2 of the TRIPS Agreement and paragraph 7 of the Doha Declaration.

REGULATION AND CLINICAL TRIALS

As noted in Chapter 3, the regulation of the safety, efficacy and quality of new medical products in developed countries has become inextricably linked to innovation, in large part because regulators determine the extent of clinical trials necessary for products to gain marketing authorization, the cost of which is a significant part of overall product development. The speed of the regulatory process is also a determining factor in how quickly new products (including generic versions of original products) reach people who need them.

Regulation

There is still a long way to go in improving developing country capacity in regulation. Evidence from WHO suggests that only one third of WHO Member States have adequate regulatory systems in place, with the remainder of the regulatory environments varying from rudimentary to adequate in places (26). Over two thirds of the world's population live in countries with marginal or inadequate regimes for assuring drug quality, safety and efficacy. A recent WHO survey of the quality of antimalarials in seven African countries revealed that between 20% and 90% of the products failed quality testing. The medicines were a mixture of locally produced and imported products (27). Use of poor quality starting materials from unreliable sources is an ongoing problem in many countries (28). The prevalence of poor quality or even harmful medicines is a waste of resources that undermines already overburdened health-care systems, puts public safety at risk and increases the likelihood of drug resistance.

According to surveys conducted by the Centre for Medicines Research International, regulatory delays and poor communication between the industry and regulatory authority assessors (evaluators) is a major cause of concern in developing countries.

Common problems associated with delays in registration may be caused by both industry and the regulatory authority – such problems in any case need to be assessed jointly (29).

The ability to regulate medicines effectively is determined by a number of factors, which include the state of economic development, infrastructure availability and the prevailing health-care system of a country. At root, the problem lies in a lack of human and financial resources devoted to regulation. Among other things, this is often the result of inadequate political commitment, exacerbated by the interest groups that benefit from loose regulation. Hence, although the policy options to rectify this situation are relatively straightforward in principle, implementation may well be much more difficult. Countries need resources, both human and financial, but political leadership is also very important. India has moved this year to set up a new regulatory structure, recognizing the importance of getting this right both for the benefit of its own people, and to improve its attractiveness as a base for clinical research and innovation. Even if more financial resources are allocated to ensuring appropriate regulatory development within a region, the availability and expertise of human resources will remain a challenge over the medium term.

WHO has played a part over a long time in bringing together regulators through the International Conference of Drug Regulatory Authorities. This provides an important platform to develop international consensus, and to assist WHO and drug regulatory authorities in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines. To seek to ensure that good quality pharmaceuticals are available, WHO sets norms and standards, develops guidelines and advises Member States on issues related to quality assurance of medicines in national and international markets. WHO assists countries in building national regulatory capacity through networking, training and information sharing.

There are other WHO initiatives, such as the Developing Countries' Vaccine Regulators Network which involves nine national regulatory authorities across five continents. The network aims to promote and support the strengthening of the regulatory capacity of national authorities of participating and other developing countries for evaluation of clinical trial proposals (including pre-clinical data and product development processes) and clinical trial data through expertise and exchange of relevant information.

Various other international and regional initiatives exist in which developing country regulators participate. The International Conference on Harmonisation (ICH),¹⁷ whose core members are the research-based industry and developed country regulators, has made significant progress in harmonizing the information requirements required in the developed world by regulators, thus mitigating some of the problems associated with differing requirements of regulatory authorities in the developed world. However, the ICH has hitherto been less successful in involving developing countries, in particular because harmonization implies a reasonable parity in existing capacities for regulation. Whilst patients in the developing world should expect to receive medicines and vaccines of the same quality, safety and efficacy as those in

¹⁷ The full name is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

developed countries, the applicability and relevance of each and every ICH requirement to the needs of the developing world needs further examination.

Cooperative action at a regional level has proved more effective in some cases in strengthening regulatory capacity at the national level. Regional associations of regulators include the Association of South-East Asian Nations (ASEAN), the Andean Community, the Gulf Cooperation Council, Mercosur and the Southern African Development Community. These offer ways to pool information on drugs in circulation, to share facilities (e.g. testing laboratories), to compare experience of side-effects of particular drugs in the post-marketing phase, to identify substandard and counterfeit drugs, and so on. Practical and pragmatic steps to share information and facilities in this way may be the most effective means to raise the quality of products marketed in developing countries.

Some success has been attained in this regard. For example, there are several initiatives from the Southern African Development Community, where 13 regulatory agencies have harmonized specific technical requirements. Changes in the practices and procedures in ASEAN member states are also proceeding towards standardizing certain regulatory requirements (30). This could benefit both regulators and industry by reducing administrative burdens.

Given the reality of inadequate regulatory capacity in many developing countries, many countries rely on the approvals (or rejections) given by developed country regulatory authorities. As noted previously, this would carry risks because the balance between risks and benefits in developing countries may be different from those in developed countries, and because specific factors in developing countries may mean that the assessment of safety or efficacy should be different. Nevertheless, the assessments of developed countries are better than no guidance at all.

The European Agency for the Evaluation of Medicinal Products (EMA) and national regulatory authorities in the European Union have been asked to support – in coordination with WHO – capacity building for national regulatory authorities of developing countries through partnerships, scientific or technical assistance, or financing. The stated goal is to focus on establishing regional centres of regulatory expertise. In announcing these changes in policy, the European Commission noted that regulatory procedures should not be used as trade obstacles which could make pharmaceutical products more expensive, the hope being to facilitate rapid access to medicinal products which meet developing countries' public health needs (31).

Under this regime, the EMA proposes to provide a scientific opinion for the evaluation of medicines to be marketed exclusively outside the Community (32). This could provide a useful basis for decisions by developing country authorities, but it would still require local expertise to assess whether the EMA's opinion made sense in local conditions. The risk-benefit assessment has to be a national decision.

A WHO prequalification project was set up in 2001 to give United Nations procurement agencies, such as UNICEF, the choice of a range of good quality products that meet the standards laid down by the project. It does not intend to replace national regulatory authorities or national authorization systems for importing medicines but draws on the expertise of some of the best national regulatory

authorities to provide a list of prequalified products that comply with unified international standards. Over time, the growing list of products that have been found to meet these standards have proved useful for anyone purchasing bulk medicines, including countries themselves and other organizations. For instance, the Global Fund to Fight AIDS, Tuberculosis and Malaria disburses money for medicines that have been prequalified by the WHO process, as well as those meeting other regulatory standards. Again this has proved useful to developing countries without the means themselves to conduct similar assessments. But the responsibility for decision-making, and the processes required for that decision-making, must remain a matter of national sovereignty.

5.6 Developing countries need to assign a higher priority to improving the regulation of medical products. Developed countries, and their regulatory institutions, should provide greater financial and technical assistance to help attain the minimum set of regulatory standards needed to ensure that good quality products are available for use. This assistance should also support infrastructure developments within a country, to ensure that good manufacturing practice and supply chain management standards are implemented and sustained.

5.7 The process of the International Conference on Harmonisation currently lacks immediate relevance to the needs of many developing countries, but those countries should maintain their participation in the process. In the meantime, developing country governments and regulatory institutions should give support to regional initiatives, tailored to the current capacities of their member countries, which offer more scope for lifting standards over time, exploiting comparative advantages, avoiding duplication, sharing information and facilities, and promoting appropriate standardization without erecting barriers to competition.

Clinical trials

Clinical trials are the final stage of getting a medical product to consumers. As more products are developed to meet the specific needs of developing countries, the capacity for developing countries to be able to mount clinical trials to a high standard is extremely important, as medical products have to be tested in the environment in which they will be used. Many exogenous factors may differ between developed and developing countries – these may include genetic make-up, nutritional status, prevalence of other diseases (e.g. HIV/AIDS, malaria), interactions with traditional remedies and a number of other social, cultural and economic factors. These may also differ among developing countries as well. Thus innovation directed at developing countries requires an adequate capacity to deal with these differences.

The trend to increasing clinical research in developing countries is, in fact, quite dramatic. According to the United States Food and Drug Administration (FDA), the number of foreign clinical investigators conducting drug research outside the United States under FDA new drug applications increased 16-fold in the last decade, from 271 in 1990 to 4 458 in 1999. Inspections by the FDA of foreign clinical investigators conducting drug research outside the United States nearly tripled, from just 22 in 1990 to 64 in 1999. The number of countries in which drug research is

conducted increased from 28 in 1990 to 79 over the same time period. The reasons for this trend include: accessibility of human subjects; ease of recruitment; population without previous access to treatment; low cost; and ease of study approval (29). Much of this clinical research may relate to cost advantages, but a proportion relates to the need to test products in the environment in which they are most likely to be used. The expansion is driven in part by the increasing use of contract research organizations by pharmaceutical companies looking for the most cost-effective ways of meeting clinical trial requirements. But it also illustrates the extent to which many developing countries already have the capacity to mount clinical trials to international standards.

This capacity exists primarily in Asia and Latin America. Our study noted that:

The present capacity for conducting clinical trials is, however, insufficient or even nonexistent in virtually all countries in sub-Saharan Africa. Strengthening the R&D capacity in developing countries by investing in African owned health research centres capable of conducting clinical trials has thus been identified as an international priority to improve public health and, indirectly, development. Efforts should be focused on the establishment and strengthening of locally controlled and managed research centres able to pursue their own priorities and R&D agenda. The existence of internationally recognized institutes will also strengthen the position of African R&D priorities in international initiatives, and increases the ability to influence cash flows. Eventually, a strong and equal position in international partnerships will offer the best opportunities for a focus on local needs and interests.

In this case, the aim for equal partnership requires the ability to provide balanced input in all aspects of the joint action, including scientific input at international level and the ability to attract co-funding. At present, far too few research centres in Africa are in this position, precluding true equal partnership (29).

Scientists in developing countries should be involved in the development of the research protocol from the beginning to ensure that local health needs of developing countries are taken account of. Otherwise, the reality will be that physicians and researchers in developing countries who take part in conducting clinical trials are placed in the role of data collectors for trials designed only to fit the needs of people in the developed world. Measures and policies should be implemented to ensure that these physicians and researchers can design and initiate clinical trials that address health problems in their own countries, rather than fulfil research protocols designed elsewhere. This would represent a real measure of capacity in this area.

Although patients with diseases may be readily available, patient recruitment in some areas remains a key challenge. Significant differences occur in how informed consent is obtained in the rural areas where the level of literacy is low. Some other problems encountered in recruitment include: inadequate transport; differing cultural backgrounds and taboos; fear of adverse events; and uncertainty about confidentiality and the lack of a network of medical services.

Companies surveyed in our study saw existing shortcomings as a function of regulatory limitations in developing countries. The majority of participants felt that

although developing countries offer many advantages as readily available sites of clinical research, the process of gaining approval to conduct clinical research is cumbersome, time-consuming and costly. In one instance it took so long to enrol patients that by the time the trial started, trials in the rest of the world had been completed. Many of the problems cited related to the lack of regulatory expertise and capacity (29).

Because of the urgency of strengthening clinical trials capacity, a new initiative, the European and Developing Countries Clinical Trials Partnership (EDCTP) was launched in 2001. The mission of the EDCTP is to accelerate the development of new clinical interventions to fight HIV/AIDS, malaria and tuberculosis in developing countries, particularly sub-Saharan Africa, and to improve generally the quality of research in relation to these diseases. The programme focuses on Phase II and Phase III trials best conducted in developing countries where these diseases are endemic and taking their worst toll. The activities of the EDCTP include:

- stepping up cooperation and networking of European national programme with a view to accelerating clinical trials of new and improved existing products, in particular drugs and vaccines, in developing countries;
- ensuring that research effectively addresses the needs and priorities of developing countries;
- helping to develop and strengthen capacities in developing countries, including the promotion of technology transfer;
- encouraging the participation of the private sector;
- mobilizing additional funds to fight the diseases that particularly affect developing countries (51).

A particularly difficult issue is ensuring proper ethical standards in clinical trials in developing countries. Concerns have been voiced that vulnerable populations in developing countries might be exploited for benefits that will accrue to people elsewhere.

Key ethical issues include:

- consent
- standards of care
- ethical review of research
- what happens once research is over?

These issues are by no means unique to developing countries, but are exacerbated by the prevailing economic and social conditions, and standards of health-care provision. Consent should be based on the principle of informing and protecting, should fit the local context, should involve simple consent forms, and ensure the trust of participants. In many cases trial participants may experience standards of care in trials not otherwise available locally, or to their neighbours. Treatment with a placebo may raise difficult issues (e.g. where a disease is endemic). Ethical review committees, which are standard in developed countries, may be difficult to constitute in developing countries, for lack of suitably skilled or experienced people. If foreigners dominate the task of ethics oversight, they may unwittingly allow transgression of local mores. After a trial is over, further difficult issues arise

concerning whether a treatment that has proved effective should be withdrawn from participants because it cannot be provided by the local health system (33).

5.8 WHO has an important role to play, in collaboration with interested parties, in helping to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards.

5.9 Apart from the European and Developing Countries Clinical Trial Partnership, donors together with medical research councils, foundations and nongovernmental organizations, need to offer more help to developing countries in strengthening clinical trials and regulatory infrastructure.

TRADITIONAL MEDICINE

The term traditional medicine is used here to cover three or even four different components to which the term is usually loosely applied. First, traditional medicine is a system of treatment, sometimes with sophisticated methods of assessing health and diagnosing ill-health. These systems normally take a holistic approach:

...that of viewing man in his totality within a wide ecological spectrum, and of emphasizing the view that ill health or disease is brought about by an imbalance, or disequilibrium, of man in his total ecological system and not only by the causative agent and pathogenic evolution (34).

Systems such as the Indian *Ayurvedic* or traditional Chinese medicine have a coherent theoretical foundation, including frameworks for classifying diseases and the medicinal plants used to treat them, and systems for classifying ill-health. By contrast, modern medicine is more reductionist and direct. While many traditional remedies rely on mixtures of natural ingredients with complex compositions to cure particular conditions, modern medicine generally seeks one active ingredient to address one condition (although, as we have seen, combinations of drugs are now increasingly common e.g. in malaria, HIV/AIDS and TB).

Second, and closely related, traditional medicine is a source of knowledge about natural remedies that are effective, and of remedies based on natural products. Thus every Indian mother knows that turmeric has wound healing properties, and this was in fact recorded in ancient times in a Sanskrit text. Third, as noted several times in this report, natural products are a rich source for discovering and isolating new modern medicines. Traditional medical knowledge can provide a shortcut, in that the product may already have a known impact – the issue is then how the active ingredients might be isolated or synthesized artificially, or how combinations of active ingredients that are effective might be reproduced on a commercial scale (see Box 5.5). Fourth, traditional medical practitioners are an important part of the health-care system in many developing countries.

In this section, the first key issue to explore is how all these components of traditional medicine might best contribute to the process of discovery, development and delivery. Second, there is a need to consider what policies, including those relating to intellectual property rights, might promote innovation and access to products. An

important ethical question is how any commercial benefits that might derive from the use of traditional knowledge should be shared with traditional knowledge holders.

Box 5.5 Natural products: building on a growing trend

Many of our current medicines are based on natural products. Approaches to improve and accelerate biomedical innovation involving natural products are expected to take place mainly during the target elucidation and lead structure discovery stages. Therefore, researchers have correctly emphasized the need for new concepts to generate large compound collections with improved structural diversity.

Natural products will also remain valuable for pharmaceutical companies because of their wide structural diversity and excellent adaptation to biologically active structures. Natural product research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs by the pharmaceutical industry. While microbial products have been the mainstay of industrial natural products discovery, in recent years phytochemistry has again become a field of active interest.

The process of finding artemisinin is particularly interesting in that the work benefited from the medical reference, *Handbook of prescriptions for emergencies* written by Hong Ge in the 3rd century, which stated that the plant was used to treat diseases with alternative fever and chill. The pharmacological evaluation in October 1971 showed positive results. The Chinese researchers isolated and purified the effective compound in 1972 and named it artemisinin.

Another important resource within the developing world is the Rio de Janeiro botanical garden. Its DNA bank maintains genetic information representing Brazilian flora and focuses on the conservation of DNA from plant species of the ecosystems that shape the Atlantic rainforest. The collection is intended to be a source of genetic material for research on phylogeny, phylo-geography and genetic structure, and it will facilitate research on genes that are responsible for biological diversity, as well as identification of genes involved in drug biosynthesis and plant resistance to pathogens.

Multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology is being explored in order to exploit the vast diversity of chemical structures and biological activities of natural products. The study of structural chemical databases, in conjunction with databases on target genes and proteins, will facilitate the creation of new chemical entities through computational molecular modelling for pharmacological evaluation.

Source: references (35-41).

DISCOVERY, DEVELOPMENT AND DELIVERY

There are important new initiatives to use traditional medical knowledge to improve public health. One is an effort to introduce scientifically and clinically validated herbal-based therapeutics in the market after rigorously ascertaining their safety and efficacy. Countries such as China and India are investing heavily in this. The concept is of moving from the traditional innovative path of "molecule to mice to men" to a path that goes from "men to mice to man". In other words, the idea is to move to a path that takes advantage of known therapeutic methods in traditional medicine to accelerate the process of discovery. Reverse pharmacology is a rediscovered paradigm which places more emphasis on clinical research of natural products. In

particular, reverse pharmacology takes the leads or observations of clinical drug or herb experience and extends them to exploratory studies and then to relevant scientific experiments – in vitro and in vivo.

There are three major knowledge domains of reverse pharmacology:

- robust documentation of biodynamic effects of drugs and herbs;
- exploratory studies involving standardization of plants and natural products, and early dose-searching studies, with relevant safety and activity end-points;
- an experimental domain characterized by in vitro and in vivo models as well as safety pharmacology to study the targets, hypothesized from the earlier studies, dose-finding for safety and efficacy, and wide clinical studies on the natural drug, with post-marketing surveillance.

In the past, pharmacology was enriched when reverse pharmacology was applied to certain poisons. Table 5.3 illustrates some examples of this. A number of other plants indigenous to India and isolated there or in Europe or North America have also been taken up for clinical and experimental studies, based on their reported therapeutic benefits. Table 5.4 lists some of these plants and indicates the new fields in drug research that the findings opened up.

Table 5.3 Reverse pharmacology relating to poisons

Medicinal plant	Experiential lead	Natural product
<i>Curare tomentosum</i>	Muscular paralysis	Tubocurarine
<i>Physostigma venenosum</i>	Ordeal poisoning	Physostigmine
<i>Claviceps purpurea</i>	Ergot poisoning	Ergotamine
<i>Strychnos nux-vomica</i>	Convulsive poisoning	Strychnine
<i>Atropa belladonna</i>	Antispasmodic	Atropine
<i>Papaver somniferum</i>	Opium poisoning	Morphine

Source: reference (42).

There is a renewed interest in this approach. China and India, in particular, are investing heavily in R&D based on these alternative paths to new drug discovery following this methodology. In India, for example, a network of over 30 research laboratories, industries, universities and institutes of traditional medicine are working on 20 diseases. Some of the breakthroughs (for example, a therapeutic for psoriasis, where Phase II clinical trials are in progress) appear to be very promising.

Table 5.4 Medicinal Plants as Leads

Medicinal Plant	Active principle	Mechanisms	New fields
<i>Rauwolfia serpentina</i>	Reserpine	Amine depletion	Hypertension, Parkinson's, depression
<i>Psoralea corylifolia</i>	Psoralens	Thymine dimmers	Vitiligo, psoriasis, leprosy
<i>Commiphora mukul</i>	Guggulsterone	BAR & FX receptors	Hyperlipidaemia, arthritis, tuberculosis

<i>Curcuma longa</i>	Curcumin	Antioxidant	Cancer, hepatitis, arthritis, diabetes
<i>Acacia catechu</i>	Epicatechins	Antioxidants	Sore throat, hepatitis, diabetes
<i>Piper longum</i>	Piperine	Bioenhancer	Tuberculosis, asthma, malaria
<i>Berberis aristata</i>	Berberine	Antimicrobial	Eye infections, diarrhoea, AIDS
<i>Azadirachta indica</i>	Azadirachtin	Antifeedant	Pesticides, skin infections, cancer

Source: reference (42).

Plants used in traditional medicine serve as a source of inspiration and as models for the synthesis of new drugs with better therapeutic, chemical or physical properties than the original compounds. Commercially, these plant-derived medicines are worth about US\$ 14 billion a year in the United States and US\$ 40 billion worldwide. Additionally, the United States National Cancer Institute regularly earmarks large appropriations to screen 50 000 natural substances for activity against cancer cell lines and the AIDS virus. China, Germany, India and Japan, among others, are also screening wild species for new drugs (43).

There is much greater interest of late in botanical medicine for a number of reasons. Problems with drug resistant microorganisms, side-effects of modern drugs, and emerging diseases where no medicines are available, have stimulated renewed interest in plants as a potential source of new medicines. As well, pharmaceutical scientists are experiencing difficulty in identifying new lead structures, templates and scaffolds in the finite world of chemical diversity.

One third of the global population still lacks regular access to essential modern medicines and this figure rises to more than half the population in certain parts of Africa and Asia. But in many developing countries, especially in rural settings, 80% of people visit traditional health practitioners and use traditional medicines (44). Thus, there is a clear need to explore ways in which traditional medicine practitioners can be used more effectively to facilitate delivery of both western biomedical innovations and traditional therapies.

Examples of the positive impact that they can provide already exist. For example, extensive experimentation and evaluation of the role traditional healers can play in addressing HIV/AIDS in Africa has been conducted over the past 20 years. While findings are far from conclusive or generalizable, there are positive lessons.

- Given the important position healers often play in the community, they can operate as powerful educators.
- Their knowledge of local beliefs and customs enables them to explain illness in ways that people understand.
- Experiments with the integration of western doctors and traditional healers, indicates the possibility to have many people referred to a physician in situations where illness would have previously gone untreated (45).

Very few systems of traditional medicine have much documentation in place. The flow of knowledge about the "little traditions" is mainly by word of mouth. In contrast, the "great traditions", such as *Ayurveda* and traditional Chinese medicine are well documented (46). Nonetheless, systematic documentation, interpretation and harmonization of concepts and practices remain major challenges in most systems of traditional medicine.

POLICIES

In respect of traditional knowledge generally, and traditional medical knowledge in particular, there is an ongoing debate about how intellectual property rights might be responsible for unfairly depriving communities of the benefits of their knowledge (e.g. when a company uses such knowledge to create commercial value, none of which flows back to the community from which the knowledge originated). Such practices are sometimes called biopiracy or misappropriation. Nevertheless it is also argued that patenting is essential to the commercialization of inventions based on legitimately accessed traditional knowledge, or associated genetic resources, and measures to restrict it would be harmful to the effort to develop new products that benefit public health.

Intimately linked to this debate is the question of how benefits should be shared between traditional knowledge holders (whether individuals or communities) and those who make use of their knowledge. The Convention on Biological Diversity requires that recipients of genetic resources covered by the Convention share "in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources...upon mutually agreed terms."(47) It also provides that this should be on the basis of prior informed consent with those involved.

Much of this debate raises issues far beyond our terms of reference and there is an established dialogue in WTO and WIPO on how progress might be made in this area. Our own perspective is rather narrower – what measures might (a) seek to promote innovation and (b) promote access to new products derived from traditional medical knowledge.

A few countries have recently introduced *sui generis* intellectual property protection for traditional knowledge which may suit their particular conditions. The purpose of intellectual property protection should be to stimulate new invention and innovation. However, in practice, regimes being considered for traditional knowledge principally seek to address the question of equitable benefit sharing, not that of stimulating innovation derived from traditional knowledge. The risk is that introducing a form of intellectual property protection for traditional knowledge may actually have the effect of restricting access by others, thereby inhibiting downstream innovation. However, the issues raised are quite complex and have been discussed extensively elsewhere (48,49).

There is a need to guard against misappropriation of genetic resources and associated knowledge, to ensure that the commercial benefits derived from traditional knowledge are fairly shared with the communities that discovered those resources and their possible medical uses, and to promote the use of such knowledge for the benefit of

public health (see Box 5.6). New measures may be required for equity reasons, and also to provide incentives for the transfer of traditional knowledge to those who can exploit it.

Box 5.6 Samoa and University of California benefit-sharing agreement on Prostratin

The University of California, Berkeley, signed an agreement with the Samoan Government to isolate from an indigenous tree the gene for a promising anti-AIDS drug and to share any royalties from the sale of a gene-derived drug with the people of Samoa.

The agreement supports Samoa's assertion of national sovereignty over the gene sequence of Prostratin, a drug extracted from the bark of the mamala tree (*Homalanthus nutans*). The drug is currently being studied by scientists around the world because of its potential to force the AIDS virus out of hibernation in the body's immune cells and into the line of fire of anti-AIDS drugs now in use.

"Prostratin is Samoa's gift to the world," explained Samoan Minister of Trade Joseph Keil. "We are pleased to accept the University of California as a full partner in the effort to isolate the Prostratin genes."

Despite Prostratin's promise as an anti-AIDS drug, its supply is limited by the fact that the drug has to be extracted from the bark and stemwood of the mamala tree. Researchers in the laboratory of Jay Keasling, professor of chemical engineering at Berkeley, plan to clone the genes from the tree that naturally produces Prostratin and insert them into bacteria to make microbial factories for the drug. A similar technology is currently being explored to produce the antimalarial drug artemisinin.

The agreement gives Samoa and the University of California Berkeley equal shares in any commercial proceeds from the genes. Samoa's 50% share will be allocated to the government, to villages, and to the families of healers who first taught ethnobotanist Dr Paul Alan Cox how to use the plant. The agreement also states that University of California Berkeley and Samoa will negotiate the distribution of the drug in developing nations at a minimal profit if Keasling is successful.

"This may be the first time that indigenous people have extended their national sovereignty over a gene sequence," said Cox, director of the Institute for Ethnobotany at the National Tropical Botanical Garden in Hawaii. "It is appropriate, since the discovery of the anti-viral properties of Prostratin was based on traditional Samoan plant medicine."

The United States National Cancer Institute, which patented Prostratin's use as an anti-HIV drug, requires any commercial developer of Prostratin to first negotiate an equitable benefit-sharing agreement with Samoa.

Source: reference (50).

One way to ensure that traditional knowledge is not unfairly exploited, and that the knowledge is also made freely available, is the creation of databases of traditional knowledge that is already in the public domain, but not readily accessible (e.g. it is in an ancient Sanskrit text). By this means, cases cannot occur where traditional knowledge is wrongly patented because patent examiners are unaware that the patent application is based on knowledge that is already, in principle, public, and therefore not a new invention. Where traditional knowledge is not already written down, or is

closely guarded by a community, it is important that such information is not included in databases without the informed consent of the community involved.

In order to address this issue, documentation and harmonization exercises have been undertaken in recent years. Traditional knowledge has so far lacked a classification system compatible with that used for patents. India's Council of Scientific and Industrial Research has sought to address this problem by creating a digital library of traditional knowledge. A modern classification based on the structure of the International Patent Classification has been evolved. A classification has been attempted for the traditional Indian *Ayurveda*, *Unani* and *Siddha* systems of medicine. The classification provides for a systematic arrangement of knowledge, and also easy dissemination and retrieval of data.

The database, comprising the digital library, has sufficient details on definitions, principles and concepts to minimize the possibility of trivial patents being granted based on traditional knowledge. The database will be valuable for providing leads for developing new therapeutics based on herbal products. At present, the size of the digital library database is 9 million pages, which is likely to grow to 31 million pages by the end of 2006. This will be available in five languages: English, French, German, Japanese and Spanish. A WIPO task force has recognized the need for a more detailed level of classification.

Putting traditional knowledge into the public domain, in a form accessible to patent examiners, should prevent direct patenting of such knowledge. However, many will use this knowledge as a basis for further inventions, which are patentable. We support the principles contained in the Convention on Biological Diversity, i.e. that there should be fair benefit sharing with the providers of that knowledge. One suggestion, currently being discussed in WTO and WIPO, is that patent applicants should be obliged to disclose the geographical origin of the knowledge on which their claimed invention is based. Such a proposal is opposed by the biotechnology and pharmaceutical industries on the grounds that it would inhibit the search for medically useful genetic resources and knowledge, for a number of practical reasons. They would prefer the use of national access regimes, unrelated to the patent system, that would include appropriate protocols for bioprospecting and for contractual terms governing prior informed consent and benefit sharing.

Analysing and sharing experiences in this complex area would be useful.

5.10 Digital libraries of traditional medical knowledge should be incorporated into the minimum search documentation lists of patent offices to ensure that the data contained within them will be considered during the processing of patent applications. Holders of the traditional knowledge should play a crucial role in deciding whether such knowledge is included in any databases and should also benefit from any commercial exploitation of the information.

5.11 All countries should consider how best to fulfil the objectives of the Convention on Biological Diversity. This could be, for instance, through the establishment of appropriate national regimes for prospecting for genetic resources and for their subsequent utilization and commercialization; contractual agreements; the disclosure of information in the patent application

of the geographical source of genetic resources from which the invention is derived and other means.

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CHAPTER 6

TOWARDS A SUSTAINABLE PLAN TO PROMOTE INNOVATION AND ACCESS

A GLOBAL CHALLENGE

The burden of infectious diseases that disproportionately affect developing countries continues to increase. Reducing the very high incidence of communicable diseases in developing countries is an overriding priority, but it is also important to consider how the growing burden of noncommunicable diseases in developing countries can be addressed. The health needs of the poor and vulnerable, in particular women and children, must receive the highest priority from the world community.

Our task is how to alleviate this enormous burden which is an affront to our sense of shared humanity. With the increasing power of science, and also a growing awareness of the fundamental inequities inherent in the disproportionate burden on developing countries, the world must find ways to tackle more effectively the health needs of poor people. This needs to take into account both the necessity of improving the access of all to new and existing products and the urgency of developing appropriate new products including vaccines, diagnostics and treatments. Among other factors, not least the organization and financing of health delivery systems, a prerequisite for access is that appropriate treatments should be available for diseases and conditions that disproportionately affect developing countries.

The Commission found that in industrialized countries there is an innovation cycle in biomedical R&D that is, to a large extent, self-sustaining. The incentive for R&D in the private sector is the existence of a large market for health-care products supported by both public and private demand, and underpinned by protection of intellectual property which allows companies to capture financial rewards from innovation. The market-driven R&D process in the private sector – in pharmaceutical and biotechnology companies – is supported by a substantial upstream research effort, funded principally by the public sector, in universities and public-sector research organizations.

This conjunction of positive conditions is generally not present in low-income countries. The innovation cycle is not self-sustaining. Upstream research capacity is generally weak or non-existent, except in a few mainly large technologically advanced countries. Many do not have sufficient resources to invest in public sector research, or a private sector with innovative capacity. Markets for products are usually small and health services underfunded. In those circumstances, the incentive effect of intellectual property rights lacks efficacy. Developing countries are therefore largely dependent on the products of innovation designed principally to meet the health-care needs of developed countries. In some cases these products meet their needs if funding is available (for instance, in the case of vaccines against universal childhood illnesses, or antibiotics) but in others, no treatments are available for prevalent diseases or are not adapted to the special conditions relating to delivery and compliance in developing countries. Also existing medicines, whether patented or not, are often too costly in the poorest settings for patients paying out of pocket or

for governments purchasing for public health programmes. Thus, current government policies and company strategies including incentive and funding mechanisms, both in developed and developing countries, have not generated sufficient biomedical innovation relevant to the needs of most developing countries. New, and even existing, treatments remain unavailable and unaffordable to those who need them.

As Bill Gates told WHO's World Health Assembly in 2005:

Political systems in rich countries work well to fuel research and fund health care delivery, but only for their own citizens. The market works well in driving the private sector to conduct research and deliver interventions, but only for people who can pay.

Unfortunately, the political and market conditions that drive high quality health care in the developed world are almost entirely absent in the rest of the world. We have to make these forces work better for the world's poorest people (1).

Too few R&D resources are directed to the health needs of developing countries. In the private sector, companies do not have the incentive to devote adequate resources to develop products specifically adapted to the needs of developing countries, because profitability is mainly to be found in rich country markets. The great majority of health research funded by the public sector takes place in developed countries, and its priorities principally reflect their own disease burden, resource position and social and economic circumstances.

An enormous cost to human and economic development arises from this. The report of the WHO Commission on Macroeconomics and Health calculated that extra expenditure on health interventions of all kinds (including R&D) in low income developing countries would, on conservative assumptions, produce direct benefits to human health (e.g. increased longevity) and to economic growth, on which improved prosperity and better health depends, of more than five times the amount of additional spending. For example, it estimated that implementation of its recommendations would reduce deaths in the developing world by 8 million per year by 2015. On that basis it called for a massive increase in funding of health services and investments in R&D. The cost of inaction, in lives lost and disabilities and lower economic growth, would be far greater than the relatively small cost of the actions it proposed (2).

A comprehensive attempt to estimate additional resource requirements for a particular disease is the recently published "Global Plan to Stop TB: 2006-2015", prepared by the Stop TB Partnership (3). Linked to the objective of meeting the MDGs, and the specific goal of halving TB prevalence and deaths compared with 1990 levels, the plan sets out the resources needed for actions, underpinned by sound epidemiological analysis and robust budget estimates. It represents a consensus view of what could be achieved by 2015, provided the necessary resources are made available both for the delivery of treatments to those in need, and investment in new diagnostics, drugs and vaccines.

Based on this analytical work, the Plan estimates total financing needs of US\$ 56 billion in the period covered by the Plan, of which US\$ 31 billion is not likely to be available based on projections of current funding levels. In the case of new

diagnostics, vaccines and drugs the total financing requirement in the period is estimated at nearly US\$ 9 billion, of which only US\$ 2.8 billion is projected to be met from existing funders, leaving a gap of US\$ 6.2 billion (or 69% of the total). It therefore estimates that additional spending averaging US\$ 3 billion each year is required in the next decade, of which US\$ 0.6 billion should be for the development of new products to fight TB.

While comprehensive exercises are not available for other important disease areas, a recent assessment of current spending on malaria R&D estimated total investment in 2004 of US\$ 323 million, of which 56% was provided by the public sector, 32% by not-for-profit institutions, and 12% by the for-profit sector. The biggest single investors were the United States Government and the Bill and Melinda Gates Foundation. Without doing detailed calculations of actual requirements, the report notes that malaria currently accounts for 3.1% of the global disease burden, but only 0.3% of health-related R&D investment. If malaria R&D were funded at the average rate for all medical conditions in relation to the global burden of disease, then it should receive over US\$ 3.3 billion per annum (4).

We also believe a significant increase in R&D on new health products, along with increased resources for delivery, is essential. And this effort has to be sustainable. Governments in both developed and developing countries should give a higher priority providing the continuing stream of innovations on which improved health care in developing countries depends, and to their delivery.

A GLOBAL RESPONSIBILITY

This tragic failure by all governments to address poverty and sickness in developing countries has become a worldwide subject of great concern. Since the beginning of this century, there has been a heightened global consciousness about this issue. This is not just because it represents an affront to commonly-held basic human values. It is also in recognition of our interdependence, and the potentially serious consequences of failure to deal with this, for all members of the world community.

The endorsement of the MDGs in 2000 emphasized the importance of investing in health improvements for economic development, as well as improving the health of poor people. In 2001, the Doha Declaration on the TRIPS agreement and public health stated that the TRIPS agreement should be interpreted in a manner supportive of the right to protect public health. During 2005 there were many other examples of this heightened consciousness. For instance, the G8 leaders in 2005 committed themselves and other developed countries to increase development assistance to Africa alone by US\$ 25 billion per annum by 2010, and to all developing countries by US\$ 50 billion per annum by the same date. There are also many specific instances of increased commitments by governments and foundations to the fight against diseases that disproportionately affect developing countries. New funding sources have arisen, in particular the Bill and Melinda Gates Foundation, and new players, including public-private partnerships, have emerged on the scene. On the part of pharmaceutical companies, heightened awareness has led to the setting up, inter alia, of dedicated R&D units devoted to diseases that particularly affect developing countries. Underpinned by the new opportunities arising from the rapid development

of science (e.g. genomics), a momentum has developed which it will be critical to sustain to promote innovation and access.

All these initiatives reflect a new awareness: relying on purely economic mechanisms cannot solve the problem. A worldwide mobilization of resources, both public and private, and political commitments at all levels, is necessary to address the issue.

Intellectual property rights have an important role to play in stimulating innovation in health-care products in countries where financial and technological capacities exist, and in relation to products for which there are profitable markets. However, the fact that a patent can be obtained may contribute little or nothing to innovation if the market is too small or scientific and technological capability inadequate. Where most consumers of health products are poor, as are the great majority in developing countries, the monopoly costs associated with patents can limit the affordability of patented health-care products required by poor people in the absence of other measures to reduce prices or increase funding. Because the balance of costs and benefits of patents will vary between countries, according to their level of development and scientific and technological infrastructure, the TRIPS agreement allows countries some flexibility in finding a balance more appropriate to their circumstances.

OUR PROPOSALS

Our Commission analysed the various effects of intellectual property rights on upstream research, the subsequent development of medical products in both developed and developing countries and the possibility of ensuring access to them in developing countries. We considered also the impact of other funding and incentive mechanisms and fostering innovation capacity in developing countries.

We present below our recommendations. These form an agenda which we think needs to be considered by developing and developed countries, as well as other governmental and non-governmental stakeholders.

CHAPTER 2 – DISCOVERY

The foundation of all innovation leading to the discovery of new health-care products is basic research in the life sciences and other scientific and technical disciplines which contribute, such as chemistry and informatics. In recent years the revolution in molecular biology and the development of wholly new branches of scientific investigation has offered the prospect that the process of biomedical innovation could be accelerated and made more effective. The process of drug discovery and development is not only a matter of science. It involves a complex interaction among a wide range of economic, social, and political actors. Governments play a critical role in providing the policy framework, including intellectual property rights, funding and tax and other incentives, but other actors in the public, private and non-profit sectors are essential components of this complex system.

In this chapter we reviewed the evidence concerning the science and the economic and policy choices faced by countries. In particular, we focused on scientific,

institutional and financial issues arising between basic research and the identification of lead compounds with possible therapeutic utility.

- What are the gaps in this process for diseases principally affecting developing countries?
- What policy measures might be appropriate to address those gaps?

The Commission concludes that it is in the interest of all countries to promote health research that addresses the health needs of developing countries and to set specific and measurable targets in this regard. To that end we made the following recommendations.

2.1 Governments of developed countries should reflect adequately this objective in their research policies. In particular, they should seek to define explicit strategies for R&D and devote a growing proportion of their total health R&D funding to the health needs of developing countries, with an emphasis on upstream and translational research.

2.2 Developing countries should establish, implement or strengthen a national programme for health research including best practices for execution and management of research, with appropriate political support, and long-term funding.

2.3 Government and funder attention should be paid to upstream research that enables and supports the acquisition of new knowledge and technologies that will facilitate the development of new products, including drugs, vaccines and diagnostic tests to tackle the health problems of developing countries. Attention should also be paid to the current inadequacy of the research tools available in these fields of research. These include techniques to understand new pathways to discovery, better ways to use bioinformatics, more suitable animal models and other disease-specific technologies.

2.4 When addressing the health needs of people in developing countries, it is important to seek innovative ways of combating Type I diseases, as well as Type II and Type III diseases. Governments and funders need to assign higher priority to combating the rapidly growing impact of Type I diseases in developing countries, and, through innovation, to finding affordable and technologically appropriate means for their diagnosis, prevention and treatment.¹⁸

2.5 Actions should be taken by WHO to find ways to make compound libraries more accessible to identify potential compounds to address diseases affecting developing countries.

2.6 WHO should bring together academics, small and large companies in pharmaceuticals and biotechnology, governments in the form of aid donors or medical research councils, foundations, public-private partnerships and patient

¹⁸ The typology of diseases is explained in Chapter 1.

and civil society groups for a standing forum to enable more organized sharing of information and greater coordination between the various players.

2.7 Countries should seek through patenting and licensing policies to maximize the availability of innovations, including research tools and platform technologies, for the development of products of relevance to public health, particularly to conditions prevalent in developing countries. Public funding bodies should introduce policies for sensible patenting and licensing practices for technologies arising from their funding to promote downstream innovation in health-care products.

2.8 Patent pools of upstream technologies may be useful in some circumstances to promote innovation relevant to developing countries. WHO and WIPO should consider playing a bigger role in promoting such arrangements, particularly to address diseases that disproportionately affect developing countries.

2.9 Developing countries need to consider in their own legislation what form of research exemption might be appropriate in their own circumstances to foster health-related research and innovation.

2.10 Countries should provide in their legislation powers to use compulsory licensing, in accordance with the TRIPS agreement, where this power might be useful as one of the means available to promote, *inter alia*, research that is directly relevant to the specific health problems of developing countries.

2.11 Developing countries should ensure that their universities and public research organizations maintain research priorities in line with their public health needs and public policy goals, in particular the need for innovative research of benefit to the health problems of their populations. This should not exclude support of health-related research which meets their industrial or export objectives and that could contribute to improved public health in other countries.

2.12 Public research institutions and universities in developed countries should seriously consider initiatives designed to ensure that access to R&D outputs relevant to the health concerns of developing countries and to products derived therefrom, are facilitated through appropriate licensing policies and practices.

CHAPTER 3 – DEVELOPMENT

Although one of the most challenging aspects of drug discovery is identifying candidate compounds, the most expensive part is the process of taking the candidate through all the required stages of pre-clinical and clinical research and the regulatory process.

This issue of improving the efficiency of the drug development and regulatory process is receiving high-level attention from the scientific community and regulatory agencies such as the United States National Institutes of Health, the Food and Drug

Administration and the EU regulatory authorities. In order to promote the development of new products for the developing world there is also an urgent need to strengthen the clinical trials and regulatory infrastructure in those countries.

This issue is important because even in developed countries, the rapidly rising costs of health care, including supplies of medicines, are a matter of intense public concern. In developing countries, and even in some developed countries, the cost of medicines, often not available through public health-care systems, can be a matter of life and death.

New players, such as private-public partnerships and developing countries with innovative capacity, have an important part to play in developing new products that can potentially be delivered at prices that are affordable in developing countries. Increased collaboration is also important, in particular between researchers in the developing and developed world, both in the public and private sectors.

But this will not be possible in the absence of enhanced and sustainable funding, particularly from governments, for R&D relevant to developing countries.

Scientific and technical considerations, on the one hand, and economic, policy and institutional issues on the other, are relevant to this issue. Looking at the range of activities from optimization of a lead compound through to regulatory review of the safety, efficacy and quality of a new product, there are a number of key issues that require careful consideration, and we recommended as follows.

3.1 Governments and the appropriate national authorities and funders should assign a higher priority to research on the development of new animal models, biomarkers, surrogate end-points and new models for assessing safety and efficacy, which would increase the efficiency of product development. They should also work with their counterparts in developing countries to formulate a mechanism to help identify research priorities in this area for Type II and Type III diseases particularly relevant to developing countries, and provide funding for this R&D.

3.2 To enhance the sustainability of public-private partnerships:

- **Current donors should sustain and increase their funding for R&D to tackle the health problems of developing countries.**
- **More donors, particularly governments, should contribute to increase funding and to help protect public-private partnerships and other R&D sponsors from changes in policy by any major donor.**
- **Funders should commit funds over longer time frames.**
- **Public-private partnerships need to continue to demonstrate that they are using their money wisely, that they have transparent and efficient mechanisms for accountability, that they coordinate and collaborate, and that they continue regularly to monitor and evaluate their activities.**

- **The pharmaceutical industry should continue to cooperate with public–private partnerships and increase contributions to their activities.**
- **Research institutions in developing countries should be increasingly involved in executing research and trials.**

3.3 WHO should initiate a process to devise mechanisms that ensure the sustainability and effectiveness of public–private partnerships by attracting new donors, both from governments and the private sector, and also to promote wider participation of research institutions from developing countries. However, governments cannot passively rely on what these partnerships could eventually deliver; there is a need for a stronger commitment on their part for an articulated and sustainable effort to address the research gaps identified in this report.

3.4 Further efforts should be made to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards. WHO has a role to play, in collaboration with interested parties, in an exploration of new initiatives that might be undertaken to achieve this goal.

3.5 Governments should continue to develop forms of advance purchase schemes which may contribute to moving later stage vaccines, medicines and diagnostics as quickly as possible through development to delivery.

3.6 Recognizing the need for an international mechanism to increase global coordination and funding of medical R&D, the sponsors of the medical R&D treaty proposal should undertake further work to develop these ideas so that governments and policy-makers may make an informed decision.

3.7 Practical initiatives that would motivate more scientists to contribute to this field through “open source” methods should be supported.

CHAPTER 4 – DELIVERY

However successful efforts might be to develop new products to address the public health problems of developing countries, they will be of no value if they cannot be made available and accessible to those who need them. Antiretrovirals for the treatment of HIV/AIDS have featured prominently in public discussions. The problem of access to medicines is certainly not limited to antiretrovirals, but concerns the whole range of medicines, whether patented or not, even when available at the lowest cost in the poorest settings, for prevention and cure as well as diagnostic tools.

For instance, in the case of malaria there is a massive gap in access, with the most effective treatments (artemisinin-based combination therapies) in short supply, and the finance available for their purchase small in relation to need.

In this chapter we examined the factors affecting the introduction of new and existing products into developing countries, including health delivery systems, regulation,

pricing, intellectual property and policies to promote competition. The following recommendations were made:

4.1 Governments need to invest appropriately in the health delivery infrastructure, and in financing the purchase of medicines and vaccines through insurance or other means, if existing and new products are to be made available to those in need of them. Political commitment is a prerequisite for bringing about a sustained improvement in the delivery infrastructure and health outcomes. Health systems research to inform policy-making and improve delivery is also important. The integration of traditional medicine networks with formal health services should be encouraged.

4.2 Developing countries should create incentives designed to train and retain health-care workers in employment.

4.3 Developed countries should support developing countries' efforts to improve health delivery systems, inter alia, by increasing the supply of their own trained health-care workers.

4.4 Governments have an important responsibility to put in place mechanisms to regulate the quality, safety and efficacy of medicines and other products. As a starting point, adherence to good manufacturing practices and effective supply chain management can ensure product quality and will also curb the circulation of counterfeit products.

4.5 Policies for biomedical innovation must take account of the fact that health systems in many developing countries remain resource-constrained. Policies must emphasize affordable innovations adapted to the realities of health-care delivery in developing countries, and covering appropriate technologies for the diagnosis, prevention and treatment of both communicable and noncommunicable diseases. Mechanisms for promoting such adaptive research in a systematic way must be improved.

4.6 All companies should adopt transparent and consistent pricing policies, and should work towards reducing prices on a more consistent basis for low and lower middle income developing countries. Products, whether originator's or generic, should be priced equitably, not just in sub-Saharan Africa and least developed countries, but also in low and lower middle income countries where there are a vast number of poor patients.

4.7 For noncommunicable diseases, governments and companies should consider how treatments, which are widely available in developed countries, can be made more accessible for patients in developing countries.

4.8 Continuing consideration needs to be given to the prices of treatments for communicable diseases, particularly of second-line drugs for HIV/AIDS treatment.

4.9 Governments of low and middle income countries where there are both rich and poor patients should formulate their funding and price regulation with a view to providing access to poor people.

4.10 Governments need to prioritize health care in their national agendas and, given the leverage to determine prices that patents confer, should adopt measures to promote competition and ensure that pricing of medicines is consistent with their public health policies. Access to drugs cannot depend on the decisions of private companies but is also a government responsibility.

4.11 Corporate donation programmes can be of great value in a number of fields in collaboration with the actions of governments and nongovernmental organizations. However, addressing health needs in developing countries requires more structured and sustainable actions by governments and other parties that stimulate accessibility to products, while generating new treatments and products adapted to the needs of developing countries.

4.12 Governments should remove any tariffs and taxes on health-care products, where appropriate, in the context of policies to enhance access to medicines. They should also monitor carefully the supply and distribution chain to minimize costs that could adversely influence the prices of medicines.

4.13 The Doha Declaration clarifies the right of governments to use compulsory licensing as a means of resolving tensions that may arise between public health and intellectual property, and to determine the grounds for using it. Developing countries should provide in their legislation for the use of compulsory licensing provisions, consistent with the TRIPS agreement, as one means to facilitate access to cheaper medicines through import or local production.

4.14 Developed countries, and other countries, with manufacturing and export capacity should take the necessary legislative steps to allow compulsory licensing for export consistent with the TRIPS agreement.

4.15 The WTO decision agreed on 30 August 2003, for countries with inadequate manufacturing capacity, has not yet been used by any importing country. Its effectiveness needs to be kept under review and appropriate changes considered to achieve a workable solution, if necessary.

4.16 Companies should adopt patent and enforcement policies that facilitate greater access to medicines needed in developing countries. In low income developing countries, they should avoid filing patents, or enforcing them in ways that might inhibit access. Companies are also encouraged to grant voluntary licences in developing countries, where this will facilitate greater access to medicines, and to accompany this with technology transfer activities.

4.17 Developing country governments should make available full and reliable information on patents granted. WHO, in cooperation with WIPO and others, should continue to pursue the establishment of a database of information about

patents, in order to remove potential barriers to availability and access resulting from uncertainty about the patent status in a country of a given product.

4.18 Developed countries and the WTO should take action to ensure compliance with the provisions of Article 66.2 of the TRIPS agreement, and to operationalize the transfer of technology for pharmaceutical production in accordance with paragraph 7 of the Doha Declaration on the TRIPS Agreement and Public Health.

4.19 The restriction of parallel imports by developed countries is likely to be beneficial for affordability in developing countries. Developing countries should retain the possibilities to benefit from differential pricing, and the ability to seek and parallel import lower priced medicines.

4.20 Developing countries need to decide in the light of their own circumstances, what provisions, consistent with the TRIPS agreement, would benefit public health, weighing the positive effects against the negative effects. A public health justification should be required for data protection rules going beyond what is required by the TRIPS agreement. There is unlikely to be such a justification in markets with a limited ability to pay and little innovative capacity. Thus, developing countries should not impose restrictions for the use of or reliance on such data in ways that would exclude fair competition or impede the use of flexibilities built into TRIPS.

4.21 In bilateral trade negotiations, it is important that governments ensure that ministries of health be properly represented in the negotiation, and that the provisions in the texts respect the principles of the Doha Declaration. Partners should consider carefully any trade-offs they may make in negotiation.

4.22 Governments and concerned international organizations should promote new purchasing mechanisms to stimulate the supply of affordable new products and to enhance the number of suppliers in order to provide a more competitive environment.

4.23 Developing countries should adopt or effectively implement competition policies and apply the pro-competitive measures allowed under the TRIPS Agreement in order to prevent or remedy anti-competitive practices related to the use of medicinal patents.

4.24 Countries should provide in national legislation for measures to encourage generic entry on patent expiry, such as the "early working" exception, and more generally policies that support greater competition between generics, whether branded or not, as an effective way to enhance access by improving affordability. Restrictions should not be placed on the use of generic names.

4.25 Developing countries should adopt or effectively implement competition policies in order to prevent or remedy anti-competitive practices related to the use of medicinal patents, including the use of pro-competitive measures available under intellectual property law.

4.26 Bilateral trade agreements should not seek to incorporate TRIPS-plus protection in ways that may reduce access to medicines in developing countries.

4.27 Governments should take action to avoid barriers to legitimate competition by considering developing guidelines for patent examiners on how properly to implement patentability criteria and, if appropriate, consider changes to national patent legislation.

CHAPTER 5 – FOSTERING INNOVATION IN DEVELOPING COUNTRIES

In the longer term, the development of innovative capacity for health research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies. The determinants of that capacity in developing countries are many. Each country has a unique set of political, economic and social institutions, which means there is no single recipe for advance. Nevertheless it is possible that lessons can be learnt from those countries which have made significant progress in this area.

The most scientifically and technologically advanced developing countries (sometimes known as innovative developing countries) are becoming significant contributors to biomedical R&D, in both the private and public sectors. They are becoming more integrated into global biomedical research networks, particularly as their advantages in terms of their ability to undertake high quality research at very competitive costs are recognized.

Apart from growing scientific and technological expertise, developing countries have a massive indigenous resource in the form of traditional medicine – both the knowledge accumulated over centuries about the medical properties of natural products, as well as unique systems for diagnosis and treatment, which have a different paradigm from “modern” medicine as it has developed in the western world. This resource is more widely used than modern medicines in most developing countries.

The possibilities exist for making better use of traditional medicine, by making traditional remedies more widely available, and by applying this knowledge to accelerate the development of new treatments.

In this chapter we addressed the building of capacity in developing countries in the fields of science and technology, regulation, clinical trials, the transfer of technology and traditional medicine, as well as intellectual property.

5.1 A prerequisite for developing innovative capacity is investment in the human resources and the knowledge base, especially the development of tertiary education. Governments must make this investment, and donors should support them.

5.2 The formation of effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal, are an important element in building innovative capacity.

Developed and developing countries should seek to intensify collaborations which will help build capacity in developing countries.

5.3 WHO, WIPO and other concerned organizations should work together to strengthen education and training on the management of intellectual property in the biomedical field, fully taking into account the needs of recipient countries and their public health policies.

5.4 Developed countries, and pharmaceutical companies (including generic producers), should take measures to promote the transfer of technology and local production of pharmaceuticals in developing countries, wherever this makes economic sense and promotes the availability, accessibility, affordability and security of supply of needed products.

5.5 Developed countries should comply with their obligations under article 66.2 of the TRIPS Agreement and paragraph 7 of the Doha Declaration.

5.6 Developing countries need to assign a higher priority to improving the regulation of medical products. Developed countries, and their regulatory institutions, should provide greater financial and technical assistance to help attain the minimum set of regulatory standards needed to ensure that good quality products are available for use. This assistance should also support infrastructure developments within a country, to ensure that good manufacturing practice and supply chain management standards are implemented and sustained.

5.7 The process of the International Conference on Harmonisation currently lacks immediate relevance to the needs of many developing countries, but those countries should maintain their participation in the process. In the meantime, developing country governments and regulatory institutions should give support to regional initiatives, tailored to the current capacities of their member countries, which offer more scope for lifting standards over time, exploiting comparative advantages, avoiding duplication, sharing information and facilities, and promoting appropriate standardization without erecting barriers to competition.

5.8 WHO has an important role to play, in collaboration with interested parties, in helping to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards.

5.9 Apart from the European & Developing Countries Clinical Trial Partnership, donors together with medical research councils, foundations and nongovernmental organizations, need to offer more help to developing countries in strengthening clinical trials and regulatory infrastructure.

5.10 Digital libraries of traditional medical knowledge should be incorporated into the minimum search documentation lists of patent offices to ensure that the data contained within them will be considered during the processing of patent applications. Holders of the traditional knowledge should play a crucial role in

deciding whether such knowledge is included in any databases and should also benefit from any commercial exploitation of the information.

5.11 All countries should consider how best to fulfil the objectives of the Convention on Biological Diversity. This could be, for instance, through the establishment of appropriate national regimes for prospecting for genetic resources and for their subsequent utilization and commercialisation; contractual agreements; the disclosure of information in the patent application of the geographical source of genetic resources from which the invention is derived and other means.

THE WAY TO SUPPORT A SUSTAINABLE GLOBAL EFFORT

As is apparent, this is a very large agenda. The issues are complex and views diverse. The numbers of partners involved is large. Further progress will require a collective effort. There is the need for a wider consultation to identify the most appropriate way forward for the health sector. It is important that the contributions of all stakeholders are taken into account so that their respective energies can be mobilized towards the achievement of a common goal: an enhanced and sustainable basis for R&D relevant to the health needs of developing countries.

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.

Funders, whether private or public, of course have the right to decide their own priorities as do research organizations, including public–private partnerships. The purpose of a Plan of Action would be to aid forward planning and collaborative action. In examples such as the Global Plan to Stop TB mentioned above, there is a value to all partners in setting out strategic goals and objectives for the medium term, and in rigorously examining the activities, resources and institutional mechanisms required if these objectives 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.

A central problem remains that previous calls for governments to invest more in health research for developing countries have so far had only limited success. Yet there is a widespread recognition that more funding is a necessity, and that it needs to be provided on a sustainable basis to support what is necessarily a long-term R&D effort.

For example, public–private partnerships currently rely in particular on philanthropic support. We think governments should do more to support the initiatives taken by foundations, thereby increasing resources available and sustainability. We endorse strongly the need for more resources if this research effort is to be sustained, and the

development of new arrangements that may facilitate the flow of new funds for greater impact. We seek a new approach which involves governments on a sustainable basis in the financing of health-related research relevant to developing countries.

Elements of this approach are contained in our recommendations but we summarize here an agenda of key issues that are worthy of consideration.

- Identification of gaps in the current coverage of research for diseases that disproportionately affect developing countries.
- Actions that might contribute to increasing the overall R&D effort on diseases that predominantly affect the developing world, and improved priority setting. For example, recognizing the possible need for increased support for those that currently receive less attention than HIV/AIDS, TB and malaria.
- Providing a sustainable source of funding for public–private partnerships and other R&D institutions in the field.
- Seeking ways to channel greater funding to research organizations in developing countries in both the public and private sectors.
- Whether common interests of product developers and producers in various areas might be better addressed collectively in areas such as facilitating clinical trials and product delivery.
- Supporting product introduction in developing countries through improved regulation, at national, regional and international level.
- Monitoring the impact of TRIPS and the Doha Declaration on innovation and access for medicines and other health-care products.
- Measuring performance and progress towards objectives, and monitoring and evaluation of programmes

In deliberating the way ahead we have considered a number of current examples that might serve both to attract additional funding to R&D devoted to the health needs of developing countries, and to improve the effectiveness of that effort.

Box 6.1 Examples from the health sector: the Global Plan to Stop TB, and the WHO Special Programme for Research and Training in Tropical Diseases
Global Plan to Stop TB

The Stop TB Partnership is responsible for the Global Plan to Stop TB. Here there are good mechanisms for coordination between the parties involved, for advocating realistically for resources required, for seeking to identify priorities, and for evaluating impact.

For instance, the implementation of the Plan is supported by a Secretariat based in WHO. The functions of the Secretariat include:

- promoting accountability, flexibility and coordination in the management of resources
- resource mobilization
- building new partnerships
- building skills and capacity at national level
- catalysing change
- monitoring and evaluating the progress of the Plan, and recommending appropriate tactical changes as necessary to achieve Plan objectives.

One of us described this initiative as follows:

I think the Global Plan is a good model – the goals are ambitious but realistic, the price tag high, but defensible and appropriate and the commitment of the TB community very strong. This plan will test the medical and technical muscle, the WHO and G8 influence and, most importantly, the international and national will and political commitment of all parties to address this epidemic. If we fail, it will not be the TB community alone that fails, it will mean that, as a society, we did not place this disease as a priority and we will have to live with that decision (5).

WHO Special Programme for Research and Training in Tropical Diseases

Another long-standing example is the WHO Special Programme for Research and Training in Tropical Diseases (TDR), supported by UNICEF, UNDP, and the World Bank. Since its establishment in 1975, it has been for a long time the central focus for the development of products to tackle diseases affecting developing countries. TDR focuses on neglected infectious diseases that disproportionately affect poor and marginalized populations. Its disease portfolio includes: African trypanosomiasis, dengue, leishmaniasis, malaria, schistosomiasis, tuberculosis, Chagas disease, leprosy, lymphatic filariasis and onchocerciasis. With a budget of about \$50 million annually, covering activities relating to ten or more diseases, it is now a relatively small player in resource terms compared to the greatly increased funding now flowing through public–private partnerships. However, given its central position in the field and its strong networks and contacts, it has the possibility of playing a more strategic role alongside its operational roles in research and training.

Box 6.2 An example from the agricultural sector: the Consultative Group on International Agricultural Research

In the apparently analogous field of agricultural research directed at the needs of developing countries, the central funding mechanism is the Consultative Group on International Agricultural Research (CGIAR), with a Secretariat based in the World Bank. This has been in existence for over 30 years. Currently the CGIAR is disbursing over US\$ 400 million per annum to a network of 15 agricultural research institutes, of which OECD governments provide more than two thirds, and the World Bank itself contributes another US\$ 50 million. The balance comes from developing country governments, international institutions (including the European Union) and foundations. Members include both developed and developing countries, as well as international organizations and foundations.

Apart from providing a single channel for donors to fund a multiplicity of research institutions in developing country agricultural research, the CGIAR also provides strategic inputs in priority setting, monitoring and evaluation, coordination and advocacy, and impact assessment.

The idea that a similar arrangement might be appropriate to health research is not new, and has been suggested by several reports and commentators over the past decade or so. For example, the Commission on Health Research for Development in 1990 viewed:

...the CGIAR...mechanisms as highly relevant to the needs of the health field. The functions of maintaining a global overview across many specific health problems backed by independent technical assessments and the capacity to mobilize resources in support of larger research efforts are sorely missing. Provided there is ample developing country representation in the decision-making process, analogues to the CGIAR...could be extremely constructive for the health field... (6).

The World Bank's 1993 World Development Report "Investing in Health" made a similar suggestion, as did the Commission on Macroeconomics and Health in 2001.

There may be some features of this example that could be adapted to the specific arrangements in the health sector, but there are a number of institutional and other features which differ in significant respects from the agricultural sector. These need to be taken into account.

It is not for us to say at this stage which of the various ideas we have mentioned, or others we have not, might represent an appropriate way forward. But we do all agree on the urgent need for action to generate more and sustainable funding for R&D to address the health needs of developing countries, and to engage governments in this endeavour more than has been the case to date.

In these circumstances we see an important role for WHO, as the lead international agency for public health, to take responsibility for pursuing this objective.

6.1 WHO should develop a Global Plan of Action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that disproportionately affect developing countries.

6.2 WHO should continue to monitor, from a public health perspective, the impact of intellectual property rights, and other factors, on the development of new products as well as access to medicines and other health-care products in developing countries.

6.3 WHO, including its regional offices, should consider the recommendations of our report, in consultation with others, and recommend how these should be taken forward in each region and country.

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ACRONYMS AND ABBREVIATIONS

AAI	Accelerating Access Initiative
AIDS	Acquired immunodeficiency syndrome
ASEAN	Association of South-East Asian Nations
CGIAR	Consultative Group on International Agricultural Research
CMH	Commission on Macroeconomics and Health (WHO)
CMRI	Centre for Medicine Research International Ltd
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases Initiative
DPT	Diphtheria, pertussis and tetanus
EDCTP	European and Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FIOCRUZ	Oswaldo Cruz Foundation (Brazil)
FTC	Federal Trade Commission (United States)
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GNP	Gross national product
HIV	Human immunodeficiency virus
HRP	WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IP	Intellectual property
IPM	International Partnership for Microbicides
IPRs	Intellectual property rights
LDCs	Least developed countries
MDGs	Millennium Development Goals
MMR	Mumps, measles and rubella
MMV	Medicines for Malaria Venture
MSF	Médecins sans Frontières
MVI	Malaria Vaccine Initiative
NCI	National Cancer Institute (United States)
NIH	National Institutes of Health (United States)
NITD	Novartis Institute for Tropical Diseases
NME	New molecular entity
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PPPs	Public-private partnerships

RCTs	Randomized controlled trials
R&D	Research and development
SARS	Severe acute respiratory syndrome
SNPs	Single nucleotide polymorphisms
STI	Swiss Tropical Institute
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TDR	Special Programme for Research and Training in Tropical Diseases
TIPRs	Transferable intellectual property rights
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

GLOSSARY

Advance purchase commitment (or contract)

An agreement, in advance of the development of a product, to purchase guaranteed amounts of the product, meeting pre-established criteria, at a specified price.

Applied research

Research directed towards specific objectives, such as the development of a new drug, therapy, or surgical procedure.

Artemisinin

A drug used to treat multi-drug resistant strains of falciparum malaria. The compound (a sesquiterpene lactone) is isolated from the shrub *Artemisia annua*.

Bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and the rate and extent of availability are similar to such a degree that their effects can be expected to be essentially the same.

Biologics

A class of systemic therapies that contain proteins derived from living cells, as opposed to traditional pharmaceutical drugs that are made up of non-living chemicals. Examples include vaccines, blood and other blood products, as well as genetic therapies.

Biomarkers

Quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness. For example, the adoption of CD4 cell counts and, subsequently, measures of viral load as biomarkers for anti-HIV drug review procedures by many national regulatory authorities.

Basic research

Studies in the biomedical area that are typically designed to expand scientific knowledge of human biology, disease mechanisms and processes, as well as to understand how drugs work.

Bolar (early working) exception

An exception to patent rights allowing a third party to undertake, without the authorization of the patentee, acts in respect of a patented product necessary for the purpose of obtaining marketing approval for the sale of a product.

Clinical trials

Any investigation in human subjects intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of an investigational product, or to identify any adverse reactions to an investigational product, or to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety or efficacy. The terms clinical trial and clinical study are synonymous.

Compound library

A collection of different chemical molecules.

Compulsory licence

A licence to exploit a patented invention granted by the state upon request of a third party.

Combinatorial chemistry

Synthesis of large numbers of chemical compounds by combining sets of chemical building blocks. Each newly synthesized compound's composition is slightly different from the previous one. This research often uses robotic systems to produce large numbers of compounds which can be tested as potential health product candidates.

Counterfeit drugs

Drugs which are deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.

Cross-licensing

The mutual exchange of licences between patent holders.

Data exclusivity

A legal provision that data collected (e.g. the results of clinical trials) for the purpose of obtaining marketing approval may not be used for a specified period by the regulatory authorities to grant approval to a generic equivalent.

Data protection

An obligation imposed on third parties to protect test data (e.g. the results of clinical trials) – usually collected in order to comply with government regulations on the safety, efficacy and quality of a broad range of products (e.g. drugs, pesticides, medical devices). For example, TRIPS provides for the protection of such data against unfair commercial use.

DALY

The disability-adjusted life year or DALY is a health gap measure that extends the concept of potential years of life lost due to premature death to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability. The DALY combines in one measure the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of 'healthy' life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability.

Differential pricing

The practice of setting different prices for different markets, typically higher prices in richer markets and lower prices in poorer markets.

Disclosure of origin

Requirement on patent applicants to disclose in patent applications the geographical origin of biological material on which the invention is based.

Deoxyribonucleic acid (DNA)

The double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.

Doha Declaration

The Declaration on the TRIPS Agreement and Public Health agreed at the Doha WTO Ministerial Meeting in 2001.

Downstream research

Applied research usually directed at the development of a product or process with a potential commercial application.

Evergreening

Evergreening is a term popularly used to describe patenting strategies that are intended to extend the patent term on the same compound.

Examination

The examination of the patent application, undertaken by a patent examiner, to determine whether the application complies with all the legal requirements for patentability set out in the legislation.

Exhaustion of rights

Principle whereby the right holders' intellectual property rights in respect of a product are considered exhausted (i.e. he or she can no longer exercise any rights) when that product has been put on the market by the right holder, or by an authorized party.

Genomics

The comprehensive study of the interactions and functional dynamics of whole sets of genes and their products.

High-throughput screening

An approach for finding new drugs which looks for chemicals that act on a particular enzyme or molecule. For example, if a chemical inactivates an enzyme it might prove to be effective in preventing a process in a cell which causes a disease. High-throughput methods enable researchers to try out thousands of different chemicals against each target very quickly using robotic handling systems and automated analysis of results.

Incremental innovation

Innovation which builds incrementally on previous innovation, as compared with "breakthrough" innovation, a completely novel means to prevent, treat or cure a particular disease.

Intellectual property rights

Rights awarded by society to individuals or organizations over inventions, literary and artistic works, symbols, names, images, and designs used in commerce. They give the titleholder the right to prevent others from making unauthorized use of their property for a limited period.

Interchangeability

A pharmaceutical product that is therapeutically equivalent to a comparator (reference) product.

Lead compound optimization

A process where lead compounds are further refined and a smaller number of potential leads are identified. These optimized leads are tested for such attributes as absorption, duration of action and delivery to the target. The results of these tests determine whether the leads have the potential to become fully-fledged candidates for product development.

Microbicide

Compounds designed to be applied inside the vagina or rectum to protect against sexually transmitted infections including HIV. They can be formulated as gels, creams, films, or suppositories.

Monoclonal antibodies

Identical antibodies due to their production from one type of immune cell, that are clones of a single parent cell. It is possible to create monoclonal antibodies that specifically bind to a substance and can then serve to detect or purify that substance. As a result, they are an important tool in biochemistry, molecular biology and medicine.

Neglected diseases

Disease states where there are inadequate, ineffective or no means to prevent, treat, diagnose or cure them (see **Type II** and **Type III** disease).

New molecular entity

A medication containing an active substance that has never before been approved for marketing in any form (term used by the United States Food and Drug Administration).

Open source

A computer programme in which the source code is available to the general public for use, and/or modification from its original design. Open source code is typically created as a collaborative effort in which programmers improve upon the code and share the changes within the community.

Parallel imports

The purchase of a patented medicine from a lawful source in an exporting country and its importation without seeking the consent of the “parallel” patent holder in the importing country.

Patent

An exclusive right awarded to an inventor to prevent others from making, selling, distributing, importing or using the invention, without licence or authorization, for a fixed period of time. In return, the patentee discloses the invention to the public. There are usually three requirements for patentability: novelty (new characteristics which are not "prior art"); inventive step or non-obviousness (knowledge not obvious to one skilled in the field); and industrial applicability or utility.

Patent pools

An agreement between two or more patent owners to license one or more of their patents to one another or third parties.

Phase I trials

Initial studies to determine the metabolism and pharmacological actions of drugs in humans, the side-effects associated with increasing doses, and to gain early evidence of effectiveness. May include healthy participants and/or patients.

Phase II trials

Controlled clinical studies conducted to evaluate the effectiveness of a drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side-effects and risks.

Phase III trials

Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained. Intended to gather additional information to evaluate the overall risk–benefit relationship of the drug and provide an adequate basis for physician labelling.

Phase IV trials

Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

Platform technologies

Any base of technologies on which other technologies or processes are built. In the case of biomedical research, a platform technology provides tools used by biotechnology and pharmaceutical companies in their discovery and development efforts.

Prior art

Publications or other public disclosures made before the filing (or priority) date of a patent application against which the novelty and inventiveness of the invention in the patent application is judged.

Recombinant DNA

A molecule of DNA consisting of DNA originating from two or more sources.

Recombinant proteins

Proteins produced by different genetically modified organisms following insertion of new DNA into their genome.

Regulation

Typically, the process by which a governmental authority reviews medical interventions for marketing authorization. Although methods vary, this normally involves determination of product safety, quality and efficacy. Regulation also involves ongoing monitoring and evaluation of safety, efficacy and quality of products that have already obtained marketing authorization.

Risk–benefit assessment

Analysis of the risks and benefits of a particular product.

Sui generis

Latin expression meaning “of its own kind”. Data exclusivity is a *sui generis* form of intellectual property protection.

Systems biology

The study of the mechanisms underlying complex biological processes as integrated systems of many, diverse, interacting components.

Trade secret

Commercially valuable information about production methods, business plans, clientele, etc. They are protected as long as they remain secret by laws which prevent acquisition by commercially unfair means and unauthorized disclosure.

Traditional knowledge

While there is no generally acceptable definition, traditional knowledge includes, but is not limited to, tradition-based creations, innovations, literary, artistic or scientific works, performances and designs. Such knowledge is often transmitted from generation to generation and is often associated with a particular people or territory.

Type I disease

Diseases that are incident in both rich and poor countries, with large numbers of vulnerable population in each. Examples of communicable diseases include measles, hepatitis B, and *Haemophilus influenzae* type b (Hib), and examples of noncommunicable diseases abound (e.g. diabetes, cardiovascular diseases, and tobacco-related illnesses).

Type II disease

Diseases that are incident in both rich and poor countries, but with a majority of cases in poor countries. Type II diseases are often termed *neglected diseases*.

Type III disease

Diseases that are overwhelmingly or exclusively incident in the developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). Type III diseases are often termed *very neglected diseases*.

WHO Prequalification Project

A project originally intended to give United Nations procurement agencies, such as UNICEF, a choice of products meeting various standards as certified by WHO. With time, other agencies and governments have found this a useful service.

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The studies may be viewed at: <http://www.who.int/intellectualproperty/studies/en/>

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¹⁹ Sadly, Jenny Lanjouw died tragically young in November 2005.

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Submissions may be viewed at: <http://www.who.int/intellectualproperty/submissions/>

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Presentations may be viewed at: <http://www.who.int/intellectualproperty/seminars/>

Workshop and open forum participants (30 May –1 June 2005): Labeeb Abboud, Félix Addor, Eyrup Akarsu, Jana Armstrong, Tenu Avafia, Reiko Aoki, Harvey Bale, Rashmi Barbhैया, Owen Barder, Anne Leonore Boffi, Jorge Bermudez, Peter Beyer, Carmine Bozzi, Tony Bunn, Michel Celi Vegas, Samantha Chaifetz, Sudip Chaudhuri, Jacob Cornides, Peter Corr, Susan Crowley, Jody Dalmacion, Francoise Dassy, Carolyn Deere, Caroline Dommen, Boris Engelson, Magali Fabre, Andrew Farlow, Nehal A. Farooque, Lila Feisee, Julian Fleet, F. Freiburghaus, Junying Fu, Lydia Garcete, Alec van Gelder, Ira Glazer, Spring Gombe, Cheri Grace, Katherine Hagen, Peter Hall, Rachelle Harris, Wolfgang Hein, Margaret Helling-Borda, Paul Herrling, David Hohman, Ton Hoek, Tim Hubbard, Kees de Joncheere, Warren Kaplan, Dominic Keating, Martin Khor, Richard Kjeldgaard, Ismail Kola, Daniel Kraus, Jean Lanjouw, Phuoc Le, Lee Li, Frank Lichtenberg, Buddhima Lokuge, James Love, Murray Lumpkin, Stephen Maurer, Jon Merz, Allison Meyer, Zafir Mirza, Mary Moran, Carlos Morel, Julian Morris, Cailin Morrison, John Mugabe, Viviana Munoz, Sisule Musungu, Mandi Mzimba, Jain Naresh, Bechir N'Daw, William New, Eric Noehrenberg, Matti Ojanen, Geoffrey Oldham, Colleen Ottoson, I. Ovando Lacroux, Davinia Ovet, Mats Parup, Carlos Passarelli, Avinash Patwardhan, Bhushan Patwardhan, Bernard Pecoul, Jon Pender, Govin Permanand, Simonetta Pirazzini, Ben Prickril, John Purves, Arti Rai, Meenakshi Raman, Sauwakon Ratanawijitrasin, Michael Rawlins, Julian Reinhard, Ted Roumel, Joan Rovira, Padmashree Gehl Sampath, Gill Samuels, K. Sanjoynaya, Krishna Sarma, Bernard Schwartlander, Sangeeta Shashikant, Priya Shetty, Daphne Shih, Gaudenz Silberschmidt, Anthony So, Christoph Spennemann, K. Ravi Srinivas, Phillip Stevens, Géraldine Suire, Susan Isiko Strba, Antony Taubman, Ellen t'Hoen, Halla Thorsteinsdottir, Nikolaus Thumm, Karen Timmermans, Francoise Torchiana, Adrian

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WHO staff from headquarters, too numerous to mention, also participated and contributed to these events. Dr Jean Lariviere (Canada) adroitly moderated both the plenary workshop sessions and the open forum. Roger Kampf, Stephen Matlin, Roy Widdus and David Winters chaired the thematic workshop sessions.

Workshop presentations may be viewed at:

<http://www.who.int/intellectualproperty/events/workshop/>

Open Forum presentations may be viewed at:

<http://www.who.int/intellectualproperty/events/openforumpresentations/en/index.html>

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In addition, the deliberations of the Commission were greatly enriched by many meetings and consultations with stakeholders around the world.

VISITS

BRAZIL, Brasilia/Rio de Janeiro:

Meetings were held with representatives of companies from ABIFINA, ABIQUIF, INTERFARMA, ALANAC, as well as officials from individual companies. Nongovernmental organizations included SOBRAVIME, IDCID – USP, ABIA & GTPI-REPRIP, GIV - Forum ONG/AIDS - SP, and MSF. Meetings were held with the Ministry of Health (STD/AIDS National Program, Minister Humberto Costa, National Health Council, and ANVISA), the Ministry for Development, Industry and External Commerce (National Institute of Industrial Property, and other departmental groups), the Ministry of External Relations (officials and Minister Celso Amorim), the Ministry of Defense (ALFOB/Army Official Laboratory), and the Oswaldo Cruz Foundation (FIOCRUZ).

<http://www.who.int/intellectualproperty/events/meeting3/en/index.html>

BELGIUM, Brussels:

Commissioners met officials from the European Federation of Pharmaceutical Industries and Association (EFPIA), GSK Biologicals, the International Chamber of Commerce, and European Commission officials from: Directorate General (DG) of Development; DG Trade; DG Enterprise; DG Market; DG SANCO; DG RTD; DG Competition; and the EMEA.

<http://www.who.int/intellectualproperty/events/meeting4/en/index.html>

CANADA, Ottawa:

Commissioners met officials from the research-based industry association (RX&D), Biotech Canada, and individual company representatives, the Canadian generic drug industry association (CGMA) and various generic company representatives. The Commission also met staff from the HIV/AIDS Legal Network, MSF Canada, CARE Canada, the Canadian Society for International Health, and the International Coalition on AIDS and Development (ICAD). Meetings were held with officials from Industry Canada, Health Canada, the

Canadian International Development Agency, Foreign Affairs Canada, and International Trade Canada.

(http://www.who.int/intellectualproperty/events/2nd_meeting/en/index.html)

INDIA, Delhi:

Commissioners met representatives of the Indian Drug Manufacturers' Association, Organisation of Pharmaceutical Producers of India and the Indian Pharmaceutical Alliance along with various company representatives from the biotechnology sector. Participants in other meetings included: University of Pune; the Centre for the Study of Global Trade System; the Affordable Medicines and Treatment Campaign; the Indian Council for Medical Research, and the Council of Scientific and Industrial Research (CSIR). Members of the Commission also attended a conference entitled "Building Innovative Pharma in India" on 5 November, 2004 organized by the Confederation of Indian Industry.

(http://www.who.int/intellectualproperty/events/india_visit/en/index.html)

MEXICO, Mexico City:

The Commission held an open session at the Ministerial Summit on Health Research in Mexico City on 17 November 2004. The session was entitled, "CIPIH: What should be its priorities?"

(http://www.who.int/intellectualproperty/events/mexico_session/en/index.html)

SOUTH AFRICA, Pretoria, Johannesburg:

The Commission held meetings with South African industry associations (Pharmaceutical Manufacturers Association and the Innovative Medicines South Africa) as well as individual company representatives, the Generic Drug Manufacturers Association, Aspen Pharmacare, Adcock Ingram, the South African National AIDS Committee (SANAC), the Trade Law Centre for Southern Africa (TRALAC), the Treatment Action Campaign (TAC), the Minister of Health and the Minister of Trade and Industry and their officials, the Medical Research Council of South Africa (SAMRC), the South African AIDS Vaccine Initiative (SAAVI), the Medicines Control Council (MCC), and the Council for Scientific and Industrial Research (CSIR).

SWITZERLAND, Bern

The Chairperson met various officials from the Swiss Intellectual Property Institute, and the health and industry ministries.

(<http://www.who.int/intellectualproperty/events/bern/en/index.html>)

SWITZERLAND, Basel,

The Chairperson met representatives of the Swiss industry association (Interfarma), Novartis and Roche, as well as the Novartis Foundation for Sustainable Development. A separate meeting was also held with Mr Daniel Vasella, the Chief Executive Officer of Novartis.

SWITZERLAND, Geneva:

First Meeting of the Commission, 5-6 April 2004

The Commission heard presentations from senior officials from WHO, representatives from international agencies (UNAIDS, UNCTAD, WIPO, WTO) and from the research-based pharmaceutical industry and civil society.

(<http://www.who.int/intellectualproperty/events/meeting1/en/index.html>)

UNITED STATES, Washington, DC:

The Commission met representatives of the Pharmaceutical Manufacturers Association of America, International Federation of Pharmaceutical Manufacturers Associations, and individual company representatives from the pharmaceutical and biotechnology sectors. It also met representatives of the American Association for the Advancement of Science, the

Consumer Project on Technology, the Department of Health and Human Services, the Food and Drug Administration, United States Patent and Trademark Office, the Federal Trade Commission, the National Cancer Institute, the National Center of Complementary and Alternative Medicine, the National Institute of Allergy and Infectious Diseases, the Office of Technology Transfer at the National Institutes of Health and Congressional staff.
(http://www.who.int/intellectualproperty/events/2nd_meeting/en/index.html)

ANNEX

Carlos Correa and Pakdee Pothisiri

As the report recognizes, patents are irrelevant for the development of the products needed to address the diseases prevailing in developing countries. Pharmaceutical companies decisively shape the global R&D agenda in this field and invest only where profitable markets exist. The extension of pharmaceutical patent protection to developing countries, mandated by the TRIPS Agreement, can do very little to prompt the development of such products, while it generates costs in terms of reduced access to the outputs of innovation. Where patents exist and are enforceable, medicines can be unaffordable for governments and patients in developing countries. This is why it is crucial to promote generics competition, which is essential to drive prices down and improve access to medicines to all, and to ensure a pro-competitive implementation of the TRIPS Agreement through the utilization, *inter alia*, of compulsory licences and government use provisions, when needed. Further analysis is required on the negative implications for public health of TRIPS-plus provisions (such as data exclusivity) contained in free trade agreements. WHO should continue to assess these developments and alert developing countries on their possible impact on public health.

More analysis is also needed on the drastic decline in the capacity of the pharmaceutical industry to innovate, in spite of the availability of new powerful scientific and technological tools. Changes in the industry's structure, the focus on highly profitable products and a relaxation of the requirements of patentability, contribute to explain the industry's emphasis on the emulation or modification of existing products rather than on the development of genuinely new compounds. The report addresses but has not sufficiently elaborated on the profound distortions currently observed in the functioning of the patent system, which allows the proliferation of pharmaceutical patents on trivial developments that are used to obstruct generics competition.

The coverage in the report of a broad set of issues ranging from discovery to delivery –which we personally did not favour – has led to the consideration of issues that are not central to the Commission's mandate and for which reliable evidence is limited. One case in point is companies' donation programs. Data on quantities, duration and other conditions of supplies, and the implications for the sustainable access to medicines need to be better examined in the appropriate context.

We regret the Commission was not able to elaborate in more detail proposals for mobilizing the financial resources and the scientific talent, particularly that available in developing countries, necessary to address the diseases that predominantly affect the poor. This report will fulfill its objective, however, if it helps WHO member countries and other stakeholders to set R&D priorities and develop a global sustainable framework to respond to that imperative.

Carlos Correa and Pakdee Pothisiri

Trevor Jones

The report contains much thoughtful and useful material which I am sure will be influential in shaping future policy and helpful to a wide group of stakeholders. Whilst I support a large proportion of report, it contains a number of proposals with which I do not agree for the reasons outlined below.

The report implies a direct link between patent ownership, product price and access in the developing world. Patents rarely confer a monopoly in a therapeutic field and are not the basis for price setting. Companies set prices largely on the ability /willingness to pay, also taking into account the country, the disease and regulation. They differentially price by country/market, offer volume-based (competition law compliant) discounts, tier prices between and within countries depending upon public or private market supply, have schemes for the medically indigent and operate company/consortium donation schemes.

Concerning access, patents are not the issue but the overwhelming poverty of individuals, absence of state healthcare financing, lack of medical personnel, transport and distribution infrastructure plus supply chain charges which can make affordable originator or generic products unaffordable. In many countries, medicines are unaffordable from whatever source, price or patent status e.g. medicines in the WHO Essential Drugs List which are now virtually all out of patent, cheap, generic products are not available to the majority of the poor. The word “price” is used in the report without qualifying whether this is the originator or generic company list price, or price to the patient /purchaser including taxes, tariffs, supply chain mark-ups etc.

The report calls for further reform of the “patent system”. There is a need to improve the competence of patent agencies and enforcement procedures in developing world countries but the basis for granting a patent and the TRIPS agreement do not need reform, especially following the WTO General Council resolution of December 6th 2005.

The report calls for further action on the patenting of “upstream” technologies. In reality this is not a problem; *vide* the recent NAS report on this issue.

The report confuses so-called “evergreening” with incremental innovation which is the lifeblood of medical progress and requires strong IPR to stimulate further innovation. The suggestion that PPP’s seek breakthrough products rather than incremental innovation as compared to the industry is simply wrong and fails to understand both the reality of their portfolios and the process of drug discovery and development.

The report proposes that companies should avoid filing or enforcing patents in developing countries. Companies do not patent in countries where there is an insufficient market and where enforcement is not possible. This does not mean that they will not then make those products available there at appropriate prices.

The report assumes that compulsory licensing will increase access. Companies can and do retain IPR whilst making alternative arrangements for access to their know-

how/ products. Countries should have the right to enact TRIPS-compliant compulsory licensing but should only use this when all other reasonable steps have been taken.

Trevor Jones

Fabio Pammolli

I. Developing countries and health policy: The need for a taxonomy

The term “developing countries” encompasses very different countries, which experience different levels of economic development and disease burdens.

In order to design solutions that have relevance in different national and local settings, relevant macroeconomic and institutional features need to be taken into account.

The analytical work that should be performed to assess which policy is relevant to which type of developing country is not fully articulated in the report. There are attempts in the report to introduce such a taxonomy, but it is not adequately used as a basis for policy recommendation. As for intellectual property rights, an undifferentiated recommendation, as the one that the reader might infer from the report, that all developing countries should lower IP standards, is not supported by analysis.

II. On Patents, Access, and Competition

As for the relation between patents and access, the following issues should have been articulated further:

- (i) Patent protection per se does not create monopoly positions in the final market. The legal definition of a relevant market for competition purposes in pharmaceuticals is a difficult and case-specific analysis.
- (ii) The patent status of pharmaceutical products does not prevent such products from being subject to either procurement schemes (formularies, tenders, buyer groups, etc.), or to direct price controls (administered prices, reference pricing schemes). Such prevalent policies in the vast majority of countries qualify the link between patent status and price levels.
- (iii) Countries that do not protect pharmaceutical patents do not necessarily experience higher rates of access, even if generic products are manufactured locally.

In general, a more systematic reference to the nature and extent of coverage and procurement schemes in pharmaceuticals and health care would have better served policy making, with a higher emphasis on the responsibility of governments and international agencies in designing solutions that can promote access, delivery, and public health.

Fabio Pammolli

Hiroko Yamane

The CIPIH contributed significantly to the international dialogue among hitherto scattered or divided groups, and created solidarity to find solutions for those who suffer from many diseases in developing countries. I share this solidarity which constitutes the basic consensus of the report.

A wealth of important information has been gathered by the CIPIH. To shed more light on current controversies on the role of patents in health policies, however, the report should have provided more evidence-based analyses of different patent policy options for developing countries, considering both their short and long-term consequences.

The Report does not analyze the role of patents in different types of developing countries (levels of development, burden of diseases, research or manufacturing capabilities etc.) in the context of their markets and industrial policies. The recommendations cover drug discovery, development and access for all Types I, II, and III, indiscriminately. Nowhere is there a clear picture of what types of medicines (old or novel) are actually needed, and which policy tools and incentives are specifically required. More attention should have been given to Type III (truly neglected) diseases which offer no commercial incentive.

The actual level of patenting, the scope of protection and the effects of such factors on price and competition were not adequately examined. Instead of collecting empirical data, the report relies on the untested assumption that relaxing IPR rules will generally benefit developing countries. The assignment of intellectual property rights, however, may lead to more efficient use of resources (information etc.) and licensing can promote the transfer of technology into the local economy. Furthermore, small patents around basic technology can work as a barrier against monopolization and help local businesses or applied research enter the market.

The report advocates “pro-competitive policy” at both ex-ante and ex-post patenting phases. However, it omits the important fact that ex-ante control is problematic, as linking correctly patentability (or patent scope) to competition in future technology or product markets is impossible.

Patents do not necessarily confer significant market power in developed countries, and the price of a drug often depends on other factors (therapeutic substitutes or price regulation). In developing countries, the real issue may be the absence of reasonable substitutes due to other factors (small market, insufficient health cover, types of quality or price control, existence of patents in developed countries, etc.). The report did not analyze the effects of patents on competition in any pharmaceutical markets in developing countries and left for future studies to explore.

In the absence of an international definition of “anti-competitive behaviour”, competition law can be applied in a non-transparent and arbitrary manner. The report should have indicated possible consequences of adopting recommended policy tools on the entry of drugs, investment and ultimately the access and innovation.

It is my hope that further analysis and study will be given to better understand these points.

Hiroko Yamane