The Pharmaceutical Innovation Platform

Sustaining Better Health For Patients Worldwide

International Federation of Pharmaceutical Manufacturers Associations
Table of Contents

Foreword 5

Executive Summary 7

Chapter I
Medicines Innovation: 11
Its value and contribution to public health

   The Value of Medicines Innovation 11
   How Much More Innovation is Needed? 12
   Measuring the Impact of Innovation 14
   Summary Points from Chapter I 19

Chapter II
The Delicate Balance: 21
Conditions for success in pharmaceutical R&D

   Understanding the Pharmaceutical R&D Process 21
   Rising Development Costs 24
   Political and Societal Challenges to Drug Development 26
   The Unique Role of the R&D Pharmaceutical Industry in Innovation 27
   Summary Points from Chapter II 31

Chapter III
The Pharmaceutical Innovation Platform: 33
Ensuring a sustained flow of new medicines to patients

   The Enabling Environment for Innovation 33
   Critical Pillars of the Pharmaceutical Innovation Platform 34
   Balancing Government Policies in Support of PIP 43
   Summary Points from Chapter III 44

Chapter IV
Spreading the Benefits of Medicines Innovation: 45
Partnerships and enlightened industrial policy

   Identifying Health Problems of Developing Countries 45
   The Pharmaceutical Innovation Platform for Developing Countries 48
   Need for Complementary Solutions to R&D 49
   How Can Developing Countries Be Involved? 50
   Summary Points from Chapter IV 52

Conclusions and Policy Recommendations 53

References 56
Global progress in addressing people’s health needs over the past century has been nothing short of spectacular. Many factors have contributed to this improvement, but one has been particularly critical: advances in medical technologies from the private sector. New medicines, vaccines and medical tools have revolutionized medical practice, making many fatal ailments curable or treatable, and significantly improving the quality of life among patients suffering from chronic diseases. Pharmaceutical innovation is at the heart of this progress.

‘Pharmaceutical Innovation Platform: Sustaining Better Health Worldwide’ is a new report from IFPMA that offers an in-depth investigation of the complex nature of the process of medical innovation. Critical resources, know-how and skills must be mobilized and managed efficiently in a high-risk environment, over a long period of time, to yield a new, innovative medicine.

New medicines are needed dramatically to address the increasing health needs and expectations of patients in every country of the world. This report helps identify various important challenges facing pharmaceutical innovation today.

The research-based pharmaceutical industry has a proven track record of bringing innovative products to patients - most drugs and vaccines in the history of modern medicine, which have revolutionized public health worldwide, have emerged from the creative and persistent efforts of this industry. Yet, the success of pharmaceutical innovation is determined largely by a mix of various public policies and regulations. This report describes the critical environment - the Pharmaceutical Innovation Platform - in which pharmaceutical companies operate and how it has a significant influence on their ability to respond to public health needs and bring new medicines to patients around the world. An informed understanding of the Pharmaceutical Innovation Platform among policy makers and public health stakeholders will help in formulating appropriate policies that will support and sustain pharmaceutical innovation, thus ensuring its continuing contribution to improving people’s health worldwide.

Many individuals have contributed to this report, providing invaluable expertise and comments. Among them, it is appropriate to single out William Looney, Senior Director, Global Policy at Pfizer, and Maciej Gajewski, Policy Research Analyst at IFPMA, without whose key contributions this report would not have been possible.

Raymond V. Gilmartin
President, IFPMA
Executive Summary

The Value of Medicines Innovation

Pharmaceutical innovation is a vital part of improving and saving lives around the world. New medicines, vaccines and other medical tools have revolutionised medical practice in the past century, leading to incredible health improvements. Indirectly, these medical technology advances have contributed to economic and social development, by building healthier and more productive societies.

Innovative medicines do not only benefit patients but are an important element of well-functioning healthcare systems. By bringing novel solutions to resolving different public health problems, new medicines enable more efficient allocation of resources, leading to savings in healthcare sector. For example, use of many modern therapies has led to a significant reduction in hospital stays and surgeries, resulting in important financial savings for healthcare systems.

The need for further pharmaceutical innovation is clear and dramatic – improvements in health around the world depend upon this innovation. Faced with evolving public health needs associated with such global phenomena as the aging of societies, epidemiological transition, growing drug resistance for infections or ongoing evolution of viruses, bacteria and microbicides, ensuring the continuity of medicines innovation is in the best interest of mankind.

Conditions for Success in Pharmaceutical R&D

The process of innovation is very complex, lengthy and indeed fragile in nature – the odds are almost overwhelmingly against actually bringing a new and successful medicine to patients. Due to its expertise and experience, the research-based pharmaceutical industry has been able to consistently bring forward new and vitally-needed medicines.

More than 100 new therapies have been approved by US, European and Japanese authorities since 1999 alone. Pharmaceutical companies discovered and developed all the most important medicines in use, many of which are considered as the greatest miracles of medicine. This innovative drive has only been strengthened over time, and the pharmaceutical industry has never had so many drug and vaccine candidates in its R&D pipeline, as it does today. More than 7,300 compounds are currently under discovery and development within the industry.

Many players are involved in the R&D process. The role of basic research is particularly important in that it contributes to understanding basic and clinical biology that help to guide further research toward producing a cure or a therapy. However, by virtue of critical resources, know-how, skills and capacities needed in the drug discovery and development process, the research-based pharmaceutical companies are the most important contributor. No other organizations or groups are able to effectively support and manage the entire pharmaceutical value chain, from discovery, through development, market approval and distribution. While others may be able to contribute to certain valuable aspects of the drug development process, it is the pharmaceutical industry’s expertise and experience in managing the entire process which is key to successful drug development.
The Pharmaceutical Innovation Platform

The pharmaceutical industry’s successful record in medicines innovation is determined by skills, resources and capacities of individual companies, but also to a significant extent by the external environment. The latter depends on a variety of government policies, and is referred to in this report as the Pharmaceutical Innovation Platform (PIP). The PIP is composed of four critical pillars characterised in the following way:

SUCCESSFUL HEALTHCARE SYSTEMS
» Efficient medical delivery and distribution systems
» Overall healthcare culture and policies promoting innovation
» Strong patients groups
» Good access to pharmaceutical information

EFFICIENT MARKETS
» Healthcare expenditures seen as investment, not cost
» Realistic assessment of the role of pharmaceuticals in improving healthcare, including the real value of incremental innovation.
» Efficient and transparent pricing and reimbursement decision-making process
» International price variations

EFFECTIVE USE OF INTELLECTUAL PROPERTY
» Effective enforcement of intellectual property rights
» Sufficient and respected market exclusivity periods
» Prevention of parallel trade

ADEQUATE AND PREDICTABLE REGULATORY REQUIREMENTS
» Stable and predictive regulatory environment
» Cooperation between regulators and industry
» Swift and transparent drug regulatory approval process
» Global harmonisation of regulatory requirements
» Adjustment of regulatory requirements to advances in science and technology

The specific character of these four pillars makes the industry particularly vulnerable to the effects of government policies. The relationship between the industry and governments is very important as policies intended to address other public priorities may in fact cut away at the basis of innovation. Often, restrictive government policies such as price controls or weak intellectual property rights do not take into account longer-term distorting effects of these policies on the pace of medicines innovation, and as a result their negative impact on public health as well as the social and economic status of society.

Thus, it is extremely important for decision-makers to understand the realities behind pharmaceutical innovation. An appreciation of the complexities of innovation and the factors which are vital for pharmaceutical companies to successfully continue innovating will alert decision-makers as to the possible, unintendedly negative, consequences of their policies. By drafting policies which support the pillars of innovation, decision-makers will be able to effectively encourage such innovation and promote the improvement of public health in their countries.

Spreading the Benefits of Innovation

This process is not only valid for industrialized countries, but in developing countries as well, particularly those leading developing countries which have the capacity to develop their own R&D-based pharmaceutical and biotech industries. Indeed, experience in Korea and similar countries shows that an innovative industry can be stimulated and encouraged by promoting the pillars of innovation.
Innovation efforts in developing countries can also be important for undertaking research on diseases and conditions which particularly affect them, including the “neglected diseases” which require further R&D than is currently being undertaken. Partnerships among established R&D companies, local R&D companies, international organizations, and local governments can be effective ways to harness the expertise of the various partners to find new treatments and cures for diseases which primarily affect poor countries.

Healthcare, science and medicine challenges are global – all parties need to collaborate to meet these challenges effectively. Innovation is the vital element in this effort: when the public sector, industry, and civil society pull together to promote innovation, public health improves and lives are saved. Indeed, pharmaceutical innovation creates real benefits for public health, such as new cures for once-fatal diseases, an increased understanding of the mechanisms of chronic conditions, and improved treatments for diseases and conditions, leading to better health outcomes, improved quality of life and a more productive society overall. Better understanding of the realities of medicines innovation among all public health stakeholders, and government policy makers in particular will make the world a better and healthier place for the world’s people and for future generations.
The Value of Medicines Innovation

Innovation is the driving force for progress in health care. Leading edge science and strong private sector competition have given birth to a revolution in new health technologies. These are transformed through rigorous testing into medicines, vaccines, devices and diagnostics that can be used safely in diverse patient populations.

Innovation begins with invention and depends on initiative, which is in turn driven by the incentives that engage the private sector in pursuit of a social welfare objective: better health for all. By developing the vast majority of new medicines on the market today, the private sector has created a unique – yet fragile – model for innovation that carries with it practical consequences for the management of the burden of disease.

The result has been a revolution in the state of global public health. Health-related technology improvements led by the introduction of new medicines are estimated to have reduced human mortality by upwards of 50 per cent between 1960 and 1990. Both developed and developing countries have shared in this benefit. All regions have made progress in human development in the past 30 years, and the number of people living in low human development countries has dropped by more than half, from 1.1 billion in 1975 to 500 million in 1999. For example, increased global immunisation coverage, reaching 80-90 percent of infants in the late 1990s, has had a significant impact on the infant mortality rate, which over the last 25 years fell by 50 percent in least developed countries. Thus, pharmaceutical innovation has been an important factor in helping governments attain their overall healthcare policy goals.

The role that health innovation plays in keeping the patient one step ahead of the changing profile of disease is even more critical today, as global demographic changes lead to older populations suffering from the twin burden of chronic non-communicable ailments and the rise of new infectious pathogens resistant to established therapies.

Health care innovation is also a key measure of economic productivity and adds value to a range of other technology applications, from information processing to manufacturing and materials management. In most industrialized countries, health care is among the largest sectors of economic activity. This trend will accelerate as populations age and the demand for health care services increases.

Innovation linked to new medical technologies has thus become an important source of competitive advantage, especially in the emerging field of life sciences – a key driver of economic growth.
in the 21st century. There is strong evidence that the overall pace of innovation is set by the pharmaceutical industry: only a few industrial sectors devote significant resources to research, and the R&D based industry leads the way in terms of funds spent as a percentage of sales (Figure 1).

**Figure 1. R&D Intensity as a Proportion of Total Sales**

![Diagram showing R&D intensity as a percentage of total sales for various industries.](image)

Source: The Department of Trade and Industry, Research and Development Scoreboard 2003

The critical question is whether this incredible pace of medical innovation can be maintained. If there is one lesson to be learned from the growth of the biopharmaceutical industry since the 1899 discovery of aspirin – the first wonder drug – it is that innovation can never be taken for granted and needs to be encouraged through enlightened public policy choices that balance risk with incentive. In many ways, the state of innovation today tells us what we can expect the status of health in society to be tomorrow.

**How Much More Innovation Is Needed?**

The World Health Organization estimates that out of more than 5,000 identified diseases, the number of disease genes discovered so far is 1,253 and the molecular characterization of clinical disorders exists for more than 1,700 diseases. Even for those diseases with relationship to disease genes, the molecular sequences needed to design a drug are largely unknown. That leaves a significant number of medical conditions whose origins are unknown and which consequently lack appropriate treatments.

Furthermore, emerging and evolving health threats are a continual challenge. The SARS crisis is the most recent example of how diseases keep extending their boundaries. Since 1970 the world has seen more than 30 new viral and bacterial diseases, and in the 1990s alone, more than 30 emerging and re-emerging infectious epidemics affected the entire world.

Health needs of developing countries are also changing with time. For example, disease patterns are converging between rich and poor countries. The global trend towards ageing populations has made cardiovascular diseases the leading cause of mortality in many developing coun-
tries, and diabetes is also gaining importance. Chronic conditions that disproportionately afflict the aged require substantial R&D efforts in order to provide satisfactory treatments and thereby reduce overall cost of these diseases.

Pharmaceutical innovation is also required to address resistance to existing therapies. In the US and Europe, resistance of the AIDS virus to the latest anti-retroviral (ARV) drugs is reaching as high as 30% in some populations.\textsuperscript{12} Drug resistance is also growing in developing countries plagued by infectious diseases such as malaria\textsuperscript{13} and TB\textsuperscript{14}. Counterfeiting exacerbates the problem, and is particularly dangerous for the anti-retroviral therapies used to treat AIDS. In a recent example, Nigeria was forced to temporarily suspend imports of a number of essential medicines after discovering up to 80 per cent of the imported volume was counterfeit\textsuperscript{15}. Another example comes from a study undertaken in seven African countries by the World Health Organisation which found that ingredient failures of two essential antimalarial products reached almost 70 per cent in some cases.\textsuperscript{16}

\textbf{Figure 2. The Status of Current Medicines: Continuous Need for Medicines Innovation}

Figure 2 illustrates that the pharmaceutical industry has developed treatments for most major disease categories. However, the need for new innovative medicines could not be greater today. The increasing problems with drug resistance mentioned above, as well as the imperfections of existing medicines, including side-effects, and the lack of preventive and curative medicines for major conditions - all highlight the importance of medicines innovation in the future.
Measuring the Impact of Medicines Innovation

The impact of pharmaceutical innovation is most notable in three key areas:

- Benefits for patients and healthcare systems
- Contribution to economic prosperity and development
- Enabling the existence of generic pharmaceutical industries

Benefits for patients and healthcare systems

Pharmaceutical innovation has had a positive impact on health as well as spurring related improvements in productivity and economic growth. The societal and individual benefits arising from effective drug treatment far outweigh the monetary costs of the medicines themselves. Moreover, for millions of patients many diseases are now classified as chronic rather than life threatening due to advances in drug delivery and treatment.

New drug therapies have allowed patients to continue to work and lead productive lives. A 1998 paper published by the US National Bureau for Economic Research found that the introduction of new “priority” drugs between 1970 and 1991 not only increased the mean age at death for the US patient population — it also raised lifetime income levels by about 0.75 to 1 per cent per annum, representing a substantial additional contribution to economic growth. Similarly, new cancer drugs increased the life expectancy of American patients diagnosed with cancer by about one year from 1975 to 1995, implying that new cancer drugs accounted for more than 10 per cent of the overall increase in life expectancy at birth in the same period in the US. In terms of improved quality of life resulting from these new therapies, the impact has been even more significant.

The bottom line for patients is access to treatment for previously untreatable conditions. Only four years after the discovery of HIV, the first drug to ameliorate symptoms of AIDS was launched and since then four new classes of antiviral drugs have been developed, with more than 80 new drugs now in clinical trials. According to recent estimates, death rates from AIDS have plunged by 80 per cent since widespread introduction of advanced antiretroviral therapies in the US and Europe in the mid 1990s. The impact of innovation is also well illustrated by cardiovascular diseases. In developed countries, mortality rates due to cardiovascular diseases decreased substantially, often exceeding 50 percent over the last thirty years. For example, the prevalence of ischemic heart disease and hypertensive heart disease has declined by roughly 70 percent in the same period.

This radical reduction in mortality rates correlates with the introduction of breakthrough therapies for cardiovascular diseases; there is significant evidence that these therapies influence both the disease prevalence rates and mortality (Figure 3).

Changing Death Sentence to a Chronic Condition

Esther Banyaditse is a woman with HIV, living in Gaborone, Botswana. She discovered she was HIV positive in February 2002. Esther became very ill, with sores, migraine headaches, and terrible body pains. When she was finally tested for HIV, her CD4 count was 160, meaning she had AIDS. She started ARV treatment at the Princess Marina Hospital, the first ARV therapy clinic in the country, and now has a CD4 count of 227.

‘People have been coming up to me asking what my secret is, because my health is so much better. I tell them I have AIDS but I’m on ARV therapy.’

Medicines and vaccines have made significant contributions to treating and curing diseases and improving patients’ quality of life.

This dramatic improvement in saving lives and health came about through both radical and incremental innovation. Pharmaceutical companies generate innovation in health needs by inventing new treatments for previously untreated health problems (radical innovation) and also developing new or improved uses for existing therapeutics (incremental innovation). The latter is crucial because the process of pharmaceutical innovation, just like any other innovative process, is built on constant improvements. This applies not only in biological sciences but also in physics, mathematics, engineering and about every human endeavour.
Chapter I - Medicines Innovation

Often underestimated, these incremental innovations significantly improve health and quality of life, by providing patients with more choice, better risk tolerance, easier dosing and administration, and fewer side-effects.

By developing second or third drug in a therapeutic class, the industry has managed to significantly improve original products, creating therapeutic classes that offer multiple agents that provide for alternative treatments often at a lower price, or can serve as back-ups in case of drug withdrawal from the market. The results in terms of efficiency and patient responsiveness add up to one outcome: better value for money (Box 1).

Faced with limited resources, public health authorities around the globe need to make difficult choices when it comes to the types of treatments they will cover. Pharmaceutical innovation is an ally in this process because of the savings that accrue to payers. Adoption of new treatments often leads to reduced hospital stays and eliminates the need for costly surgical interventions. One study found that replacing an older medicine with one 15 years newer increases drug costs by an average of $18, but reduces hospital and other non-drug costs by $129, meaning that for each additional $1 spent on newer pharmaceuticals, $6.17 is saved in total health spending.


Bring New Hope

An estimated 250,000 women in North America alone are affected by breast cancer. These women normally undergo surgery, followed by chemotherapy. Then comes ‘adjuvant’ treatment with tamoxifen — a drug which dramatically improves a woman’s odds of remaining cancer-free, but which is only beneficial for five years. Now a new drug is clinically tested with very promising results.

‘When you get the initial diagnosis, it’s scary facing your mortality. Then, coming to the end of tamoxifen it’s frightening again’, says Kathy Anderson, a Canadian elementary-school principal who took part in a clinical trial of a new ‘adjuvant’ treatment. ‘These results send a message of hope – I’d hope that all women would have a chance at this standard of care.’

Figure 3. Benefits of Selected Medicines in the Treatment of Cardiovascular Diseases

drugs – proton pump inhibitors – in the late 1980s, the management of peptic ulcer diseases has been revolutionized. For example, in Sweden, from 1956 to 1986, elective surgical operations for peptic ulcers steadily declined from 72.1 to 10.7 per 100,000 inhabitants. Similar changes can be observed in other countries24.

At the same time, many recent innovations encompass a long-term “pay off” because they delay the transition from a chronic treatable condition to more costly acute care. Viewed in these terms, the more technologically sophisticated a product is, the less one pays for treating a disease. If the first generation of a treatment may move therapy from symptomatic to a “half way” technology status (with limited benefits to patients and healthcare systems), the next generation of a treatment will likely make a disease manageable and reduce treatment costs significantly25.

Innovation is cost-effective and helps save money for the health system overall.

Box 2 illustrates different forms of economic benefits from the application of innovative medicines, including restored lifetime earnings, avoided treatment and healthcare costs, and avoided disability. It is worth noting, however, that some drugs improve the quality of people’s lives even as they produce a potential rise in costs, thus creating an important dilemma to public health policy makers.26


Box 1. Benefits of Incremental Innovation

New formulations with extended indications
Reformulated drugs provide improved safety and efficacy, and extend the range of indications in the original therapeutic area. For example, new formulations of antibiotics, originally limited to parenteral use only, such as oral preparations or inhaled use resulted with extended indications in Bowel preparation, hepatic coma, skin, eye and ear infections, or cystic fibrosis.

Availability of different agents in one therapeutic class
Multiple medicines in one therapeutic class offer various advantages. For example, for central diseases nervous system, where overall response rates to medicine are 50 percent or less, patients who fail to respond to one drug, often respond to another agent of that class.

Improved dose delivery systems
Advanced delivery systems such as transdermal delivery, delayed-onset extended-release oral formulation, liposomes, or polymers provide sustained therapeutic drug levels for longer periods of time. They also enable smaller or fewer doses, a less invasive mode of administration, and prolonged circulation of short-lived compounds.

Incremental innovation leads to cost savings
An example of incremental innovation, such as the introduction of controlled-release dosage forms for cardiovascular therapies, significantly improves treatment compliance and implies lower aggregate healthcare costs linked to reduced physician, hospital and laboratory interventions.
Chapter I - Medicines Innovation

Contribution to economic prosperity and development

The innovative pharmaceutical industry is a key element of the global knowledge economy. R&D-based pharmaceutical companies accounted for 10 percent of the total of OECD member countries R&D budget estimated at $450 billion across all sectors in 2001. In some countries, such as Denmark or the United Kingdom, the share of the pharmaceutical industry in total business enterprise R&D exceeds 20 percent.

In a broader perspective, both private and public investment in life sciences and development of related technologies is widely recognised as a key engine that will drive and determine economic prosperity in the long term.

Pharmaceutical R&D also represents a major contribution to broad health research. The 2001 report of the WHO Commission on Macroeconomics and Health correctly notes that development cannot take root without this kind of broad-based investment in health. For economies as a whole, the rates of return on investments in health and health research significantly outscore investments in other sectors of economy. The benefits of better health for an economy are enormous and include increased production, a more productive labour force, greater competitiveness in the economy, lower unemployment, higher tax revenues, and as mentioned before, a sounder public finance situation.

The R&D-based pharmaceutical industry is the biggest non-public investor in health research worldwide. In 1998 it accounted for 42 percent of the global health research budget which includes support from public sector sources. Total R&D expenditures by pharmaceutical and biotechnology companies in 2002 reached almost $50 billion; in the US alone, the industry spends almost 50% more on health research than the National Institutes of Health (NIH) – the biggest public health research organisation in the world with a total 2003 budget of over $27 billion.

Pharmaceutical innovation also creates favourable conditions for the growth of other high-tech sectors. For example, in the US, large pharmaceutical companies now account for almost one-quarter of all biotech investment, i.e. three times more than the entire venture capital investment in this sector. At the same time, the biotech industry generates about half of its revenue from licensing to large drug firms, up from 10-20% just a few years ago. Such interdependence

**Box 2. Potential Economic Benefits of Innovations in Pharmaceuticals**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>Economic Benefit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic retinopathy and blindness</td>
<td>Glucose-lowering drugs</td>
<td>$1.2-1.6 billion in avoided disability</td>
</tr>
<tr>
<td>Acute lymphocytic leukaemia (ALL)</td>
<td>Anticancer drugs</td>
<td>$1 billion due to restored lifetime earnings</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>Curative therapy for <em>H pylori</em></td>
<td>$760 million in avoided treatment costs</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>Estrogen therapy</td>
<td>$333 million in avoided long-term care</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Antipsychotic drugs</td>
<td>$148 million in annual direct and indirect costs</td>
</tr>
</tbody>
</table>

* Based on the US data


**Contribution to economic prosperity and development**

The innovative pharmaceutical industry is a platform for high tech industrialization, creating momentum for economic development.
The Pharmaceutical Innovation Platform spreads to a wider range of players and institutions, actively contributing to R&D activities in the medical devices sector, advanced genomics, IT and chemicals.

Many developing countries understand the importance of innovation driven industries, including pharmaceuticals, for future economic growth. For example, life sciences innovation is a centrepiece of long-term industrial policy blueprints now being implemented by governments in India, China and Korea, as well as other markets (Box 3).

Enabling the existence and growth of generic pharmaceutical companies

The right to manufacture a drug developed through private sector pharmaceutical R&D comes immediately after patents have expired – often even before. This provides an essentially free asset for generic companies. The downstream financial value of such products is enormous. Major patented products, currently selling over $1 billion worldwide, for which patents will expire within the next five years, are worth $80 billion in projected sales.

Furthermore, the effective patent life is shorter due to tougher regulatory approval requirements before launch and other factors. The time an inventor actually benefits from a patent – while the product is available for sale – is as short as 6.5 years today, compared with 10.8 years in 1997 (Box 4).

All this provides fantastic growth opportunities for generic companies, which are estimated to maintain the double-digit growth in the coming years. However, the apparent success of the generic industry is only possible thanks to the actual invention and rigorous testing by research-based pharmaceutical companies. Innovative medicines are like blood in the veins of generic industry without which it would not simply exist. If the process of innovation were to stop, i.e. no more new medicines were developed; generic industry would become another ‘commodity’ sector such as steel, corn or chemicals sectors – uncompetitive, with indistinguishable products, and no growth and profit opportunities.

Having succeeded in attracting manufacturing industries, countries such as South Korea, Taiwan, and Singapore are now moving toward the knowledge economy. Science and technology policies in these countries are creating a positive environment for investment in technology-oriented industries, including biopharmaceuticals.

In Singapore, a Ministerial Committee was established in 2000 to work with leading international experts in the biomedical industry to create a Singaporean research-based pharmaceutical industry. So far, virtually all big pharma companies are present in Singapore, with a few companies already investing in R&D, and many more running various development activities.

In South Korea a large-scale program was launched in 1994 to place Korea’s biotechnological capabilities at globally competitive levels by 2007. Total investment is estimated at $15 billion, 60 percent of which will come from the private industry.

**Box 3. Investing in Pharmaceuticals**

Having succeeded in attracting manufacturing industries, countries such as South Korea, Taiwan, and Singapore are now moving toward the knowledge economy. Science and technology policies in these countries are creating a positive environment for investment in technology-oriented industries, including biopharmaceuticals.

In Singapore, a Ministerial Committee was established in 2000 to work with leading international experts in the biomedical industry to create a Singaporean research-based pharmaceutical industry. So far, virtually all big pharma companies are present in Singapore, with a few companies already investing in R&D, and many more running various development activities.

In South Korea a large-scale program was launched in 1994 to place Korea’s biotechnological capabilities at globally competitive levels by 2007. Total investment is estimated at $15 billion, 60 percent of which will come from the private industry.

**Box 3. Investing in Pharmaceuticals**


Enabling the existence and growth of generic pharmaceutical companies

The right to manufacture a drug developed through private sector pharmaceutical R&D comes immediately after patents have expired – often even before. This provides an essentially free asset for generic companies. The downstream financial value of such products is enormous. Major patented products, currently selling over $1 billion worldwide, for which patents will expire within the next five years, are worth $80 billion in projected sales.

Furthermore, the effective patent life is shorter due to tougher regulatory approval requirements before launch and other factors. The time an inventor actually benefits from a patent – while the product is available for sale – is as short as 6.5 years today, compared with 10.8 years in 1997 (Box 4).

All this provides fantastic growth opportunities for generic companies, which are estimated to maintain the double-digit growth in the coming years. However, the apparent success of the generic industry is only possible thanks to the actual invention and rigorous testing by research-based pharmaceutical companies. Innovative medicines are like blood in the veins of generic industry without which it would not simply exist. If the process of innovation were to stop, i.e. no more new medicines were developed; generic industry would become another ‘commodity’ sector such as steel, corn or chemicals sectors – uncompetitive, with indistinguishable products, and no growth and profit opportunities.
**Chapter I - Medicines Innovation**

**Box 4. Average Patent Exclusivity Periods for NCES Approved during 1997-2001**

<table>
<thead>
<tr>
<th>Year</th>
<th>Shortest Durationa</th>
<th>Longest Durationb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>10.8</td>
<td>13.4</td>
</tr>
<tr>
<td>1998</td>
<td>13.0</td>
<td>15.0</td>
</tr>
<tr>
<td>1999</td>
<td>8.6</td>
<td>10.2</td>
</tr>
<tr>
<td>2000</td>
<td>8.3</td>
<td>11.9</td>
</tr>
<tr>
<td>2001</td>
<td>6.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Average, 1997-2001</td>
<td>9.8</td>
<td>12.3</td>
</tr>
</tbody>
</table>

*a* Average number of years between the NDA approval and the earliest possible patent (or exclusivity) expiration.

*b* Average number of years between the NDA approval and the latest possible patent (or exclusivity) expiration.


---

**Summary Points from Chapter I**

- Continued medicines R&D is necessary not only for improved treatments, but also to address the many conditions that currently lack an adequate therapeutic option.

- Innovative medicines have created dramatic improvements in saving lives and treating diseases and conditions.

- Innovative drug therapies contribute to efficiencies in patient care, enhancing quality while reducing or eliminating the need for more costly treatments.

- Pharma R&D makes a substantial contribution to economic and social development by spurring advances in healthcare outcomes overall.

- New medicines developed by R&D firms create the building blocks for a vigorous generic drug industry, allowing for significant price competition.
Chapter II

The Delicate Balance

Conditions for success in pharmaceutical R&D

Understanding the Pharmaceutical R&D Process

Risk is the fundamental element in pharmaceutical R&D. It is not enough to discover a promising compound. Success actually depends on minimizing the time and associated costs to bring a compound forward from a scientific ‘idea’ from basic research, to discovery of a compound, through development, to final regulatory approval. It is the private sector that has the cumulative knowledge and resources to successfully manage this risk, as evidenced by the industry’s consistent track record in introducing medicines currently used by patients around the world (Box 5).37, 38

Many of these medicines are now available as inexpensive generics, with a proven record of cost-effectiveness in rich and poor nations alike. In support of this, it is worth looking at the WHO Essential Drugs List (EDL): 90 percent of the more that 300 products that comprise the list were developed by the R&D-based pharmaceutical industry for human use.39

The pharmaceutical industry, by virtue of its cumulative knowledge, technical skills and financial resources, is the engine of discovery and development of the vast majority of modern medicines.

Box 5. Most important treatments for major global diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Health burden (% of global deaths/DALYs)</th>
<th>Existing treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV / AIDS</td>
<td>4.9 / 5.7</td>
<td>All 21 drugs in 4 different therapeutic classes have been developed by pharmaceutical companies</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>6.9 / 6.3</td>
<td>All recent and effective antibiotics have been discovered and developed by pharmaceutical companies</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>29.3 / 9.9</td>
<td>All drugs in 8 different therapeutic classes have been discovered and developed by pharmaceutical companies</td>
</tr>
<tr>
<td>Cancer</td>
<td>12.5 / 5.1</td>
<td>All most effective drugs in 8 different therapeutic classes have been discovered and developed by pharmaceutical companies</td>
</tr>
<tr>
<td>Depression</td>
<td>0 / 4.5</td>
<td>All recent drugs in 4 different therapeutic classes have been discovered and developed by pharmaceutical companies</td>
</tr>
</tbody>
</table>

It is in the best interests of society to preserve the delicate balance that has brought so many breakthroughs to patients. After all, conditions that shape the initial discovery process for medicines are set in motion one to two decades before they reach pharmacy shelves. A host of intervening economic, technological and socio-political factors can affect pipeline flow in the interim. Pre-emptive regulatory and political pressures on the industry can thus be very damaging.

With the persistent uncertainty in managing R&D taken as a given, some observers contend that changing market and regulatory conditions, as well as a more challenging discovery environment, are negatively influencing R&D productivity overall.\textsuperscript{40, 41, 42}

The average cost of bringing a new product to market in the US, where most new medicines are invented today\textsuperscript{43}, is around $800 million in year 2000 dollars, a 2.5 fold increase over the average cost in 1990\textsuperscript{44}. This amount further increases if the post-market approval expense for assessing long-term safety and efficacy is included in calculations.\textsuperscript{45} In the past six years (1998-2003) 73 percent of drug approvals by the US Food and Drug Administration involved some form of postmarketing commitment by the company, compared with 25 percent in the period 1970-84.\textsuperscript{46}

At least half of these costs can be attributed to direct out-of-pocket expenditures borne by the innovative firm – i.e. investments that do not include costs of laboratories, buildings, equipment, etc. These direct costs of R&D have grown dramatically as a consequence of the average number of patients in clinical trials tripling since the early 1980s, to reach over 5,000 today. The number of clinical trials per new drug application (NDA) has doubled in the same period.\textsuperscript{47} In addition to lengthy development times (12 to 15 years), other major factors driving up costs are the need to invest in new information and processing technologies, and low success rates. Overall, the industry is seeking to defy the odds by putting more resources into R&D, and since 1995 it increased its R&D budgets by almost 75 percent, from $32 billion to almost $50 billion in 2003.\textsuperscript{32}

Despite the steady increase in R&D costs, the major pharmaceutical companies have continued to remain productive sources of science. The number of potential medicines in development by the end of 2003 was the highest ever, reaching more than 7,300 drug and vaccine candidates.
Yet despite this increase, the industry faces a challenge in that returns on the investments in R&D are only modestly above the underlying cost of capital. If the number of drug candidates has grown steadily over the last decade both in preclinical and Phase I and II clinical trials, no corresponding rise in the number of Phase III drugs have been observed, reflecting the growing number of costly late-stage failures.48

Figure 5 below clearly shows that medicines do not flow automatically from government-funded basic research, such as the identification of a gene for a specific disease. A great deal of work is required in applied research and development, which is allocated among basic research and efficacy, safety, compliance, medical and regulatory activities. The development process, which is different than discovery and takes the longest time to complete, starts only after a company has identified potential drug candidates.49 It is a very active process that requires substantial investments, specific technical expertise, detailed logistics coordination, and a considerable time frame.

Even at the later stages of this process, there is no guarantee of success. As Figure 4 also shows, only a tiny fraction – less than one per cent – of molecules that the industry has brought to patent actually make it to human trials. In fact, creating one successful drug requires on average the detailed study and screening of 1 million compounds and thousands of molecules.50 Late stage failures have increased as the demands of regulators become more stringent. Phase III failures went up from 30 percent to 50 percent in 2000,51 while the FDA sent back more than 21 products applications with requests for additional data in 2001.52 Such failures and the unanticipated costs they incur on the applicant (the company) means that fewer resources are available to be put back at the beginning of the pipeline, to finance promising leads. By way of example, between 1997 and 2001, 12 drugs with combined peak sales potential of more than $11 billion

---

**Figure 5. Process of Pharmaceutical R&D**

<table>
<thead>
<tr>
<th>R&amp;D Stage</th>
<th>Research &amp; Discovery</th>
<th>Preclinical development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Registration</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Activities</td>
<td>Drawing on basic exploratory research to identify targets, initial research on new compounds is carried out in the laboratory (high throughput screening, lead identification and optimization) to select the most promising compounds.</td>
<td>Successful compounds are then tested in humans in 3 phases of clinical trials:</td>
<td>If the results of clinical trials are satisfactory in terms of quality, efficacy and safety, a regulatory dossier is presented to the regulatory authorities for approval.</td>
<td>Post-marketing studies involving thousands of patients are initiated after the launch of the medicine, to identify any previously unforeseen side effects.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success Rate*</td>
<td>Less than 1%</td>
<td>70%</td>
<td>50%</td>
<td>50%</td>
<td>90%</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>4-6 years</td>
<td>1 year</td>
<td>1-1.5 years</td>
<td>1-2 years</td>
<td>2-3 years</td>
<td>1-2 years</td>
<td>Several years</td>
</tr>
</tbody>
</table>

* Success rates reflect the number of drug candidates that successfully pass through to the next R&D stage.
were removed from the market; in the same period, major companies terminated 28 product candidates with potential peak sales of more than $20 billion, in Phases II or III.\(^5\)

The conclusion shared by most experts is that pharmaceutical R&D is becoming more complex due to a combination of scientific, regulatory and political factors.\(^5\) These in turn ensure that costs to the innovator will rise, exposing even the largest and most integrated firms to a greater amount of risk. Analysts say that to maintain profit growth, pharmaceutical firms need to bring three new drugs to market a year, but since 2000, the top two firms have produced only three between them in the US market, which is the largest and most important pharmaceutical market.\(^5\)

Rising development costs

Arguably, one of the most serious challenges facing the pharmaceutical industry is how to handle ever-escalating costs without sacrificing the unique ability to produce innovative new medicines.\(^5\) Drug R&D has become more expensive overall because the number of biological targets has increased and the diseases being investigated are more complex and difficult to study. Furthermore, clinical trials require a progressively larger number of subjects and must frequently be conducted across borders — increasing the logistical difficulties and hence the costs.

However, while genomics is increasing the number of biological targets,\(^5\) and combinatorial chemistry and chemical libraries are raising the number of potential drug candidates,\(^5\) neither necessarily increases the prospect for positive matches between the two.\(^5\) Even when the genetic basis of an ailment is known, as is the case with Alzheimer disease, actually designing a drug that can stop progression of the disease can still take decades.\(^5\)

The potential for expensive failures at the clinical level is accentuated by the accumulation of non-validated targets. Some of this risk can be mitigated by a greater focus on strategies that draw out those drug candidates less likely to fail pre-clinical testing. While it may pay off, it also adds two years or more to the drug development timeline and thus significantly reduces the innovator’s opportunity to recoup these up-front development costs before the patent term expires.\(^5\)

New survey and testing technologies also require significant up-front investments. The life cycle of these technologies is shrinking, forcing R&D managers to spend more just to keep pace. The testing and diagnostic equipment that companies rely on to screen and identify promising compounds is superseded by technological advances every three to four years, compared to 10 years or more in the recent past, and there are more technologies available than any one company can invest in. The cumulative size of this investment is substantial. The top 11 pharmaceutical companies will collectively spend almost $7.4 billion on IT alone in 2005, up from $5 billion in 2000.\(^5\)
Phase II and III clinical trials involving human subjects are the main source of the rise in costs. They constitute the major component of the so-called ‘critical path’, i.e. the part of R&D process, which begins when candidate products are selected for development, and includes preclinical and clinical studies (Figure 6). Over the past decade, these costs have risen at a rate five times higher than that for pre-clinical costs. In 1998 alone, the industry spent $7 billion on clinical trials, i.e. more than one third of the R&D budget and this ratio has continued to increase ever since.

The US Food and Drug Administration (FDA) points out that many of the easy targets for drug development have already been identified and so the focus of R&D has shifted to development of drugs for complex, multi-symptomatic and multi-factorial chronic diseases. This requires clinical evaluations in larger patient groups and in longer studies. Diseases that have relatively modest physiological effects on relatively healthy people – such as depression – often require more complex and extended trials to obtain convincing positive results.

The FDA also notes that the escalation of development costs is due to the fact that scientific and technical tools utilised in the clinical development process to assess drugs’ safety, efficacy and quality are substantially outdated. This implies the difficulty, at any point, of predicting ultimate success with a novel candidate, and in particular, the inability to predict failures before compounds enter expensive human testing.

Two other factors inflate development costs. First, better scientific understanding of pharmacology and toxicology has led to demands for post-marketing commitments to study safety issues and ensure that drugs are cost-effective in the patient population. Second, regulatory require-
ments have changed. Regulatory agencies like the US FDA and the EMEA (European Medicines Evaluation Agency) now insist that applicants for drug approval submit larger databases to verify safety and document side effects in more diverse sub-populations, including children, women and the very old. The industry does not dispute the need for these developments, but substantial additional costs associated with these requirements need to be recognised.

Political and societal challenges to drug development

The pharmaceutical industry copes with various commercial and regulatory pressures within the context of a political climate that does not always recognize the importance of the industry’s leadership role in developing scores of life-saving drugs. Government cost-containment initiatives aimed squarely at the drugs budget and resulting in loss of confidence within the investor community raise questions about whether the innovative drive of the industry can be sustained.

This also leaves little room to address the special needs of the poor in countries with neither infrastructure nor the financing to capture the benefits of new medicines innovation. Indeed, very often no connection is made between the prices paid in advanced industrial countries and the capacity of the industry to meet the need for medicines in poor developing countries, where there is no capacity to pay at any price. Essentially, access for this group requires that medicines be either given away or priced below manufacturing costs — a long-standing practice of pharmaceutical companies.

Government cost-containment policies may have a significant negative impact on innovation investment decisions. For example, the advent of price-sensitive managed care practices in the US, combined with pressures on reimbursement in Europe and Japan, lie at least partly behind the decrease in regulatory submissions. In the mid 1990s, for example, US pharmaceutical companies took the view that managed care would reimburse only major breakthrough medicines, so the industry aimed for a higher level of risk and unprecedented disease targets - and failed more frequently.

There is a growing trend throughout the industrialized world to exclude from reimbursement those medicines judged selectively as “marginal improvements”. In some cases, payers now insist on a demonstration of a product’s cost-effectiveness even before it is placed on the market for actual use by patients. This can have a perverse impact on the choices an innovative company makes in allocating funds for development. It may force companies to limit investigations to the largest therapeutic areas instead of conditions where the science is most promising. Reliance on this and other punitive cost-containment tools has also restricted the growth of smaller biotechnology companies in Europe, while the industry has yet to establish a foothold in Japan. Patients suffer because the investment pool is necessarily much smaller and niche firms willing to invest in “orphan” diseases are at a huge financial disadvantage.

Misunderstandings about the real impact of patent protection are another source of external pressure on R&D. Some government decision-makers assume that high prices for medicines are attributable to patents, and thus they promote policies to weaken patent protection or reduce the effective patent life of a product as a means to reduce healthcare costs. Such policies ignore the fact that:

- Patents are in force on only about 30 to 40 per cent of the global prescription volume.
- Nearly all patented products in use today face competition from two to ten close substitute molecules able to treat the same condition— and frequently do so at a lower price than the originator.
- In least developed countries, patents exist only on less than 2 percent of medicines from the WHO’s Essential Drugs List.
R&D companies are thus subject to competitive rivals from both the innovative (during patent life) and generic (after patent expiry) ends of the commercial spectrum. The point is that while patent protection may provide a temporary period of exclusivity, it does not confer a monopoly. The ideas that comprise a patent filing are open to the public domain and competitors are free to use this information in developing variations to serve the same therapeutic need. Weakening patent protection will simply further reduce innovators’ capacities to finance additional research into new and innovative products.

The Unique Role of the R&D Pharmaceutical Industry in Innovation

Despite the difficult, risky, and expensive nature of pharmaceutical R&D, it is nevertheless important to note that the R&D-based pharmaceutical industry has been successful in overcoming these barriers to bring needed medicines to patients around the world. The world’s leading companies have collectively validated about 500 targets – the biological mechanisms through which drugs work. They have also created large compound libraries, containing as many as two million molecules apiece and providing for an invaluable source of new medicines. During the last 10 years, pharmaceutical companies have submitted more than 700 new drugs and vaccines for marketing authorization.

These achievements are particularly remarkable in light of the challenges facing R&D that show how difficult innovation can be to achieve in real-life conditions. Scientific, financial and political factors all have an important impact on the innovation capacity of the pharmaceutical industry. This is very important, as only the private sector has the specialist skills and broad knowledge base to successfully discover, develop and bring a promising compound to regulatory approval. The role of other stakeholders, such as government or academia, is complementary and highly valuable, but limited in terms of real market impact. Only pharmaceutical companies however, have the ability to manage the entire chain of R&D, starting with early discovery and research and moving forward to clinical testing, manufacturing, distribution and marketing (Figure 7).

The role of public sector health research in drug and vaccine R&D merits particular attention. There is much evidence that the existence of public research institutes leads to the generation of new technologies and provides critical manpower to the industry. For example, in Singapore, the 16 public research institutes have developed more than 70 new products and processes with the industry, commercialised more than 20 products, and trained more than 580 researchers.

In 2001, government direct support for health–related R&D in OECD countries was about $27.8 billion, or approximately 0.1 percent of their combined GDP. The level of public investment in health-related R&D differs from one country to another; in 2002, it represented well over 0.2 percent of GDP in the US but only 0.05 percent in the EU and 0.03 percent in Japan. Consequently, in terms of direct public support for health R&D, the US accounts for over 75 percent of the OECD total, compared with only 16 percent for the EU. The outstanding example of the importance of publicly-funded research is the work of the US National Institutes of Health with the pharmaceutical industry to promote the development of new medicines (Box 6). It should be noted that the NIH supports the exploration of fundamental biological mechanisms and even in those few cases where an NIH-invented technology is an identifiable part of a final product, that invention would typically be one of numerous components that would go into building that product.

Large diversified pharmaceutical companies have the necessary capacities to develop and commercialise the bioscience research taking place both in public research institutes and specialised
**The Pharmaceutical Innovation Platform**

**Figure 7. Different Players and Their Roles in the Pharmaceutical R&D Process**

<table>
<thead>
<tr>
<th>R&amp;D Stage</th>
<th>Research &amp; Discovery</th>
<th>Preclinical development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Registration</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Sector</td>
<td>Health research institutes (e.g. NIH, universities, medical schools, hospitals, etc.) play an important role in generating basic 'untargeted' research leading to important scientific discoveries enabling further ‘targeted’ drug/vaccine discovery and development. Many of these institutions receive specific research funds from the pharmaceutical industry.</td>
<td>Public hospitals, clinicians and centres of clinical excellence are a necessary component of clinical development infrastructure. Another potentially important role is related to research on new tools used in clinical development to assess efficacy and safety of tested drugs</td>
<td>Regulatory authorities set standards and evaluate product dossiers, thus playing an important role in shaping the operational environment for companies.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialised Companies</td>
<td>Small, specialised companies play an increasing role in research and discovery, focusing on very narrow therapeutic areas. These companies have become an important source of potential new drugs/vaccines which are further developed by major pharmaceutical companies.</td>
<td>Very limited capacities of small companies in terms of clinical development. Some companies conduct Phase I and II trials but are unable to conduct Phase III trials</td>
<td>Practically no role.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharma Companies</td>
<td>The pharmaceutical industry dedicates significant proportion of their R&amp;D budgets on early research and discovery. With their accumulated resources (e.g. compound libraries), technologies (e.g. high throughput screening, combinatorial chemistry), human resources and know-how, the companies remain the main contributors to drug discovery and preclinical development.</td>
<td>Pharmaceutical companies play a critical role in clinical development. They are the biggest sponsors of clinical trials and they have developed unique skills and capacities necessary to conduct such trials.</td>
<td>Pharmaceutical companies play a unique role in submitting product dossiers to regulatory authorities, interacting with regulators during the approval process and conducting post-marketing clinical trials.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Box 6. Cooperative Research and Development Agreements (CRADAS)**

The Federal Technology Transfer Act of 1986 mandated the US Public Health Service to encourage and facilitate collaboration between public research institutes, academia and private sector for the benefit of public health. CRADA is one vehicle for this collaboration.

A CRADA is an agreement between public (NIH, academia) and private (pharmaceutical industry, biotech industry) parties under which both parties provide personnel, services, equipment, resources and know-how toward the conduct of specified research or development efforts.

In April 1995, a review of CRADA activities of NIH found that the agreements significantly advanced biomedical research by allowing the exchange and use of experimental compounds, proprietary research materials, reagents, scientific advice, and private financial resources between government and industry scientists. The vast majority of CRADAs result in new scientific knowledge, not new products.

companies that are satellites to academic research “hubs” or “clusters”. These smaller firms have very narrow fields of research competence and their product portfolio is often limited to just a few compounds. Nevertheless, they play an important role in supplying platform technologies and discovering novel compounds.\textsuperscript{84} Investments and risk capital from big pharmaceutical companies help these firms develop and refine their products and bring them to market, not only commercializing useful products for the benefit of the public, but also creating revenue streams for these small biotech firms to invest in further innovation. Over the quarter-century of the sector’s existence, stock-market investors have put somewhere close to $100 billion into this industry, and cumulative losses for the public biotech companies have exceeded $40 billion.\textsuperscript{85} It is no exaggeration to conclude that without the deep pockets of the major pharmaceutical R&D companies, a healthy and vibrant biotech sector would not exist.

The in-house capabilities of major pharmaceutical companies remain unchallenged when it comes to managing broad portfolios of test compounds and the consequent ability to generate a sustainable flow of new products.\textsuperscript{86} This gives these companies the ability to strike a balance between some ambitious, high-risk projects – which, if successful, would create a radical new approach to treatment – and lower risk projects that offer an incremental gain in an established therapy. One of the key challenges involved in this process is the constant adjustment of the research portfolio to maintain this balance across the ten to fifteen year period from discovery research through to the final development stage of regulatory submission. Again, large pharmaceutical firms can minimize the risks through development alliances with other companies linked to licensing and contract research.

Pharmaceutical companies also make substantial capital investments in their own R&D capacities on a regular basis just to keep up with emerging technology. High-throughput screening and combinatorial chemistry are just two examples of technologies that can enhance the efficiency of identifying useful drug targets.

In practice, there are more technologies available than one company can invest in. Consequently, pharmaceutical companies have over time developed a unique sense of how to tap into the latest process innovations, a skill that cannot easily be replicated by an industry outsider. The vast libraries of compounds unleashed by these new technologies form an important element in the industry’s expanding knowledge base.\textsuperscript{86}

Another unique capability of the R&D industry is its ability to organize and manage large-scale, internationally based clinical trials. Indeed, major pharmaceutical companies are practically the only ones able to successfully run complex clinical trials because they have the adequate funding, facilities and human resources to apply to the task (Box 7). By way of example, the pivotal clinical trials alone that are necessary for drug approval cost in the range of $100 million, which is unaffordable for most of biotechnology firms with assets of $20 million or less.\textsuperscript{87} This part of the R&D process can last as long as 7-8 years with no guarantee that the final report from clinical trials and the dossier prepared for submission to regulatory authorities will be approved. FDA estimates that a compound entering phase I of clinical trials has only an 8 percent chance of reaching the market.\textsuperscript{64} Leading pharmaceutical companies, each with twenty or more clinical trials centers around the world, are thus practically the only ones with sufficient capacities to successfully conduct large clinical trials.

The preparation of the product dossier for submission to the regulatory authorities is a crucial element as it determines the end-result of years of efforts in research and development. Pharmaceutical companies, as originators of drugs and vaccines, need advanced access to the skills and resources to fulfill all these requirements – in notable contrast to generic producers, who simply rely on existing data from earlier clinical trials financed by the innovative companies to gain regulatory approval. The difference in underlying costs is very significant – in the order of magnitude of hundreds of millions of dollars.
Once a product has been developed and approved, quality manufacturing of the product brings it to consumers. Again, the R&D industry has unique advantages, as major R&D companies have mastered the tasks of assuring quality control, designing and implementing manufacturing processes and plants, and constructing and commissioning primary and secondary manufacturing plants. All these activities, while linked to post-development processes, need to be organized during the development phase.

In many cases entire plants must be commissioned and built before a product is even approved. For example, one company is currently constructing a new $90 million manufacturing facility to help produce the key ingredient in a product that is still in Phase III and which may never reach the market if it fails to meet the safety and efficacy requirements. Given that a failure in adhering to the highest quality standards may result in direct and immediate wide-scale damage to human health, the importance of perfecting high quality, efficient manufacturing processes must not be underestimated (Box 8).

Pharmaceutical companies not only invest substantial amounts in modern, integrated and multipurpose plants, but they also have to manage properly the logistics of such plants, in order to adapt the production capacities to changes in demand (both downward and upward). This demonstrates a critical reality: only the leading R&D companies are able to assure quality manufacturing, reliable marketing and distribution, and post-marketing surveillance requested by regulatory agencies—consistently, on a worldwide basis.
Box 8. The Complex and Expensive World of Pharmaceutical Manufacturing

Pharmaceutical manufacturing rarely attracts significant attention. Meanwhile, it is arguably the most capital-intensive of all processes within the pharmaceutical value chain. According to one estimate, in 2001, 16 top pharmaceutical companies spent no less than $90 billion on manufacturing which accounted for 36 percent of industry’s costs, more than double the R&D share.

With increasing technological sophistication of new medicines on one hand and the ever more stringent regulatory requirements on the other, manufacturing will become yet even more demanding. One company has recently invested over $1.5 billion in what is to become the world’s largest biopharmaceutical facility that will provide global supply of just two products. Another company has announced its $640 million investment in two manufacturing plants to ramp up the production of the company’s two biotechnology products. Finally, the complexity of modern pharmaceutical manufacturing is illustrated by the fact that it takes an entire year’s work of 1,200 employees to manufacture just 200 grams of a genetically engineered product.

Summary Points from Chapter II

- The process of pharmaceutical R&D remains long and complicated. R&D is also becoming more complex due to a combination of scientific and political factors. The financial risks are high because without regulatory approval there is no market.

- R&D costs are rising, particularly for clinical trials, as the focus shifts to complex, multi-symptomatic diseases that require evaluations in larger patient groups and over a longer period of time.

- Innovative new medicines remain a favorite target for government budget cost-cutters, providing a clear and easy target because access to medicines is easy to control compared to other health services that comprise a far larger share of overall spending on health – in most OECD countries, drugs represent only around 10 percent of total costs, and this has been constant for the last 40 years.

- There is no alternative model or structure able to deliver the R&D output of the research-based pharma industry, a process that has evolved slowly over a century of progress in drug discovery and development.
Chapter 3

The Pharmaceutical Innovation Platform: Ensuring a sustained flow of new medicines to patients

The Enabling Environment for Innovation

As shown in the previous chapter, pharmaceutical companies have developed unique skills to master the innovative process and deliver medicines that contribute to a prosperous and productive society. Industry’s ability to continue such innovation depends on the following factors:

- **Financial capacity** – generating the up-front cash needed to invest in R&D;
- **A strong base in the science of drug discovery** – to understand the causes and mechanisms of disease;
- **Technical know-how** – the management and logistical skills to transform scientific discoveries into practical knowledge and products;
- **Marshalling human knowledge and ingenuity** – the ability to navigate the often-elusive pathways of technology and science.

Mobilization of each of these factors allowed medical discovery to flourish in the 20th century. Today, the challenge is to keep the momentum going so that researchers can address a new era of resurgent infectious diseases and more complex chronic conditions. An obvious example of the problems and constraints related to future innovation in medicines is HIV/AIDS and the industry’s efforts to develop both preventive vaccines and drugs that will actually kill the virus and cure those already infected. In the two decades following the discovery of HIV, the R&D industry has developed more than 20 effective treatments for AIDS.88 However, despite the advanced state of knowledge and the considerable research underway, many promising HIV/AIDS drug and vaccine candidates that could be developed into revolutionary treatments or cures are still at early stages of the R&D process. There is as yet still no cure for AIDS, as well as for many cancers and other deadly diseases and conditions. Thus, the sustainability of the current model of pharmaceutical innovation is absolutely critical to successfully fighting these diseases.

Pharmaceutical R&D has been successful on the basis of a business model that has been a key factor in the discovery, development and marketing of life-saving and health-enhancing drugs. Called the **Pharmaceutical Innovation Platform – PIP**, it depends on an interdependent “circle of innovation” composed of four critical pillars:

1. Successful health care systems;
2. Efficient markets;
3. Effective use of intellectual property;
4. Predictable and adequate regulatory requirements.
Healthcare Systems are decisive in determining the level of distribution and thus the access to new products, whereas Efficient Markets concern primarily marketing and sales, which generate the income and profits that determine the amount of resources available for future innovation. Intellectual Property Protection (IPP) should be regarded as the principal incentive for conducting any research, as it protects the fruits of innovative research from imitation before the actual product is registered and manufactured for use in the patient population. Regulatory Requirements determines both the length and the cost of development process and mandates standards in the areas of safety, quality and efficacy of products (Figure 8).

Public policy decisions can have far reaching consequences on any one of these four pillars and indeed on the entire PIP. In fact, interventions by state authorities and public agencies shape the production cycle of the R&D industry to a considerable extent, influencing private sector decisions on both supply (R&D, manufacturing, marketing) and demand (payers, insurers) for prescription pharmaceuticals. A proper understanding of these underlying processes is thus essential for policy makers, who through their own actions decisively affect the operating environment of the industry.

Critical Pillars of the Pharmaceutical Innovation Platform

Successful Healthcare Systems

Healthcare systems represent a complex mechanism through which health products, services and care are delivered to patients. They involve various stakeholders whose objectives may differ significantly. The pharmaceutical industry has an important stake in healthcare systems as a provider of innovative medicines. Healthcare systems directly or indirectly influence prospects for the uptake of these medicines and thus have important impact on future innovation. They involve both “push” and “pull” mechanisms through which innovation is encouraged and rewarded at the same time. An example of a “push” mechanism is when an overall culture promotes science and innovation, serving as a source of added value that bolsters independent private research. In contrast, experience has shown that a culture and political system that denigrates innovation in favour of promoting mere copying strongly discourages innovation.
Chapter III: The Pharmaceutical Innovation Platform

Healthcare systems encompass various elements and represent interests of different stakeholders – governments, citizens, health care providers and funders. All these stakeholders have their own objectives, which overlap and interact, and it is the role of government policymakers to balance these often-competing aims. Ideally, healthcare systems should encourage appropriate innovation and the expeditious introduction of innovative pharmaceutical products for the benefit of public health. Pharmaceutical innovation can, and does, help policy-makers achieve their overall healthcare policy goals, as described in Chapter I.

An illustrative example of how a broad healthcare environment can influence medicines innovation comes from a comparison between US and EU. The steady departure of R&D investment away from Europe, to the US, is mainly attributed to major differences in health system developments between these two regions over past years. Flexible scientific and economic system, availability of a broad portfolio of financial and fiscal incentives for scientific and technological innovation, institutional structure of public biomedical research, together with specific systemic solutions applied in the health system itself make for the competitive advantage of the US over Europe. Similar observations can be made when comparing the US and Japan.

In order to reverse this deteriorating trend, the European Commission has initiated the so-called G10 Process – a high-level consultation among key policy and decision makers representing the European Commission, pharmaceutical industry and other stakeholders. The report resulting from these discussions highlighted the urgent need for various actions and initiatives to improve the overall healthcare environment in the EU, with an aim to ameliorate competitiveness of the European pharmaceutical industry and attain high levels of public health in the EU. Examples of proposed policies include measures to improve the timing of reimbursement and pricing negotiations, create competitive generic markets, enhance patients’ information and incentivise research in general.

In Japan, the government is implementing its ‘Pharmaceutical Industry Vision’ – a strategy to reinforce the global competitiveness of the Japanese pharmaceutical industry. Within this framework various specific measures have been proposed to create an attractive drug discovery environment in Japan, including the creation of the new Pharmaceuticals and Medical Devices Agency (PMDA) to help speed up diffusion of new medicines, and price system reform to improve the attractiveness of the Japanese pharmaceutical market.

The role of the healthcare system is particularly significant on the level of uptake of innovation and its diffusion – the “pull” function. It is often the case that the potential of a drug or a vaccine is hampered by the lack of effective healthcare infrastructure and consequent inability to treat patients who might benefit. Well-equipped health centres and hospitals with highly trained professional staff have a substantial impact on the extent of dissemination of modern medicines and medical tools. Similarly, new therapeutics may not reach patients, or the process of getting such new products to patients will be much longer, if distribution systems and communication channels at all levels are ineffective and inefficient.

In many European countries uptake of new drugs is hampered by inefficiency and bureaucratic controls on healthcare infrastructure combined with a lack of information that would allow patients easier access to accurate pharmaceutical product information. Consequently, the number of new molecular entities (NMEs) launched in the US is much higher than in other major pharmaceutical markets. Between 1997 and 1999, 100 NMEs were launched in the US, compared with 43 in Canada, 37 in Japan and 66 in the UK.

Finally, the uptake of new medicines may be hampered by the low level of responsiveness of the healthcare system to treatment guidelines formulated by medical authorities. In the UK for example, despite legally binding treatment guidelines being published that are meant to increase the uptake of a range of medicines, the actual level of implementation of these guidelines have been low by the National Health Service (NHS).
The role of patients in health systems is particularly important. In the US and to lesser a extent in Europe, increased participation of patients in decisions regarding their treatment regimens should be viewed as a positive development. Patients are highly motivated to seek out the latest and the most effective treatments, which is undoubtedly improving the economics of innovation by accelerating the widespread uptake of new medicines. This ongoing change is sometimes referred to as a transition of health systems from physician-oriented to patient-oriented in which all of the components cater to the patient rather than the physician.101

A positive example comes from the US, where despite stringent regulatory requirements (probably the most demanding in the world), innovative products gain relatively rapid access to the market due to high levels of competition within distribution systems and the active participation of patient groups – who benefit in turn from open communication about new therapies.

**Efficient Markets**

In theory, effective markets should allow for an efficient allocation of resources. In most cases, however, the working of pharmaceutical markets is shaped by such issues as the adequacy of health funding, budget allocation systems and the process of price/reimbursement negotiation between pharmaceutical companies and all-powerful government agencies.

Instead of being able to work in an environment characterised by genuine market forces, pharmaceutical companies notice a tendency among policy makers to focus on pharmaceuticals as the primary source of budgetary savings. Unfortunately, modern healthcare systems are characterised by a very complex cost structure whereby many of the costs tend to be indirect or at least uneasy to identify. Medicines expenditures are the easiest to identify and thus are the easiest targets for cost-reduction policies.

In fact, price controls on pharmaceutical products have become more prevalent around the world and are reaching levels whereby the long-term profitability of pharmaceutical companies is endangered. In fact, price controls on pharmaceutical products are reaching levels whereby the long-term financial sustainability of pharmaceutical innovation is endangered.102 It is no longer
unusual for prices of individual patented products to be frozen for a decade or more, without even an adjustment against inflation.

Another form of controlling prices is through reference pricing systems whereby reimbursement authorities review prices for a group of products and then set a single fixed price at which they will reimburse patients for the purchase of all covered drugs in each group. These systems have proven to be ineffective as cost-containment measures are (often reducing the ability to gain from generic competition), damaging to the R&D process, and of no value in terms of improvement of health outcomes.103, 104, 105

In addition, many governments now pay considerable attention to regulatory regimes in other national markets and, more specifically, have taken to ‘bench-marking’ actual prices of medicines across groups of similar countries, despite the difficulties of making accurate comparisons. Such cross border reference pricing further discourages innovation and promotes the spread of inappropriate public policies.

Furthermore, new monitoring mechanisms and national guidelines, based upon cost as well as clinical effectiveness, have put doctors under pressure to use older (generic) treatments as widely as possible and to be cautious in using higher priced new products. In this case, patients in need are refused specific treatments that would otherwise significantly reduce underlying economic and social costs. Such developments clearly have serious repercussions on patients and for society (Box 9).

### Box 9. Europe’s Negative Precedent: Control over Healthcare Infrastructure Limits Access to Innovation

- More than 2.5 million asthmatics in Germany receive no proper treatment.
- Despite cardiovascular diseases being Europe’s major cause of death, in Germany 74 percent, in the UK 77 percent and in Italy 83 percent of all eligible patients do not receive up-to-date treatment for high cholesterol.
- In France, less than 50 percent of multiple sclerosis patients eligible for treatment with beta interferons actually receive it.
- In the UK, in 1997 only one in fourteen breast cancer patients, clinically eligible for the newest type of medication, received it.


This is despite some concerns being raised regarding the appropriateness of thresholds used to evaluate new treatments, which overwhelmingly focus on cost effectiveness and the use of QALYs (quality-adjusted life years) to determine incremental cost-effectiveness ratios.106 It is argued that more emphasis should be given to submissions from patients groups as well as patients’ and clinical experts’ testimonies in preparing health technology appraisals. Also, given the importance of a drug class as the fundamental therapeutic unit which reflects the role of incremental innovation in medicines,107 it is vital for such evaluations to reward the benefits of improved drugs in each class.

Such negative developments are often explained by the prevalent tendency among policy makers to look for short-term benefits and savings that may bring immediate relief to overcharged healthcare budgets, working in favour of political agendas. Paradoxically, these short-term ben-
efits imply substantial costs in the long-term, making the whole healthcare system even more vulnerable to financial pressures. This has been already mentioned in Chapter I when discussing long-term monetary benefits resulting from the use of therapies to treat chronic diseases. Systemic healthcare reforms which are based on thorough analysis of the cost structure, and which prioritise well-being of patients as a central policy objective are more effective in promoting quality health care than short-sighted budget cuts.89

Efficient allocation of resources on cost-effective drug treatments rather than on other healthcare interventions is an option chosen by some governments. They tend to be more open in allowing access to state reimbursement and formularies for newer medicines as well as being more flexible in price negotiations with pharmaceutical companies. By doing so, they create a win-win situation whereby both national healthcare systems and pharmaceutical companies gain clear benefits. The former improve the health status of patients while spurring economic growth and leading to financial savings in the long run; the latter can recoup the costs of R&D and continue the process of innovation. Such arrangements are thus crucial for the whole system of pharmaceutical innovation, which is largely financed through the sale of existing products and where success or failure is determined by the actions of payers and physicians.

A constructive example of a more long-term view is provided by the experience in the US. Not only the largest pharmaceutical market but also the only major one that has resisted price controls so far, the United States is widely recognised as the centre of pharmaceutical innovation. Most R&D costs are recouped through competitive market-based pricing in the US, and a growing preference among European companies to move their R&D operations to the US appears to confirm this fact.98

Market factors affecting innovation are not limited to the national context. Indeed, one effective market mechanism is the ability of companies to charge different prices in different countries. There are many factors influencing price variations for pharmaceutical products among different countries including such aspects as the size of the market, the development of the national economy, per capita income, local medical usage patterns, taxes and other mark-ups on prices, inflation and fluctuation of exchange rates. Price variations are also evident within countries, and tend to ensure increased access. Even in the poorest countries, there is a segment of the population with the ability to pay western industrialized market prices. Allowing the industry to do so can ensure the capacity to finance access to the very poor, at concessional prices, without restricting the returns to finance future R&D.

Price variations have a significant impact on the availability of medicines in different markets:

- Consumers (countries) who are charged the lower prices would be unable to purchase at a higher price. In other words, consumers in a much greater number of markets have access to new medicines.
- Patients consume a larger total volume of medicines, so a larger proportion of the global patient population base has access to new products.

International price variations for pharmaceuticals help provide companies with the cash flow and resources to finance large R&D budgets, as they facilitate simultaneous launch of new products in many markets. For example, the most recently launched products are available in 50 to 65 countries worldwide in just 1-3 years after their approval, compared to 5-10 years needed to achieve the same result for drugs developed a decade ago.108 Consequently, price variations allow the burden of R&D costs to be spread across a larger consumer base. This contributes to minimizing the financial risk of R&D investment on one hand, and improves the diffusion of innovative pharmaceuticals among populations at different income levels.109

How to Assess Drug’s Utility for Patients?

Mr Ross Hulbert, an arthritis patient from New Zealand, has battled the disease for 29 years, enduring pain, weight loss, operations, injections and depression.

‘How do you put figure on pain and suffering and loss of quality of life? I believe that if there are drugs available that can put rheumatoid arthritis into remission… then those drugs should be made more readily available’
Effective Use of Intellectual Property

IPP transforms the intangible capital generated by pharmaceutical companies during the process of R&D into financial flows indispensable to continue the cyclical process of innovation. As such, it should be regarded as the heart of the whole system of pharmaceutical innovation. The dependence of the pharmaceutical industry on intellectual property protection (IPP), and in particular of the temporary exclusivity granted by patent protection, is arguably the highest compared to other industries. The reason is simple: once the value of a molecule for treating a particular disease has been established by the innovator and satisfies regulatory requirements, it is relatively easy to imitate manufacturing processes and commercialise generic copies of medicines within the chemical and biological sciences.

Patents for products last nominally for twenty years from the time of grant by national patent offices in all WTO members who have implemented the WTO’s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). However, meeting the exacting technical regulatory requirements of the product licensing authorities now takes, on average, ten years from the point at which a patent is granted for an invention, which is the effective starting point for the product development process.

It should be noted that, in practice, the period of market exclusivity due to patent protection is much shorter, as a result of therapeutic competition, i.e. the introduction of competing products in the same therapeutic class shortly after the launch of the breakthrough product (Figure 11). By way of example, major products launched in the late 1980s enjoyed market exclusivity of 4 to 6 years, while products launched a decade later could only benefit from 0.5 to 2 years of market exclusivity. This has important implications for companies, as their long-term financial projections are largely based on expected exclusivity periods.
The already shortened effective patent life is further cut by government policies designed to speed the entry of generics into the market by weakening patent protection and other IPRs. For example, the “Bolar” provisions in some countries, allowing early working of a patented substance, allow generic companies to perfect their manufacturing processes during the product’s patent life. Also calls to forcibly break a patent, otherwise known as compulsory licensing, could have a serious negative effect on innovation because they would deprive the patent holder of financial incentives to innovate in the future.\textsuperscript{114}

Data exclusivity is another form of intellectual property protection independent of patent protection. As described in Chapter II, developing a patented discovery into an approved saleable product requires amassing large amounts of data over many years on pharmacology, toxicology, clinical trials, manufacturing processes and product quality etc. These data are submitted in confidence as a single dossier to the relevant technical regulatory approval body in national (or EU) jurisdictions to gain a license to sell the product by the innovator. Article 39(3) of the TRIPS Agreement obliges WTO Member States to ensure that this data package shall be maintained confidential or exclusive to the originator for a fixed period from the date at which it was submitted to the government authorities.\textsuperscript{115}

Another contentious issue regarding IPP is the concept of international exhaustion of patents. The rule in most countries is national exhaustion, where import can be stopped by the patent-holder. In contrast, if governments decide to promote international exhaustion of patents, then the patented products can be imported into the market without the authorization of the patent-holder, a process that is also called “parallel trade”. Within the European Union, international exhaustion exists and patented medicines can be traded freely within and across national borders but not into the EU from non-EU states. On the other hand, in the US, the law permits contracts that
prevent parallel trade into the US. Internationally, the WTO leaves each member state free to establish its own regime for exhaustion of intellectual property rights.\textsuperscript{116}

Parallel trade is sometimes seen as an important tool to reduce prices, as a purchaser could theoretically buy drugs at the lowest prices anywhere in the world. However, promoting such a policy would lead to negative effects internationally. As parallel trade always diverts products from low-price markets to higher-priced ones, parallel trade diverts drugs away from poor populations, depriving them of the drugs that they need. Furthermore, parallel trade distorts the pricing strategy of pharmaceutical companies based on international price variations, reducing the access to medicines for poorer countries and depriving innovators of revenues needed for further innovation.

Policies currently being put forward in the US to allow re-importation of cheaper, price-controlled pharmaceuticals from Canada and the EU would have strong adverse effects on both R&D decisions in the US and drug supply in Canada and the EU\textsuperscript{117}. Parallel trade thus works against patients and pharmaceutical companies themselves – and the key beneficiaries of parallel trade practices are in fact parallel traders, who keep the profits for themselves. Also, parallel-traded medicines may potentially pose a threat to patient safety – as reported recently, 80 percent of drugs received by one company from parallel distributors failed MHRA (Medicines and Healthcare products Regulatory Agency in the UK) guidelines, and 45 percent of these failed on safety grounds.\textsuperscript{118} Similar alarming findings have been reported recently during the US FDA inspections.

\textbf{Adequate and Predictable Regulatory Requirements}

Over the past 50 years, increasingly sophisticated systems have been developed by government health authorities to grant licenses to companies wishing to sell prescription medicines. To obtain a license to sell a medicine, three broad sets of requirements - backed by comprehensive and extensive documentation - must be met, covering the efficacy, quality and safety characteristics of a given medicine.

As such, technical regulations play a very important role for the entire health care system. In particular:

\textbullet\textit{ Patients} are assured that a new product they use meets national standards for safety, efficacy and quality.

\textbullet\textit{ Healthcare providers and authorities} are assured that a new medicine not only meets safety and quality standards but also that its efficacy meets the required standards, improving treatment outcomes.
Pharmaceutical companies know that by meeting requirements of regulatory authorities and by having valid intellectual property protection on the product, they will be granted an exclusive license to market a new medicine.

The increasing tendency among regulatory authorities to make the process of drug approval more stringent contributes to the upsurge of R&D costs. The temptation is to insist on more and longer toxicity tests; to increase the number of animals used; to broaden the range of species; and to add new tests as these become available — all to achieve the absolute assurance of safety. However, if this trend continues, the cost of drug development may soon reach exorbitant levels, making future medicines practically unaffordable.56

This risk is not unimaginable, as shown by the recent example of antibiotics. It has been argued that because of the FDA’s imposition of tighter requirements for approving antibacterial drugs the industry’s ability to provide a reliable pipeline of new antibiotics for treatment of serious infections has been impaired.119 Such unexpected and negative changes of regulatory guidelines create uncertainty for drug companies that may have lasting impact on their investment decisions.

Given the effects of globalisation on marketing strategies of pharmaceutical companies there is a mutual interest in progressing towards a common submission of regulatory dossiers for all countries. This is necessary so that the management of R&D does not get tied up in additional costly red tape as new drugs are submitted for registration approval in multiple countries. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an important step forward in making drug registration swifter and more efficient internationally (Box 10).

Drug regulatory authorities do not only impose technical guidelines related to drug development, but also establish standards for handling and controlling pharmaceutical manufacturing processes, such as Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), and Good Clinical Practice (GCP). In order to comply with these standards, companies have to validate all facilities, equipment and processes (including software) they use by establishing documented evidence that all these components perform in a reliable and consistent manner. In some cases, such as utilisation of sophisticated IT solutions in manufacturing, pharmaceutical companies’ drive for innovation may be in fact constrained by the regulatory requirements, which impose important additional costs on the application of such advances.120

**Box 10. Remit and Achievements of ICH**

**Purpose**
ICH was created in 1990 in order to increase international harmonization of technical requirements to ensure that safe, effective, and high quality medicine are developed and registered in the most efficient and cost effective manner, i.e. by preventing unnecessary duplication of clinical trials and minimizing the use of animal testing without compromising safety and effectiveness.

**Members**
ICH is comprised of representatives of the regulatory bodies and research-based industry in the EU, Japan and the USA — i.e. six founding parties. The Observers to ICH are representatives from the World Health Organisation (WHO), European Free Trade Association (EFTA) and Canada. IFPMA hosts the secretariat of ICH.

**Achievements and current work**
- ICH has harmonised more than 50 technical guidelines on quality, pre-clinical and clinical aspects, as well as established an international medical terminology – MedDRA
- ICH is developing a Common Technical Document (CTD), i.e. a common format to be used for new product submissions to regulatory authorities in the three main industrial regions: the EU, Japan and the USA
- ICH helps to modernise regulatory approaches
Consequently, significant benefits could be achieved if drug regulatory authorities applied a more pro-active and flexible approach to their processes and procedures, thus keeping up with the latest scientific and technology advances in the R&D process. This could result in a faster and less costly development process, and more productive and efficient manufacturing of pharmaceuticals as well. For example, the FDA’s endorsement of process analytical technology (PAT) has enabled the pharmaceutical companies to utilise state-of-the-art technologies and tools to assess the quality of medicines during the process of their production, rather than only after they have been produced. This has important implications for the overall quality, efficiency and cost profile of the manufacturing process.\textsuperscript{121}

Major regulatory authorities such as the US FDA, the pan-European EMEA and the newly established PMDA in Japan, are now starting to recognise the need to facilitate drug regulation in order to create regulatory systems that would improve prospects for medicines innovation in the future.\textsuperscript{64, 94, 122}

**Balancing Government Policies in Support of the Pharmaceutical Innovation Platform**

The critical pillars of the Pharmaceutical Innovation Platform envision two important goals for government policies: public health and economic (industrial) competitiveness. These broad objectives have often been seen as mutually exclusive but in reality, they are not. As expressed by Erkki Liikanen, a former member of the European Commission, and one of the drivers of the G10 Process, ‘we must not lose sight of the fact that the key objective of improving competitiveness is to bring benefits to patients’.\textsuperscript{123}

Policy makers must understand the four pillars described above to make policy decisions that would have a desired long-term effect on both public health outcomes and economic prospects and competitiveness of the pharmaceutical industry. The latter is critical in determining the industry’s capacity to innovate, and to meet the evolving health needs of patients.

Government policy makers need a broad cross-cutting perspective which goes beyond the responsibility and expertise of one single discipline. Healthcare systems, which in principle are designed to serve public health, have a vital role in determining uptake of innovation and encour-

---

**Figure 13: Key Characteristics of Technical Regulation Which Promote Innovation**

- Stable and predictive regulatory environment
- Cooperation between regulators and industry
- Smooth drug regulatory approval process
- Harmonisation of regulatory requirements globally
- Adjustment of regulatory requirements to advances in science and technology

Ensure quality, safety and efficacy of products
Create stable environment for R&D

---

A proper policy mix can both benefit public health and create favourable conditions for sustainable medicines innovation.
aging future R&D efforts. Thus, the institutional and functional design of healthcare systems should be paralleled by adequate resource allocation through effective markets. These two elements should be tuned and synchronised to create a comprehensive policy mix encompassing and balancing different health aims, such as prevention, treatment, care as well as ensuring the all-important sustainable progress of innovation in health technologies, including medicines. Achieving the optimal equilibrium is not an easy task; especially since public health is an ever-evolving, dynamic process that needs constant policy adjustments.

Government policy makers not only determine the demand side of the pharmaceutical industry through their health policies and resource allocation decisions, but also have an important influence on the actual R&D process and its cost structure. One prominent example is provided by technical regulations governing clinical trials. A number of leading regulators now recognise that these ever more stringent regulations are actually impeding the industry’s ability to produce affordable new drugs, and paradoxically work to the disadvantage of government budgets, healthcare systems and patients. This necessitates a thorough cost-benefit analysis of existing regulations as well as identification of possible options for streamlining the regulatory processes. Again, the equilibrium needs to be found between safety concerns and underlying regulations, and financial capacities of governments to absorb the ever-escalating costs of drug development.

The Pharmaceutical Innovation Platform represents a specific policy mix that is essential to create favourable conditions for medicines innovation. It is meant to help policy makers to identify and pursue best policy options and thus ensure that the public health needs are met in the most efficient and sustainable manner.

Summary Points from Chapter III

- Open market conditions, bolstered by a strong regulatory environment, provides the enabling environment for a healthy R&D industry.
- Innovative R&D is based on a business model that stands on four critical and inter-connected pillars of performance:
  - Successful healthcare systems
  - Efficient markets based on sustainable financing
  - Effective intellectual property protection
  - Adequate and predictable regulatory requirements
- Interventionist public policies affecting any one or more of the four pillars create an imbalance that can reduce the private sector investments that drive new medicines R&D.
- Intellectual Property Protection (IPP) remains the heart of the entire system of pharmaceutical innovation and efforts to weaken it will only limit the discovery and development of needed new therapies.
Identifying Health Problems of Developing Countries

The previous chapters have described the importance of innovation in general, as well as the components of the Pharmaceutical Innovation Platform (PIP), which promotes private-sector led innovation. While this discussion has focused mainly on factors at play in industrialized-country markets, the PIP is also very relevant to the needs of developing countries.

The Pharmaceutical Innovation Platform is a generator of effective medicines, and many of these are available today at low cost to treat diseases specific to developing countries. Yet the R&D-based pharmaceutical industry has been criticized for the deteriorating public health status of the poorest developing countries.

The arguments advanced by activists critical of the R&D-based pharmaceutical industry point to the industry’s alleged lack of R&D efforts to address diseases prevalent in developing countries.125 They argue that virtually all diseases prevalent in developing countries are “neglected” and that the pharmaceutical industry has invested almost nothing in R&D for these diseases. Furthermore, some critics consider industry’s patents the key barrier to making the existing drugs affordable and available to poor populations. Some health activists even argue that the current R&D paradigm needs to be changed in order to address health problems of the poor, and in particular a group of diseases referred to as “neglected diseases”.126

The issue of drug R&D for diseases prevalent in developing countries indeed deserves more attention, as it is directly linked to the core objective of pharmaceutical industry, i.e. pharmaceutical innovation. As such, misconceptions and misrepresentations need to be addressed.

For example, a key allegation made by industry critics is that only about 10 percent of the global health research budget (private and public) is used for research into 90 percent of the world’s health problems.127 However, this is factually incorrect. Non-communicable diseases, cancers, neuropsychiatric disorders or diabetes account for roughly 60 percent of global deaths and it seems reasonable to argue that the bulk of pharmaceutical R&D ought rightly to be concentrated on these indications (Figure 14). Many of these diseases can now be effectively treated with inexpensive, off-patent medicines.

Furthermore, if the global disease burden was adjusted for diseases, which are not directly treatable with medicines — i.e. maternal and perinatal conditions, nutritional deficiencies and injuries together accounting for more than 20 percent of global deaths — it would become even more
apparent that the pharmaceutical industry is actually addressing the great majority of global health needs.

Furthermore major non-communicable diseases are gaining in importance as a factor in mortality and morbidity in developing countries, with cardiovascular diseases alone responsible for one-third of deaths. In fact, in absolute numbers, more people die of non-communicable diseases in developing countries than in developed ones. This growing burden (or “double burden”) has real potential to hinder social and economic development and is a part of the ongoing epidemiological transition of developing countries. As shown in Figure 15, the number of deaths caused by infectious and parasitic diseases practically equals the number of deaths due to cardiovascular diseases occurring in developing countries. In its World Health Report 2003, WHO uses even the term “neglected global epidemics” when referring to cardiovascular diseases, diabetes and tobacco-related illnesses.

It is also important to recognise that ‘neglected’ diseases are not always the most critical health challenge; each country in the developing world is different. In July 2001, a joint working group comprised of experts from the World Health Organisation (WHO) and research-based pharmaceutical industry, found that only three diseases were truly ‘neglected’: African trypanosomiasis, leishmaniasis, and Chagas disease.129

Similar conclusions were drawn by a group of experts from the WHO’s Special Program for Research and Training in Tropical Diseases (TDR) in a study published in 2002.130 Figure 16 compares global daily mortality of major diseases affecting developing countries, including the three “neglected” diseases. Interestingly, according to WHO, the key factors behind the excessive mortality caused by these diseases include unavailability of health services and failure to use prevention and treatment strategies, rather than the unavailability of medicines.131 Also, many of diseases endemic in the world’s poorest countries for which no effective treatments are available have been successfully addressed through diseases-specific programmes.132
Chapter IV: Spreading the Benefits of Medicines Innovation

Figure 15. Weighted Distribution of Deaths Caused by Major Global Diseases (Deaths as per mil of relevant population)


Figure 16. Global Daily Deaths per Major Communicable Diseases

* Neglected diseases are defined as African trypanosomiasis, Chagas disease, and leishmaniasis.

The Pharmaceutical Innovation Platform for Developing Countries

Over decades, the pharmaceutical industry has discovered and developed effective and safe medicines that address health problems of developing countries. These innovative efforts have covered both the infectious conditions traditionally attributed to poor countries, such as HIV/AIDS, tuberculosis, malaria, or tropical parasitic ailments, and non-communicable conditions, now emerging as a serious “double burden” for these countries. Today, a clear majority of the key essential medicines to treat both conditions are off patent\(^\text{133}\) and available at low cost, offering opportunities for radical health improvement if governments can marshal the resources and political will.

The truth is that for the great majority of disorders there are effective treatments; where new drugs are needed, substantial R&D efforts are underway.\(^\text{134}\) This is the case with the industry’s relatively swift response to HIV/AIDS, which has already been described in Chapter I. Similarly, important efforts are made to develop new medicines for other infectious diseases, such as malaria and tuberculosis. Several novel products have been developed by pharmaceutical companies to fight malaria over last decade, and a number of companies have established research centers exclusively focusing on tuberculosis and other infectious diseases (Box 11).

Finally, it should be emphasised that pharmaceutical companies have also developed or adapted numerous effective drugs to fight diseases endemic in the world’s poorest countries, such as blinding trachoma, guinea worm, leprosy, lymphatic filariasis, polio, onchocerciasis, Chagas disease, leishmaniasis, or African trypanosomiasis. These products have been central to establishing multi-stakeholder initiatives that aim to improve the health status of the affected populations.

---

**Box 11. Examples of R&D Efforts for Malaria and Tuberculosis**

**Malaria:**
- **Roche** introduced Larium®, **GSK** introduced Malarone® (both offer entirely novel approaches to the treatment of uncomplicated malaria).
- **Novartis**, in collaboration with pharmaceutical companies from China has developed CoArtem®, a combination of natural and semi-synthetic products considered as the most potent anti-malarial currently available.
- **GSK** has recently developed Lapdap®, a new antimalarial product designed especially for developing countries. Currently, **GSK** has two anti-malaria drugs in development (Phase I and III of clinical trials), as well as a potent malaria vaccine in Phase III.
- **Pfizer** is conducting advanced stage clinical studies for a new potent antimalarial combination product involving chloroquine and the anti-infective Zithromax®

**Tuberculosis:**
- **AstraZeneca** has invested $40 million so far in its state-of-the-art research facilities totally dedicated to TB research in Bangalore, India. Approximately 100 scientists are working at the Bangalore Research Institute, which is integrated into AstraZeneca’s Global Discovery Organisation, to find a new treatment for TB and it is hoped a candidate drug will be identified in the next few years.
- **Novartis** has set up the Novartis Institute for Tropical Diseases, a $122 million research institute which will focus on R&D into TB and Dengue fever.
- **GSK** is conducting R&D into diseases of the developing world at its research facility at Tres Cantos in Spain. Among diseases researched, TB remains a substantial target. GSK also cooperates in a project called the TB Vaccine Cluster, a joint academic-industry consortium working on the early stages of TB vaccine R&D.
Need for Complementary Solutions to R&D

The specificity of health problems faced by developing countries is linked to the extreme scarcity of resources available for healthcare. This implies lack of effective markets for pharmaceutical products, underdeveloped healthcare infrastructures, poor human resources capabilities, insufficient political will and no patent protection — all of which are key components of the PIP. Given the fact that pharmaceutical R&D is risky, complex, time consuming and expensive, developing a new medicine designed exclusively for use in developing countries is a difficult decision when judged purely on commercial terms. For this reason, involvement of other partners to share the cost and risk is a constructive way to address the health problems of poor populations.

In practice, for new products to be developed, the public sector (or other donors) needs to provide drug companies with a framework in which there are clear incentives to invest in R&D and to harness their invaluable assets for the benefit of the world’s poorest populations. One approach, which combines the merits of the Pharmaceutical Innovation Platform, as a proven source of new medicines, together with financial and political capacities of partners representing both the private and public sectors, is the public-private partnership. This form of collaboration between multiple partners representing different sectors and capacities mobilises the complementary resources (technology, know-how, funding, political support, etc.) necessary to discover and develop new drugs for “uneconomical” diseases.

Malaria is a prominent example of a disease for which the combined efforts of governments, international organisations, donor agencies and the pharmaceutical industry have yielded useful results. In just three years since its establishment, Medicines for Malaria Venture (MMV) — a public-private partnership initiated by the pharmaceutical industry — has managed to create what is widely viewed as “the largest antimalarial drug research portfolio since World War II” comprising more than 20 projects at different stages of development. Using public and philanthropic funds, the partnership manages a balanced portfolio of projects managed by academic and pharmaceutical partners from developed and developing countries. Several other product development partnerships have been modelled on the experience of MMV, including the Global Alliance for TB Drug Development (TB Alliance) or the Malaria Vaccine Initiative (MVI).

A common feature of these partnerships is the prospect for faster and cheaper drug development, paced by commitments by the public sector to marshall the significant financial resources required. However it is still too early to know if the potential of this partnership approach will be able to match the track record of the business model invented by the pharmaceutical industry, which is so far the only proven way to invent, test and develop new therapies.

To adequately address the problem of lack of efficient and safe medicines for those few diseases affecting exclusively developing countries, two elements are indispensable:

☞ Employment of the unique capacities of the pharmaceutical industry; and
☞ Involvement of the public sector to compensate for gaps in the PIP.

In developed countries, a similar problem has been successfully addressed through so-called ‘orphan drug legislation’, which creates frameworks combining ‘push’ and ‘pull’ mechanisms incentivising pharmaceutical companies to undertake R&D for rare (‘orphan’) diseases. The incentives offered by governments through these schemes range from tax credits and fast track approvals to extended market exclusivity for products developed. In this way, both small biotech and large pharmaceutical companies are encouraged to invest in R&D in otherwise ‘uneconomical’ diseases.

Arguably, similar frameworks could be created to address diseases endemic in developing countries for which new medicines are needed. However, the measures employed would have to be
tailored to the context of developing countries. For example, instead of offering simple market exclusivity, which is of little use in developing countries (because of the absence of a functioning market), such schemes could include an option of transferable market exclusivity. Thus, a company with a new leishmaniasis drug could seek bids from other companies for its exclusive marketing extension right. Such a solution does not require direct public funding, and the arising costs could be proportionally distributed among many developed and emerging markets.¹⁴²

Yet, another solution to encourage drug R&D into diseases of the poor is a ‘pull’ mechanism in the form of a purchase fund. Such a fund could cover a number of diseases concerned (e.g. the three “neglected” diseases: African trypanosomiasis, Chagas disease and leishmaniasis), thus creating a ‘market’ for future medicines developed.¹⁴³ This in turn would work as an incentive for pharmaceutical companies to invest in R&D and develop needed drugs. An example of a purchase fund that triggers pharmaceutical R&D into vaccines is the Global Alliance for Vaccines and Immunisation (GAVI). This global initiative co-founded by the pharmaceutical industry has led to significant improvements in financing higher levels of immunisation in developing countries, making the development of new vaccines for developing countries feasible.

Both public-private partnerships and the above-mentioned ‘push’ and ‘pull’ mechanisms offer prospects for employing the most efficient way of drug discovery and development, as embodied in the Pharmaceutical Innovation Platform. These options are not mutually exclusive and can be used as appropriate for research into specific diseases. Each of them presents a different set of challenges, but the bottom line is that to be successful each requires a visible and sustained commitment from the public sector.

How Can Developing Countries Be Involved?

Drug development remains to date an almost exclusively first world phenomenon. In the period 1997-2001 out of 184 new molecular entities only 4 were developed outside of the European Union, the United States and Japan.¹⁴⁴ However, India, Brazil, and China together account for more than 40 percent of the world’s population and a substantial part of global deaths and DALYs. The disease profiles of their populations are extremely heterogeneous including diseases formerly associated with developed countries such as cardiovascular diseases, cancers, diabetes¹⁴⁵ or neuropsychiatric disorders as well as diseases of the poor like tuberculosis, and region-endemic diseases such as Chagas disease, schistosomiasis, and lymphatic filariasis.

These countries, through pharmaceutical R&D, could both meet their domestic health needs and contribute to global research efforts. Given the growing need for new innovative medicines worldwide, it seems reasonable to argue that the establishment of research-based pharmaceutical industries in such key developing countries would benefit patients worldwide, and generate important financial rewards for the host countries. The list of advantages for the host countries covers social, economic and political benefits (Box 12).

A key group of developing countries that includes China, India, Brazil (but also Thailand, Malaysia, South Africa or Argentina) is well positioned to establish their own domestic research-based pharmaceutical industries, or at least contribute to global pharmaceutical R&D efforts. These countries possess resources, skills and capacities that are central for the pharmaceutical industry. In particular, countries such as India, China or Brazil are renowned for their human resources in natural sciences and technical disciplines, which provide a solid base for further industrial development.

The same countries have also world-class research institutes and technological excellence in such areas as biotechnology or chemistry that are core skills in pharmaceuticals. Also, a number of these countries already have experience in quality manufacturing of modern drugs and vaccines, active ingredients production and to some extent in the synthesis of new compounds and...
Chapter IV: Spreading the Benefits of Medicines Innovation

downstream clinical trials. For example, pharmaceutical and biotech companies from China and South Korea already participate in joint R&D partnerships with academic researchers and multinational companies aiming at developing drugs for malaria and tuberculosis – the MMV and GATB are but two examples.

It is believed that key developing countries could be cost-competitive with pharmaceutical multinationals in funding the cost of developmental research. For example, large Indian generic companies claim they could be financially competitive in new drug development by tapping the lower cost base in their own home market. They see the key attractiveness of conducting R&D in India as lower costs of manpower and infrastructure, cheaper maintenance of equipment, and availability of raw materials and “e-technical” scientists.

Another important source of competitive advantage for some of these countries may be their particular access to biodiversity and traditional knowledge resources. These resources may be used as a base for development of both a commercialised traditional medicines industry (which is becoming more and more popular among patients in developed countries), and a modern pharmaceutical industry.

Using natural resources as potentially valuable sources of novel biologically active molecules can facilitate this transition. It has been claimed that about 140 new drugs have originated directly from natural sources. Examples include:

- Anticancer drug from the Pacific yew tree bark, or paclitaxel, marketed by Bristol Myers Squib as TAXOL;
- Anti-malaria drug COARTEM/RIAMET using Artemisia annua or sweet wormwood and developed by Novartis;
- Aspirin from Salix spp;
- Quinine from Chinona ledgeriana;
- Pilocarpine from Pilocarpus jaborandi;
- Physostigmine from Physostigma venosum;
- Tubocurarine from Chondodendron tomentosum

Box 12. Potential Social, Political and Economic Benefits of Pharmaceutical R&D

- Establishment of high value-added, high technology sector; industry diversification
- International credibility and a raised country profile as host to high technology investment across the broader front
- Development and commercialization of public sector research
- Increased potential for inward investment and joint ventures
- Better access to modern technology and information and technology transfer
- High quality jobs – deployment of graduates/PhDs from universities
- Reduced or limited brain drain
- Improved health care through access to newer medicines
- Country capacity to understand and use state-of-the-art science
- Resolving country-specific disease/medical problems

Encouraging Pharmaceutical R&D in Developing Countries, IFPMA, 2003

Box 13. Examples of Transforming Natural Resources into Modern Medicines

The Pharmaceutical Innovation Platform

Celebrating the Success

In South Korea, US FDA approval of a new antibiotic discovered by a domestic pharmaceutical company was a national event. As expressed by Dr. Yang, the CEO of the company:

‘In the 105-year history of the drug industry in Korea we have not had any drug approved by advanced countries like the United State. It’s really epoch-making.’

Summary Points from chapter IV

❖ The moral imperatives to address neglected diseases must be acknowledged but without losing track of the fact that they count for only a very small part of the overall disease burden of developing countries.

❖ Public-private partnerships that pool research capabilities are a way to overcome the skewed R&D investment climate associated with neglected diseases.

❖ The research-based pharmaceutical industry recognizes that drugs can only provide part of the answer to the health problems of developing countries. Working in partnership with other private and public sector bodies it is making a notable contribution towards finding and implementing sustainable system-wide reform policies and solutions for these countries.

❖ Medicines innovation should not be seen as an industrial asset for rich countries alone. The experience of the PIP business model is now being transferred to those developing economies who have the resources, skills and capacities to develop their own pharmaceutical R&D industry.

A good example of an advanced developing country that is supporting the growth of a research-based pharmaceutical industry is South Korea. By virtue of its outstanding human resources and government policies it is emerging as a pharmaceutical innovator on the global arena. By 2002, the Korean pharmaceutical and biotech companies had 78 and 167 drug candidates in development, respectively. Significantly, the great majority of these projects focus on diseases such as cancer, neuropsychiatric diseases, but also osteoporosis, or ulcers and many of them have been already out-licensed to global pharmaceutical companies. Despite the apparent need for pharmaceutical innovation in key developing countries – a need that could contribute to finding new solutions to the problem of neglected diseases – not enough is being done to make it happen. Instead of supporting the four key elements required to build the PIP model, these countries still promote policies that benefit local, copy-based pharmaceutical industries at the expense of innovation.

Switching from an industrial policy that promotes imitation to one that advances innovation can carry important social and economic benefits. According to the UNDP, technological breakthroughs ‘are pushing forward the frontiers of how people can use technology to eradicate poverty’, as they ‘are creating new possibilities for improving health and nutrition, expanding knowledge, [and] stimulating economic growth’.

The Pharmaceutical Innovation Platform
Health is a critical component of human well-being and welfare, and as such it deserves careful handling through adequate policy choices. There are various social, economic, cultural and behavioural factors directly or indirectly influencing health status. This report, however, has focused on the role and importance of medicines innovation for public health and consequently it has discussed critical elements of the current successful system that generates such innovation.

As described in Chapter I, new medicines, vaccines and other medical tools have contributed to the dramatic gains in health experienced by the world’s population over the past half century of medical progress. Effective use of new medicines has let to increased longevity and improved quality of life of patients. Benefits of new medicines is much broader and includes important economic and social benefits for patients (e.g. restored earnings), healthcare systems (e.g. reduced costs) and the economy at large (e.g. improved productivity). Thus, innovative medicines should be seen as a critical resource for public health – a resource that serves the interests of all public health stakeholders.

As with any other resources, innovative medicines, in order to yield the highest value, require responsible utilisation. One important particularity of medicines is the fact that they operate in a very dynamic environment of public health, characterised by such ongoing developments as the epidemiological and demographic transitions, disease evolution, or drug resistance. This implies

---

**Figure 17. Dynamic Continuum of Medicines Innovation**

![Dynamic Continuum of Medicines Innovation](image-url)
the necessity for continued R&D efforts, not only to improve the existing armamentarium of therapies and treatments but also to create new medicines that could address the ever-growing public health needs (Figure 17).

Ensuring the continuity of medicines innovation is at the heart of sustainable utilisation of medicines as the strategic public health resource. As Chapter II has illustrated, developing a new medicine is a particularly demanding and challenging endeavour, which requires the mobilisation of a critical mass of very specific assets, including human knowledge and ingenuity, scientific and technological excellence and know-how, specialised equipment, and above all — substantial financial capacity. As has been argued, a large number of diverse players participate in the pharmaceutical innovation process, creating the entire complex system of innovation. However, it is the research-based pharmaceutical industry that is the growth engine of this system. Only pharmaceutical companies dispose of all elements necessary to successfully manage the entire chain of R&D, and they are the only ones to have a proven and sustained track record of new medicines discovery, development and global distribution.

Pharmaceutical companies bear the heavy burden of risk associated with drug R&D: sustaining the ever-escalating R&D investments over long time periods is particularly risky in pharmaceutical R&D process where failure rates remain extremely high. Given that most of R&D investments are generated by the pharmaceutical industry, the pharmaceutical R&D cycle is thus dependent on the financial flows resulting from medicines currently marketed. This realisation is crucial for policy makers to understand how medicines innovation functions and how it should be nurtured. As the pharmaceutical industry is unique in that it is one of the few industries in which the government plays an important role and strictly regulates many aspects of its operations, only when policy-makers have a thorough understanding of the industry’s modus operandi and the challenges it is facing can medicines innovation be sustained.

A broad general framework developed in Chapter III – the Pharmaceutical Innovation Platform – is comprised of four major policy pillars, on which the success of the pharmaceutical industry has been built, and which can be briefly characterised in the following way:

- **SUCCESSFUL HEALTHCARE SYSTEMS**
  Successful healthcare systems facilitate the entry of new medicines into their markets by removing overly bureaucratic obstacles to drug registration and by making approval procedures efficient and effective. Patients are allowed access to accurate and responsible pharmaceutical product information and have input into new treatment guidelines that are promptly implemented. Indeed, in progressive countries, healthcare systems shift from being “physician-oriented” towards being “patient-oriented”.

- **EFFICIENT MARKETS**
  Efficient markets are the source of financial flows that are re-invested to develop new treatments and therapies in the future. They represent direct mechanism for rewarding medicines innovation. Governments promote the efficiency of their markets if they value innovation on the basis of its long-term effects for patient’s well-being and health status, as well as the aggregate long-term performance of the entire healthcare systems. Because each country is different, and each government formulates a unique policy mix, pharmaceutical companies differentiate prices of their products, which helps diffusing innovation in the most efficient way.

- **EFFECTIVE USE OF INTELLECTUAL PROPERTY**
  Governments wishing to promote innovation implement policies which recognize the key role of intellectual property protection in promoting innovation. Such policies allow for sufficient and enforced market exclusivity periods so that domestic and for-
Conclusions and Policy Recommendations

Foreign innovators can reap the benefits of their inventions. Such protection provides for an important impetus for continued innovation in the future, which is key to future public health needs. By preventing international exhaustion of patents, governments recognize not only the negative impact of such parallel trade on innovation, but also how parallel trade cuts at the basis of differential pricing systems designed to expand access to needed medicines, as well as the possibility of opening their markets to counterfeit and substandard drugs through parallel trade.

Efficient and Effective Technical Regulation Systems

Regulatory requirements represent a critical component of medicines innovation, ensuring that new medicines reaching patients are safe, efficient and of highest quality. Because regulatory costs substantially drive the costs of new medicines, it is in the interest of governments and patients to make the regulatory process as swift and effective as possible, without compromising safety and quality standards. Progressive governments see a strong interest in accepting common submission of regulatory dossiers for all countries in order to avoid unnecessary duplication of registration dossiers. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an important step forward in making drug registration swifter and more efficient internationally. Also, national regulatory authorities introduce new procedures and rules to streamline and perfect clinical development and registration of new products.

These four pillars determine the ability of the pharmaceutical industry to prosper and innovate, having substantial impact on each of the stages of the pharmaceutical value-added chain. Thus, policy decisions under each of these pillars should be preceded by important considerations regarding expected outcomes. In particular, short-term policy objectives, such as for example reducing budgetary expenditures for health, should be balanced against longer-term results for patients, healthcare systems, and the pace of medicines innovation. Many seemingly immediate and easy gains may have important negative public health repercussions in the future. Because the pharmaceutical R&D cycle is long and uncertain in itself, unfavourable policy shifts may have damaging effects on the future of innovation, resulting in dangerous science and technology gaps, which can be irreversible.

Health needs are global and consequently, appropriate policy formulation is valid for both developed and developing countries. As argued in Chapter IV, medicines innovation has delivered effective treatments and therapies for all major diseases affecting patients worldwide. In some cases, where a disease is endemic only among the poorest countries, none of the four pillars of the Pharmaceutical Innovation Platform exists, which in turn hampers the likelihood of sufficient R&D efforts. Pharmaceutical companies have demonstrated their ability to proactively address such difficult situations, initiating important collaborations with other R&D players and partnering with public sector institutions through public-private partnerships to find the most adequate solution. Sharing responsibilities and risks among a broader group of public health stakeholders enables to harness the unique skills and capacities of the pharmaceutical industry for the benefit of poor populations.

Finally, a group of leading developing countries, with certain established R&D capacities, are most likely to benefit from the Pharmaceutical Innovation Platform. A policy mix supportive of medicines innovation, if applied in these countries, could trigger domestic R&D-driven industries and result in important social and economic benefits. Through enlightened policies, these countries could both contribute to global research efforts and address their own specific health needs. Indeed, in the era of the knowledge economy, it is in these countries own interest to pursue policies that stimulate the competitiveness of their pharmaceutical industries to become global leaders of medicines innovation.
References

8. SARS has also proven the critical role of pharmaceutical companies in finding new cures. Just months after the outbreak of the epidemic there were nine biopharmaceutical companies working on drug/vaccine candidates for SARS. Scrip, 7-9 May 2003.
27. STI Scoreboard 2003, OECD, Directorate of Science, Technology and Innovation.


42 Luce C.B., Total value of innovation: Choosing metrics that matter in health sciences. Ernst & Young 2004.


46 FDA requiring more postmarketing studies, Scrip, No. 2970, 16 July 2004.


49 i.e. having completed various drug discovery processes that serve to identify whether many compounds bind with the target selected in the discovery phase (identification), and whether the chemistry of the identified lead can be improved to give better potency, safety, solubility and other characteristics (optimisation). Biological assay development is crucial to successful drug development, as these assays support the entire process of development, serving as measures of the effects of compounds tested.

50 According to a survey by the Japan Pharmaceutical Manufacturers Association (JPMA) only one in almost 5,500 synthesised and extracted compounds received regulatory approval in the period 1998-2002. JPMA, Data Book 2004.


57 For example, the number of new targets expected from the Human Genome Project is between 3,000 and 10,000, compared with approximately 500 targets known today. Drews J., Journal of National Biotechnology, 1996.

59 High throughput screening (HTS) permits parallel testing of very large number of compounds. It increases yearly throughput of a typical lead discovery group from about 75,000 samples tested on about 20 targets to over a million samples tested on over 100 targets.


61 Barrett A., Arndt M., No quick cure for big pharma: why the industry’s down cycle won’t be over soon. BusinessWeek Online, 6 May 2002.


63 Datamonitor, IT and Big Pharma: Vendor Pharmageddon or Economic Downturn, 2003.


66 The FDA calls for the intensification of research needed to improve the “critical path”, i.e. the development phase of R&D process, seeing it as the most important factor hampering the delivery of innovative medical products today.


71 See for example the case of National Horizon Scanning Centre, at http://www.publichealth.bham.ac.uk/horizon/


74 Fuhrmans V., Rare diseases force families to fund medical research. The Wall Street Journal, 26 February 2003.

75 7,602 of the 10,375 drugs listed on the FDA’s Orange Book have generic counterparts. See http://www.rphonline.org/aboutgenerics/factsabout.html


92 JPMA, Japan’s pharmaceutical industry. Office for Pharmaceutical Industry Research, 2003.


113 Sykes R.B., 2000, idem.


116 World Trade Organisation, Declaration on the TRIPS Agreement and Public Health, Paragraph 5d.


122 EMEA, Roadmap to 2010: Preparing the ground for the future, March 2004.


This is the so-called 10/90 gap, advocated by the Global Forum for Health Research. See for example Global Forum for Health Research, The 10/90 Report on Health Research 2000.

For the purpose of this chart, numbers of annual deaths occurring in developed and developing countries have been expressed as a pro mil (1:1000) of total population of developed (1,354 million) and developing countries (4,770 million). Consequently, a more relative disease burden could be estimated for major disease groups.


In reality, the absolute majority of medicines needed in developing countries (i.e. medicines which are on the WHO Essential Drugs List) are not patented in the countries concerned. Of the 314 WHO essential medicines, at most 17 are patentable anywhere in the world (including 12 antiretrovirals and one antifungal), yielding an overall frequency of granted patents and pending applications of 1.4% for all the cases studied, with most of that accounted for by the antiretrovirals of one company. Attaran A., How do patents and economic policies affect access to essential medicines in developing countries? Health Affairs; Vol. 23, No. 3, 2004.


Kettler H. E., Narrowing the gap between provision and need for medicines in developing countries, Office for Health Economics, London 2000.


SCRIP data and EFPA calculations.

The world’s greatest number of diabetes cases are in China and India.


Indian drug research at fraction of global costs. Scrip, No. 2863, 2 July 2003.


The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) is a non-profit, non-governmental Organization (NGO) representing more than 60 national industry organizations from both developed and developing countries. Member companies of the IFPMA are the major global research-based pharmaceutical and vaccine companies.