Global Pharmaceutical Policy

Ensuring Medicines for Tomorrow's World

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Frederick M. Abbott

Edward Ball Eminent Scholar Professor of International Law, Florida State University College of Law, USA

Graham Dukes

External Professor of Drug Policy Studies, Institute of General Practice and Community Health (Section for International Health), University of Oslo, Norway

Edward Elgar
Cheltenham, UK • Northampton, MA, USA

Published by
Edward Elgar Publishing Limited
The Lypiatts
15 Lansdown Road
Cheltenham
Glos GL50 2JA
UK

Edward Elgar Publishing, Inc.
William Pratt House
9 Dewey Court
Northampton
Massachusetts 01060
USA

A catalogue record for this book
is available from the British Library

Library of Congress Control Number: 2009930852

ISBN 978 1 84844 090 6

Printed and bound by MPG Books Group, UK

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Preface

Two major developments at the outset of 2009 lend a special timeliness to the publication of this book. First, the Democratic administration of President Barack Obama took the reigns of health policy in Washington, DC, promptly signaling a determination to reform the way that health care is provided in the United States. Second, a global financial crisis has sent shockwaves throughout virtually all sectors of economic activity in practically every country of the world. These two developments, taken together, suggest that policymakers will pay increasingly serious attention to the way medicines are developed, distributed and used.

Wealthier societies can no longer afford wasteful and ineffective public health expenditure. Poorer societies face even greater burdens than before. Governments throughout the developing world face extreme difficulty in funding medicines procurement. Under these background conditions, this book analyzes and offers suggestions to improve the global pharmaceutical regulatory system.

The originator pharmaceutical industry confronts its own financial crisis, and is unlikely to greet a critical examination of its role with equanimity. However, our objective is not to question the important role that industry plays in promoting research or manufacturing products of high quality. It is instead to ask whether there are better ways to make use of the vast resources committed in this field, and to improve the level of prevention and treatment available to everyone.

We hope you will find this book a useful contribution to the urgent dialogue.

Frederick Abbott
Tallahassee, Florida USA

Graham Dukes
Oslo, Norway

Acknowledgments

Issues surrounding a proper framework for regulation of the global pharmaceutical sector are complex, and have been the subject of analysis and debate for many years. Devising a proper framework is a long-term project, and most likely the approach will be piecemeal. It seemed opportune in the Spring of 2007 to bring together a number of the most creative and forward-looking thinkers on this subject – collectively with a vast experience in medicine, law and technology – to discuss the 'state-of-the-art' in global pharmaceutical regulation and proposals that might be in the works for improving the existing framework. To that end, a three-day open-ended dialogue was held at Florida State University College of Law in Tallahassee Florida, with about 30 participants from across the geographic and subject matter spectrum in pharmaceutical regulation.

This book is in large measure a tangible output of that meeting in Florida but updated to 2009. The text is the 'own work' of the two authors, but to provide additional perspective we have included various brief 'text boxes' on the basis of presentations by meeting participants. In addition, we have solicited input from several other experts, also presented in boxes at various points in the text.

We extend our thanks to all of the participants in the Florida meeting, listed here, and to additional contributors, also listed. We hope that by broadening the intellectual base of the book we provide our audience with a more richly informed perspective.

Florida meeting participants: Frederick Abbott, Ryan Abbott, Tahir Amin, Wilbert Bannenberg, Jorge Bermudez, Timothy Cross, Graham Dukes, Paulo Etcheverry, Carsten Fink, Joseph Fortunak, John Fraser, Marta Gabrieloni, Ellen 't Hoen, Maria Fernanda Hurtado, Elisabet Helsing, M. Fabiana Jorge, Lorelei Ritchie de Larena, David Lee, James Love, Precious Matsoso, Thomas Mays, Priti Radhakrishnan, Jerome Reichman, Pedro Roffe, Dilp Shah, Michael Steffen, Robynn Sturm, Antony Taubman, Yolanda Tayler, Gina Vea, Howard Zucker

Additional contributors: Arthur Daemmerich, Hilbrand Haak, Daniel W. Sigelman

We extend a special note of thanks to Fred's wife, Cathy Abbott, who spent long hours transforming our rough text into a readable end product.

Cross-Atlantic collaborations require reconciliation of different linguistic cultures. Cathy has done a superb job of mediating among our English-language traditions.

Abbreviations

APIs	active pharmaceutical ingredients
ASEAN	Association of South East Asian Nations
CBD	Convention on Biological Diversity
CDER	Center for Drug Evaluation and Research
CPMP	Committee for Proprietary Medicinal Products
DFID	Department for International Development
DNDi	Drugs for Neglected Disease Institute
DTC	direct to consumer
EMEA	European Medicines Evaluation Agency
EC	European Commission
EU	European Union
EURODIS	European Organization for Rare Diseases
FAO	Food and Agriculture Organization
FDA	US Food and Drug Administration
FTA	free trade agreement
GAVI	Global Alliance for Vaccines and Immunization
GMP	Good Manufacturing Practice
HCV	hepatitis C virus
ICH	International Conference on Harmonization
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
INCB	International Narcotics Control Board
IND	Investigation Exemption for a New Drug
LDC	Less Developed Country
MABs	monoclonal antibodies
MHRA	Medicines and Healthcare Products Regulatory Agency
MMV	Medicines for Malaria Venture
NGO	non-governmental organization
NICE	National Institute for Health and Clinical Excellence
NIH	US National Institutes of Health
NSF	National Science Foundation
OGTR	Office of the Gene Technology Regulator
OTC	over-the-counter

PhRMA	Pharmaceutical Research and Manufacturers of America
PPP	public-private partnership
R&D	research and development
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
SSRIs	Selective serotonin reuptake inhibitors
TDR	Special Programme for Research and Training in Tropical Diseases
TK	traditional knowledge
UMC	Uppsala Monitoring Center
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Contents

1. The challenges we face

OUR OBJECTIVE

Pharmaceutical products play a central role in the prevention and treatment of disease. Making safe and effective pharmaceutical products available and affordable to individuals around the world is a central challenge to the global governance system. There are however myriad obstacles to achieving and maintaining effective worldwide availability of medicines.

Despite the fact that people around the world face largely similar challenges from disease, the policy framework for promoting innovation and regulating pharmaceutical supply is remarkably disjointed. Innovation policy, insofar as it is implemented at all, is established on a country-to-country basis with minimal attention to coordination of research and development. Regulatory structures are almost equally fragmented. Each country has its own set of approval standards and regulatory procedures that must be dealt with, and only to a limited extent are there cooperative procedures or systems of mutual recognition. Corporate decisions concerning where to concentrate innovative efforts, what to produce, where to supply it and on what terms are based on the likely impact on profits and capital markets.[1]

There are wide disparities in levels of income both among countries and within countries. Prices that are reasonably affordable for individuals covered by health insurance in developed countries are likely to be unaffordable for individuals without health insurance in developed and developing countries. There are compelling needs for new medicines to treat diseases affecting both the rich and poor, such as diabetes, cancer, heart disease and the degenerative disorders of old age. Innovation in these areas is costly, yet even with substantial sums invested in research and development rates of innovation are surprisingly low. There are equally compelling needs for new medicines to treat disease conditions predominantly afflicting tropical regions where poverty rates are typically high. Far less is invested in the diseases of the poor because of a lack of market demand.

Medicines must be safe and effective. Making and keeping them so is a challenge for both private and public sector suppliers, for the regulators charged with promoting and protecting public health and for the policy makers who determine the framework within which regulation operates.

This book examines the state of play of the international system for the development and supply of pharmaceutical products, and offers insights into how some of its challenges might be addressed. This system is enormously complex, with many moving parts, and there is not likely to be a quick fix for the many challenges. There are quite a few good ideas circulating among individuals and groups involved in formulating and implementing public policy in the field of medicines. This book was inspired by a roundtable among such individuals and groups hosted at Florida State University College of Law in the spring of 2007. At that roundtable, a number of the ideas discussed in this book were put forward and debated. The perspectives of some roundtable participants (and others) are incorporated at various points in the book, often in 'boxes'. Certainly new initiatives are needed in this field, and existing initiatives can and should be improved. We try to identify and explain those areas in which present policies are not working, and we offer suggestions regarding ways to improve them. We put forward our own proposals regarding directions that global public policy in the field of medicines should take. We do not claim a monopoly on promising ideas. We hope that this volume will succeed at least in moving the dialogue on these subjects forward.

OVERVIEW

Broadly speaking, there are two main categories of pharmaceutical products available on world markets. The first consists of newer originator medicines that are covered by patent protection (and/or the protection afforded in some instances by regulatory marketing exclusivity) and are typically sold at substantially higher prices than older established medicines. These originator medicines are developed, produced and sold by a handful of large multinational innovator companies, virtually all of which are based in the industrialized countries. The second category comprises generic medicines that are not (or are no longer) subject to patent or marketing exclusivity protection, and that are typically sold at substantially lower prices than originator products – commonly no more than 5 percent or 10 percent of the former price. Generic products are produced by a wide range of companies, ranging from small-scale to major multinational operators, based throughout the world. Generic pharmaceutical products sell in much larger volumes worldwide than originator products but, because of the immense price difference, gross revenues from sales of originator pharmaceuticals far exceed those from generic products. In 2007 total worldwide revenues from sales of pharmaceutical products amounted to approximately $650 billion, of which $550 billion went to the originator companies and $100 billion to the generic companies.

INNOVATION POLICY

Research and development (R&D) aimed at the creation of new medicines is well understood to be necessary for the prevention and treatment of disease, and policies designed to promote innovation are a core component of global public policy in this field. Industry has done much through information campaigns to create the popular impression that major pharmaceutical companies have been consistently successful and efficient in ensuring innovation. In actual fact, as shown in Chapters 2 and 3, the rate of innovation over the past decade has been decidedly low and the medicines developed have not always been well attuned to actual needs. Publicly funded research has made a significant contribution to the progress that has been made, a contribution that is not always sufficiently recognized.

The history of pharmaceutical innovation in modern times has involved periods of ebb and flow. A decade or two of rapid advance across a range of disease targets, generally based on a major technological advance, tends to be followed by a period in which few new treatments are developed, leading to concern as to whether the possibilities for innovation have been exhausted. Today we are in a period of low tide. Few significant new products are being introduced. Most of the products being brought to market by the pharmaceutical originators are minor modifications of earlier products. Perhaps most significantly, the widely proclaimed new era of biotechnology has yet to prove its ability to deliver on the enthusiastic claims that have been made for it.

A number of reasons have been suggested for the present low rate of innovation. First, the originator pharmaceuticals market is influenced by perverse incentives. Innovator companies find they are well rewarded for making minor modifications to previously patented products so as to effectively extend the life of monopolies (so-called 'evergreening'), a low-risk practice that is highly lucrative. Perverse incentives also encourage investment in lifestyle drugs for which there is an ever-present consumer demand. Because capital markets are most concerned about profits, senior management at the originator companies is less inclined to take risks than to pursue relatively safe bets on product line extensions.

Second, it is sometimes suggested that the low-hanging fruit of pharmaceutical innovation already has been plucked. In particular, innovations for which synthetic organic chemistry is capable have largely been identified, and more complex large-molecule and biological materials innovations promised by the biotechnology industry are more costly and difficult than perhaps initially assumed.

It may be – as the industry suggests – that spectacular success in the biotechnology sector is just around the corner. Indeed, looked at from a

long-term perspective, the biotech industry is in its infancy. The human organism may be more complicated than biotechnologists expected when they first began to decode the human genome, but patience may be rewarded as more complex biological systems are better understood.

Third, the originator pharmaceutical industry has gone through two decades of consolidation, and the net result of consolidation is a reduction in the targets of opportunity being pursued by R&D laboratories.

Fourth, there is a disconnect – apparent worldwide – between research in university and research institute laboratories and the realities of producing new medicines. There is a shortage of individuals qualified and willing to 'translate' laboratory innovation into products entering the marketplace, and in a position where they can ensure that this happens.

A number of proposals have been made to retool the mechanisms for promoting innovation in the pharmaceutical sector. These include reforming patent laws so as to remove perverse incentives to extend the life of patents through minor modifications, changing the type of remedies that are available to patent holders able to prove infringement, developing alternative quasi-patents that would provide more limited types of exclusivity for minor modifications, shifting the focus of innovation promotion to the use of prizes to address specifically identified disease targets, expanding and improving the use of government (and private foundation) subsidies to channel R&D investment more appropriately, and working to disaggregate the reward for developing innovative products from the prices consumers ultimately pay for medicine.

A critical aspect of the innovation equation involves the lack of attention to diseases primarily affecting individuals in poor and primarily tropical countries, the so-called neglected diseases. These are diseases like sleeping sickness, dengue fever and Chagas disease. Because the individuals who require treatments for these diseases are without financial resources, there is, as noted above, no market-based incentive for investing in R&D on pharmaceutical products to treat them. During the past five or six years a number of public-private partnerships have evolved to pursue research on these treatments, and so far the prognosis is fairly good. But these efforts must be sustained, and this will require continued effort and attention.

There are a significant number of obstacles to overcome when attempting to define and recommend truly global policies on innovation. The financial and human resources available to governments and private sector investors differ widely. The disease profiles of countries vary depending on a variety of factors, including climate, geography and income level. Industrial policy as regards promoting the development and/or maintenance of pharmaceutical manufacturing is an important element affecting innovation policy.

Governments are also limited in the range of innovation policies they

may adopt as a consequence of more or less globally applicable rules adopted for countries that are members of the World Trade Organization (WTO) that is now virtually all-embracing. These rules are embodied in the Agreement on Trade-Related Aspects of Intellectual Property Rights (or TRIPS Agreement) that entered into force on 1 January 1995. The TRIPS Agreement requires all WTO member countries to provide protection for pharmaceutical products and processes (with certain exceptions remaining for 'least developed' countries). A ten-year transition period that permitted developing countries like India to avoid granting protection expired on 1 January 2005, so that essentially all countries with advanced pharmaceutical production capacity are today required to provide patent protection.

Patents are not the only form of intellectual property protection available to pharmaceutical originators. Public health regulatory authorities in a substantial number of major jurisdictions grant a period of marketing exclusivity to the first party that obtains approval for a new pharmaceutical product. The theory behind such exclusivity is that it rewards the originator company for investing in clinical trials. In the European Union (EU), there is a ten-year (plus one) marketing exclusivity period. In the United States, there is a five-year period, subject to supplementary clinical data-based extensions. These grants of marketing exclusivity are supplementary to patent protection, and serve to inhibit the introduction of generic versions of originator products. The United States and EU have very actively promoted the adoption of marketing exclusivity grants in other countries, including developing countries. Marketing exclusivity rights strongly enhance the power of the originator pharmaceutical companies, particularly in markets where they have not secured patents, or have secured weak patents. There is presently ongoing in the United States a critical debate in Congress concerning the extent to which originator biotechnology-based pharmaceutical products (so-called 'biosimilars') will be protected against generic competition by marketing exclusivity rules. The outcome of this debate will have an important global effect because complex biotech medicines are typically exported from the major developed countries, and because the United States recently has been successful in causing other countries to emulate its rules.

The TRIPS Agreement allows flexibility in the way governments implement their patent law, and it provides a number of exception mechanisms, such as authority to grant government use and compulsory licenses that bypass the patent holder. It remains, however, arguable whether TRIPS flexibility and exceptions are sufficient to permit developing countries, in particular, sufficient leeway to protect their best interests and to develop their own innovative pharmaceutical sectors. Moreover, the United States has led the way in striking bilateral trade deals with developed and

developing countries that limit even further the options available in innovation policy. (These matters are discussed in Chapter 2.) This is the environment in which government policy makers presently operate.

Economies of scale play an important role in innovation and in the development of successful pharmaceutical manufacturing industries. If it is not feasible to coordinate innovation policy at a global level, it may be wise to concentrate efforts at the regional level where similarities among national capacities and needs are likely to outweigh differences, and where legal frameworks established by regional economic arrangements may provide necessary institutional structures. The theme of the potential for enhanced regional coordination and collaboration is found throughout this book.

The World Health Organization (WHO) was established to promote global public health. During the past three or four years the WHO has more actively debated innovation policy and the role that the organization may play in promoting innovation. With the adoption of a Global Strategy and Plan of Action in 2008, the World Health Assembly (the senior governing body of the WHO) has taken a significant step toward proactively encouraging new models of innovation. There is reason to be cautious about the progress that can be made at the WHO because of factors that affect governance at all multilateral organizations. With 200 national governments represented and myriad stakeholder interest groups, with the pharmaceutical industry highly active as one of the nongovernmental organizations (NGOs) in consultation with the agency, it may be difficult to reach consensus decisions that will exert a meaningful effect on national governments in the near to medium term. Over the long term we may expect the WHO to take a larger role in the development and implementation of innovation policy. For the shorter term we expect that concrete action will mainly take place at the national and regional levels.

Regardless of the way the structure of innovation policy is determined, it is essential that all countries and regions have reasonable access to new technologies that are necessary to develop and produce appropriate medicines. The international legal structure and international financial mechanisms must be tailored in a way that promotes rather than inhibits dissemination of knowledge. Innovation policy must be designed to encourage invention by providing suitable reward, but not at the expense of human suffering.

REGULATION OF SAFETY AND EFFICACY

Regulation of the pharmaceutical sector is aimed primarily at ensuring that all of the products used to treat patients are safe and effective, regardless

of whether they are originator or generic products. There is a great deal of subject matter under the tent of safety and efficacy. The process of regulation begins in earnest when an originator company seeks approval from regulatory authorities for the introduction of a new product.

Determining whether a new medicine is indeed safe and provides therapeutic benefit (that is, is efficacious) is one of the most difficult areas of pharmaceutical regulation. New products seeking regulatory approval typically must have undergone a series of clinical trials proceeding from a basic test of safety (Phase 1), to a limited test of efficacy (Phase 2), to a wider test of efficacy and safety involving a substantial pool of human subjects (Phase 3). Based on our current state of knowledge, it is perhaps surprising that it remains so difficult to predict whether a medicine that has shown some promise in test tubes (*in vitro*), or in animal testing (*in vivo*), will prove safe and effective when tested on groups of human subjects. Even when the findings in pre-marketing studies in man are positive it remains difficult to extrapolate from these in order to anticipate the effects of medicines taken over longer periods of time. Recent experience with the Cox-2 inhibitors (wherein use for an extended period proved to pose a significantly heightened risk of coronary event) illustrates this point, as well as the absolute necessity for complete openness as regards the results of clinical work.

In principle, medicines should not harm the patients whom they are intended to treat. Yet this is not an absolute standard. Most medicines have some undesirable side effects, at least in certain patients. The objective of regulation is to make sure that these side effects are appropriately proportionate to the benefits the medicines are conferring. We should not put patients at risk in treating common headaches. We may elect to tolerate more significant risk in treating late stage cancer.

In recent years there has been very substantial criticism of a common industrial and regulatory practice of maintaining the confidentiality of the results of clinical trials. This prevents independent researchers from having a close look at the data underlying the conclusions presented to regulators. As a result of this criticism – based on unfortunate real world events – there is now a modest trend toward disclosure of clinical trial results, largely on a voluntary basis in some countries. There are proposals, discussed in this book, to require making all clinical trial results public, or even to shift responsibility for the conduct of clinical trials to the public sector.

It is of some interest that clinical trials in most countries are primarily designed to compare the new medicine with a placebo, and not with existing therapies for the same condition. The regulator approves a new medicine not because it is better than the established medicines, but because it