



Topic 5
How Does the Regulatory Framework
Affect Incentives for Research and Development?

Prepared for
World Health Organization's
Commission on Intellectual Property Rights,
Innovation, and Public Health (CIPIH)

Response Prepared by
USP CIPIH Advisory Panel
International Health Expert Committee
of USP's Council of Experts

November 16, 2005

Authors

This paper is the work of a USP Advisory Panel whose members' names, together with those of contributing USP staff, are included in Attachment 1.

The Advisory Panel worked in accordance with USP's rules and procedures at the direction of the International Health Expert Committee of USP's Council of Experts, whose members' names are included in Attachment 2.



Table of Contents

Executive Summary	5
Introduction.....	7
Coincident Papers	8
General Themes	8
Developing Countries: The Challenges	8
Disease Burden	8
Table 1. Current Disease Portfolio.....	9
Discovery and Research and Development	10
Regulatory Capacity.....	10
Poverty and Health Care Workers	11
Counterfeit and Substandard Medicines	11
Science and Technology: Possibilities for Hope	12
Molecular Biology	12
Discovery	14
Genetics/Genomics and Pharmacogenetics/Pharmacogenomics.....	14
Computer Modeling and Other Information Technology Tools.....	15
Biomarkers and Surrogate Markers	15
Comparisons to Placebo versus Controls.....	15
Adaptive Trial Designs	16
Bayesian Statistics	16
Subpopulation Studies	16
Information Management.....	17
Technology to Combat Counterfeits.....	17
Outcomes Studies/Pharmacoeconomics Studies.....	17
Regulatory Decision-making: Special Needs of Developing Countries.....	17
New Medicines	17
Efficacy and Effectiveness.....	18
Measurement of Risks/Adverse Events	18
Risk–benefit Trade-offs	19
Risk–benefit Trade-off Judgments.....	20
Cost-effectiveness in Regulatory Decision-making.....	20
Implications for Developing Countries.....	21
Multisource (Generic) Medicines	21
Over-the-Counter Medicines	23
Access: Special Challenges in Developing Countries	23
Accessibility.....	23
Availability	23

Affordability	24
International Norms	24
National Regulation	24
Acceptability	25
Capacity Building	26
The WHO Pre-qualification Project.....	27
European Certificate of Suitability	27
USP Dietary Supplement Verification Program	28
Emerging Regulatory Landscapes	28
Example for Registration: US FDA.....	28
Example for Pricing: Australia’s Pharmaceutical Benefits Price Authority.....	30
Examples for Quality of Care: The UK’s National Institute for Clinical Excellence and the US Health Plan Employer Data and Information Set	31
Examples for Patient Safety: The UK’s National Patient Safety Agency and the US Joint Commission for the Accreditation of Healthcare Organizations	31
Collaborations in Developing Countries: Hope for the Future.....	32
Collaborations for Discovery and Research and Development	33
Collaborations for Registration of New Medicines: Potential Opportunities	34
Efficacy	34
Risk	35
Quality.....	35
Collaborative Action for a Scientific Opinion	35
Collaborations for Multisource Interchangeable Medicines.....	35
Collaborative Standards-setting Activities	36
Developing Countries: The Role of Practitioners and Patients	37
The Way Forward: A Global Health Care Secretariat	38
References.....	41

EXECUTIVE SUMMARY

Regulatory agencies in developing countries are resource constrained in terms of staffing, standards, systems, and training. Staffing is probably the key challenge, but sound, consistent standards (laws, regulations, guidances, private and public quality standards—including physical standards as appropriate) also are needed, both for information to be supplied in regulatory and other filings to allow sound decision-making and for other conformity assessments. For discovery, development, registration, and utilization, standards themselves devolve on a sound scientific and technical understanding of the information needed to market and utilize a medicine. The methods of science rely on core questions—Is a medicine safe and does it have effectiveness? What are its risks? What is its quality? These questions lead to hypothesis-testing studies, the outcomes of which should support regulatory decisions to allow and maintain market access. Unfortunately, research is expensive, and the answers may be difficult to fashion into acceptable approaches, given lack of resources, outdated laws and regulations, bureaucratic inertia or corruption, and public or private opposition. Beyond these primary (and well-known) topics, a new regulatory landscape is emerging based on pricing and payment decisions, outcomes/pharmacoeconomic studies, evidence-based quality of care, and patient safety considerations. Taken together, these various approaches speak to rational use of a medicine in the overall context of cost-effective and evidence-based health care delivery.

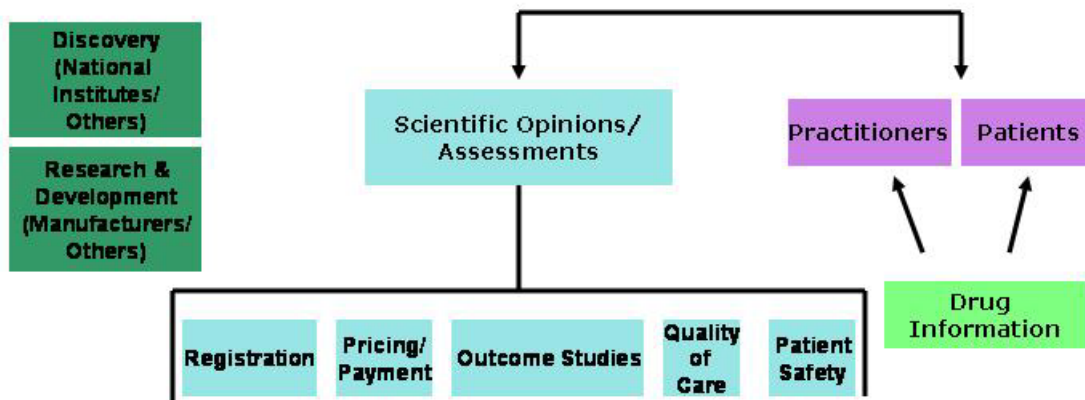
With these various factors in mind, this paper postulates that regulators of developing countries may be in a remarkable position to advance, by collaborative activities, basic research, discovery, drug development, registration, utilization, and related approaches for medicines (with allied activities) to prevent and treat diseases that have plagued humankind for centuries—and for medicines to treat other conditions as well. In the past several years, national, sub-regional, regional, trans-regional, and global activities for collective action have appeared and offer hope. These not only have yielded needed registration and other standards but also have engaged regulators in the conduct of bilateral and multilateral conformity assessment activities. They have thus moved beyond information sharing and harmonization to yield useful results; i.e., they are action oriented. The general theme of this paper is that these efforts should be strengthened and, when possible, expanded and consolidated. Ultimate consolidation is based on a vision of a collaborative global regulatory enterprise with multiple components, involving representatives from all countries, and yielding decisions suitable for national adoption. The components would focus on a) discovery; b) research and development; c) sound regulatory decision-making and, when appropriate, rapid registration decisions and postapproval change and other controls; d) optimal pricing/payment strategies; e) evidence-based health care delivery based on outcomes/pharmacoeconomic studies, f) quality of care, and g) safe medicine use.

As a further proposal, this paper argues for close involvement of practitioners and patients throughout the overall process and urges for them a dominant role after registration. Specifically, it proposes a consortium of practitioners and patients to

advance optimal health care, including pharmaceutical care, based on continually updated drug information. Independent, credible, authoritative practitioner and consumer experts would transform prospectively and retrospectively designed research studies and observational data into knowledge-based information monographs and wisdom-based brief summaries and alerts, following the paradigm of

data → information → knowledge → wisdom.

An overarching theme is the need for action. With sufficient (but not exorbitant) resources, a collective effort based on this shifting duality of inputs (regulators to the community and community to regulators) may promote, as overarching strategic objectives, rational use of medicines and good, cost-effective health care delivery practices. The overall structure to achieve these strategic objectives is postulated to be a health care secretariat, shown in the figure below, operating in close cooperation with the World Health Organization, with frequent and continuing input from governmental and practitioner/consumer experts from all countries of the world and in particular from developing countries. This input would yield science and policy decisions that would be suitable for national adoption, based on local acceptance and modification if needed.



INTRODUCTION

The Commission on Intellectual Property Rights, Innovation, and Public Health (CIPRH) developed a list of 10 topics with associated papers (Attachment 3). Topic 5—*How Does the Regulatory Framework Affect Incentives for Research and Development?*—is one of these. The Terms of Reference for Topic 5 are available on-line (1). The goals/study considerations in the terms of reference for Topic 5 are:

1. Generate practical proposals for risk–benefit balance in regulatory frameworks, recognizing needs of the developed and developing world.
2. Focus on problems of safety, quality, and efficacy of drugs for developing countries with minimal regulatory control and little medical supervision.
3. Postapproval requirements and pharmacovigilance require special attention.
4. Consider also generic drugs, including patent issues.

In these contexts, review how the regulatory framework affects incentives for—and costs of—research and development (R&D) and access, particularly with respect to medical products for developing countries, including:

- Growth of regulatory requirements as they influence cost and incentives for R&D investment in medicines needed in developing countries.
- Review the impact of national and international arrangements for the introduction of new drugs and generics (International Conference on Harmonization [ICH], World Health Organization [WHO], regional, and national standards and requirements) with relevance to approval of/access to medicines in developing countries.
- Consider the challenges of regulating new medical technologies with implications for developing countries.
- Consider regulatory policies to facilitate the marketing approval of generic medicines.
- Make proposals about possible changes in regulatory approaches, at both national and international levels, that could contribute to faster and more cost-effective regulatory procedures to facilitate the introduction of new medicines and biologicals in developing countries.

Recognizing the breadth and complexity of the issues to be dealt with, this paper provides broad summaries of key systems. These systems involve individuals and groups (the “who”) working either alone or collaboratively according to complex national and international systems (the “how”) to achieve better health care for patients in developing countries (the “where”), focusing on current and new medicines to treat neglected diseases (the “what”). The authors apologize in advance if this overview omits key systems or insufficiently describes those that are discussed.

Coincident Papers

The following papers are also prepared to address Topic 5:

- *A Proposal for a Regulatory Framework and Introduce Incentives for Research and Development*. Authors: P. Matsoso et al.
- *Drug Regulation and Incentives for Innovation: The Case of ASEAN*. Author: S. Ratanawijitrasin, Ph.D.

An executive summary of each paper appears in Attachments 4 and 5, respectively. This paper does not reproduce the information and analyses of these papers, which should be viewed as complementary.

General Themes

The general themes of CIPIH's endeavors were articulated and discussed during meetings at WHO in Geneva May 30–June 1, 2005.¹ Four themes were considered at these meetings (4). Of the four, Theme D is most pertinent to this paper.

- Theme A: Current trends in terms of the global burden of disease and how they inform R&D financing priorities;
- Theme B: How does the intellectual property (IP) system affect R&D and access, and how might national patent systems need to change?
- Theme C: What new ideas can stimulate innovation and promote access? Can we improve the R&D process for medicinal products?
- Theme D: Which policies may lead to the development of innovative capacity in developing countries, including regulatory systems?

DEVELOPING COUNTRIES: THE CHALLENGES

Disease Burden

The term *neglected diseases* refers generally to tropical infectious diseases that are seriously disabling or life-threatening, that disproportionately affect millions of people in developing countries, and that have limited or no treatment options (5). At times they re-emerge from a quiescent state, posing new challenges to developing countries in making drugs available and affordable for them. A brief discussion of the pathogenesis and treatment options for example neglected diseases appears in Attachment 6. With the exception of HIV/AIDS and newer viral diseases (Marburg and Ebola viruses), most neglected diseases have afflicted humanity for millennia. They not only kill but also result at times in severe disfigurement and chronic disability, thereby presenting a continuing social and economic burden. The extent to which these diseases have affected health and productivity has led to considerable research about their biology and epidemiology with at times advancement of effective control and treatment approaches. Sometimes major successes (smallpox eradication) and the possibility of success (polio eradication) advance the public health from one of deep concern to one of dramatic

¹ See also WHO's earlier work on essential drugs (1999) and a multicountry study of drug regulation (2002) (2, 3).

achievement. Among the several neglected diseases, HIV/AIDS, malaria, and tuberculosis now are considered major public health challenges for less-developed countries (LDCs), but all cause great suffering and economic loss (Table 1).

Table 1. Current disease portfolio

	TDR* disease category	Disease burden DALYs [†] (thousands)			Deaths (thousands)		
		Total	Male	Female	Total	Male	Female
African trypanosomiasis	<u>1</u>	1,598	1,029	568	50	32	18
Dengue	<u>1</u>	653	287	366	21	10	11
Leishmaniasis	<u>1</u>	2,357	1410	946	59	35	24
Malaria	<u>2</u>	42,280	20,024	22,256	1,124	532	592
Schistosomiasis	<u>2</u>	1,760	1081	678	15	11	5
Tuberculosis	<u>2</u>	36,040	22,629	13,411	1,644	1,075	569
Chagas disease	<u>3</u>	649	333	316	13	7	6
Leprosy	<u>3</u>	177	98	79	4	3	2
Lymphatic filariasis	<u>3</u>	5,644	4,317	1,327	0	0	0
Onchocerciasis	<u>3</u>	987	571	416	0	0	0

Source: [World Health Report, 2004](#)

*TDR—UNICEF/UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases

[†]DALYs—Disability-adjusted Life Years (the number of healthy years of life lost due to premature death and disability).

Good medicines are available to treat some neglected diseases, sometimes at a low cost (6). The main challenge in these instances is one of health care delivery and infrastructure to obtain available medicines for patients who would benefit from them (7, 8). As living conditions improve and health care standards rise, opportunities for transmission of neglected diseases frequently diminish. In consequence, neglected diseases are now rarely seen in populations that enjoy good access to health services and a reasonable standard of living. To some extent the term “neglected” diseases is a term of art. Even in developing countries, the absence of good medicines and acceptable health care infrastructures transforms chronic illnesses such as stroke, heart attack, cancer, and diabetes into “neglected diseases.”

Discovery and R&D

Regulatory authorities in a developing country often lack the most minimal resources that could be used to communicate policy directives to discovery and R&D teams. At times even the political will to do so is lacking. Filling this gap sometimes are policy decisions from senior government officials who may lack substantive knowledge in comparison to pharmaceutical scientists and public health officials who work in more developed countries. Coupled with a lack of financial resources, many developing countries simply have no capacity to identify and act in support of a viable discovery or R&D enterprise. This view may be tempered by the observation that some developing countries are participating in clinical research, partly because studies can be carried out only where the populations are suffering from neglected diseases.

In many of these countries there are qualified individual physicians, pharmacists, nurses, and other health care professionals who have appropriate training and who have carried out high-quality clinical research, often in cooperation with a foreign sponsor, a foreign academic institution, a public-private partnership, or a specific manufacturer. Many international pharmaceutical companies are conducting clinical studies in developing countries with the goal of using data from these locales as a part of filing for marketing authorization in developed countries. Although these studies exclude the poorest countries, many of these trials are carried out according to the standards of developed nations and therefore advance local clinical research capacity. This advance thus seems to be occurring because of interest in accessing larger patient populations, perhaps at a lower cost. Beyond this advance lie many other opportunities for public and private health institutes to advance discovery and research and development into neglected diseases of the poorest countries. The concept of a global “institute of health”—focusing on discovery and early development of medicines and other approaches to treat and prevent illnesses of the world’s poorest populations—surely merits consideration and would not be beyond the economic capability of the world’s nations at this time. Again, just as this paper proposes global collective action for registration and use of medicines, such an institute, working collaboratively with national institutes and private entities, would seem to be a highly effective means of advancing the availability of good medicines.

Regulatory Capacity

Regulatory agencies in developing countries frequently lack the human resources needed to engage in standards-setting and conformity-assessment activities in support of market access (for overview see reference 9). Given their expense, drug databases and journals are not available, nor are the information systems needed to track processes and ensure transparency. Operational activities of a developing country’s regulatory authority do not always permit Good Manufacturing Practices (GMP) inspections, adequate supply chain management, product quality monitoring, and control of counterfeit and substandard drugs. A net result at times is a framework that has many laws but not the capability for conformity assessment and/or enforcement. Regulatory decisions are based on values held by decision makers, which may differ substantially in developing countries from those in developed countries, leading to a different set of decision criteria. For example,

differences in disease patterns, available funds, and other factors may lead to differences in risk–benefit considerations for drug marketing authorization decisions. A vignette describing the limitations of a regulatory authority in a small country (population <15 million), which is characteristic of many countries in the world, appears in Attachment 7. A more complete analysis of the challenges confronting developing country drug regulatory authorities has been provided in a WHO theme paper titled *Effective Drug Regulation: What Can Countries Do?* (10) and in a parallel publication titled *Effective Drug Regulation: A Multicountry Study* (11).

Poverty and Health Care Workers

Neglected diseases are diseases of poverty, occurring at times in areas with an almost complete absence of a health care infrastructure and severe shortages of health care workers. For example, in a 2004 survey the International Council of Nurses reports that worldwide the nurse:population ratio varies from fewer than 10 per 100,000 population to more than 1000 per 100,000, a difference of two orders of magnitude. The average ratio in Europe—the region with the highest nurse:patient ratio and the region where neglected diseases have for the most part been banished—is 10 times that of Africa and Southeast Asia, where neglected diseases are common. The average ratio in North America is 10 times that in South America. Geographical misdistribution of health care workers contributes to the problem of delivering good-quality care to patients with neglected diseases. Sub-Saharan African nations are projected to have a shortfall of 600,000 nurses needed to meet the United Nations Millennium Development Goals (see Attachment 8). HIV/AIDS in sub-Saharan Africa increases demands for health services at the same time that it is reducing health workforce availability and performance—given that the disease is increasing the internal and international migration of nurses and other health care workers from the region, in turn creating heavier workloads for those who remain. WHO reported in 2005 that in the European region there were approximately 33 doctors per 10,000 population, but in Africa the number fell to only 1.8 (12)

Counterfeit and Substandard Medicines

Quality of medicines is a source of great concern worldwide, particularly in many developing countries. Recent reports indicate that the availability of substandard and counterfeit drugs has reached a disturbing proportion in developing countries (13–16). Of the poor-quality medicines reported to WHO between 1982 and 1999, almost 70% were from developing countries. The rising cost of drugs generally creates a corresponding increase in incentive to produce fake drugs because of profit margin. Use of poor-quality drugs has serious health consequences and wastes scarce resources. Some examples of reported cases are:

- In 1992, at least 233 children died in Bangladesh after swallowing a pain reliever that also contained antifreeze.
- Between April and June 1998 in India, 36 children younger than six years of age experienced sudden unexplained kidney failure after taking a locally manufactured “cough syrup” that was contaminated with diethylene glycol. Thirty-three of these children died.

- In 1999, at least 30 people died in Cambodia after taking sulphadoxine–pyrimethamine (an older, less effective antimalarial drug) that was sold to them as artesunate, a newer and more effective medicine for treating malaria.

Other human costs of poor-quality medicines include loss of work and income due to death, disability, or extended duration of disease. WHO estimates that 10% (about US\$21 billion) of global pharmaceutical commerce involves counterfeits (17). The International Conference of Drug Regulatory Authorities (ICDRA) brings together regulators from more than 100 countries and has addressed the topic in several meetings. For example, the ICDRA meeting in Madrid in 2004 was dedicated to counterfeit medicines and recommended further work on an international framework to fight counterfeit medicines (18). WHO had recently published a short but informative guide to pharmacovigilance and steps that can be taken to ensure the safety of medicines and reporting of adverse events (19). The Internet has allowed counterfeiters a “direct-to-consumer” means of bringing their fraudulent wares to unsuspecting buyers throughout the world, an unfortunate example of an important technologic advance bringing harm instead of progress. National certification activities (20) for accreditation of internet sites might be expanded to correct the problem.

SCIENCE AND TECHNOLOGY: POSSIBILITIES FOR HOPE

Molecular Biology

The molecular biology of neglected diseases may offer great success in helping to identify lead discovery and facilitating the development drug candidates. The genomic blueprints of many pathogens are becoming available. This provides, in principle, a complete list of a pathogen’s potential targets for the development of drugs. Comparison of target sequences versus comparable human genetic sequences should help identify targets that can be attacked specifically in the pathogen, but intensive work will be needed to translate this understanding into clinically useful medicines. For example, “knock-out” animals—developed to express a deficit of a protein or proteins of interest—may be useful to help researchers determine the result of not expressing a target protein or enzyme system.

For malaria, genetic alteration in *Plasmodium falciparum* may be the biomarker for drug resistance. The genomic sequence of this protozoan parasite has been completed and can serve as an informational base for the use of whole-genome strategies such as genetic mapping, microarrays, and bioinformatics. Genetic markers of anopheline vectors also are available, and thus genetic modification of mosquitoes may be an alternative strategy for malaria control. For tuberculosis, research in gene expression of the mycobacterium at all stages of the infection may hold promise for developing a more effective vaccine. Several soluble immunological markers of disease are active in tuberculosis.

For African Trypanosomiasis, specific host and parasite biomarkers recently have been identified and tested, allowing the development of more specific and sensitive diagnostic and stage-determination tools. Proteomic signature analysis has been used for accurate

diagnosis of the infection. Urinary nitrites and nitrates are good biomarkers for the brain levels of nitric oxide associated with parasite penetration into the brain. Sleep-onset rapid eye movement episodes occur at the beginning of late-stage trypanosomiasis.

For South American Trypanosomiasis (Chagas' disease), genetic expression after host–pathogen interaction at the establishment and chronic phases of the disease may be biomarkers for drug development. Natriuretic peptides can be used as prognostic and diagnostic markers of Chagas' disease. It has been reported that brain natriuretic peptide predicts survival in Chagas' disease more effectively than does atrial natriuretic peptide. Magnetic resonance imaging is an excellent marker for monitoring heart functionality from the acute through the chronic phase of infection and for monitoring the efficacy of cardioprotective or immune therapeutic agents.

For Dengue Fever, specific risks for this infection are progressive development into dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). DHF/DSS is a dynamic illness, and clinical manifestations change quickly. For this reason, a series of samples collected at different times for biochemical markers are needed to monitor and predict disease progress. Early markers for the development of DHF/DSS include duration from fever onset to defervescence, defined as the temperature falling and remaining at $<38^{\circ}\text{C}$. The appearance of IgM antiplatelet antibodies causing the destruction of platelets is a predictor for development of thrombocytopenia. In addition, serum IL-6 level can be considered an early marker for capillary plasma leakage, the most characteristic feature of DHF/DSS and an indicator of disease severity that results from structural damage to endothelial cells. A study in Mumbai reported that predictive markers for DSS were younger age at onset, altered sensorium, paralytic ileus, and significantly deranged partial thromboplastin times. Several promising vaccine candidates in the form of live attenuated and chimeric vaccines have been developed and are currently in human clinical trials.

For Visceral Leishmaniasis, several recombinant proteins have been developed to accomplish accurate diagnosis. A recombinant kinesin protein of 39 KDa (rk 39) is the most promising. The antigen used in various test formats has been proved highly sensitive and specific. Molecular techniques targeting various genes of the parasite also have been reported. Lymphotoxin- α and tumor necrosis factor were reported to play distinct roles in the control of *Leishmania donovani* infection. Also, apoptosis of monocytes, CD4^{+} , and $\text{CD4}^{+} \text{CCR5}^{+}$ T cells could be involved in the failure of cell-mediated immunity that is responsible for severe immune depression in visceral Leishmaniasis.

For Buruli Ulcer, the causative agent is *Mycobacterium ulcerans*. This mycobacterium is sensitive to several antimycobacterial agents in vitro. However, these classical antibiotics are much less effective against Buruli ulcer, probably due to the poor blood supply in the skin lesions. Bacillus Calmette-Guerin (BCG) vaccination has a mild but significant protective effect. Information gleaned from the genome sequence of *M. ulcerans* could be used to design more effective vaccines or new drug agents.

Discovery

Much remains to be done to ensure the availability of good-quality medicines in developing countries, but there are many examples of emerging science and technology opportunities that can facilitate research and development strategies for medicines used to treat neglected diseases. For example, combinatorial chemistry has made available many compounds for testing against drug targets. High-throughput screening and automation allow this testing to occur rapidly, but only in a regulatory environment that encourages and collaborates with leading researchers. Often a 3-dimensional structure of a target protein is available or can be modeled based on its homology to a related protein structure. The techniques of structure-based design and/or virtual screening (“docking” target and ligand structures in the computer) can be used to find promising compounds to synthesize and test experimentally. Although finding a lead compound may occur quickly, further work is needed to find a drug candidate, which must have suitable pharmacokinetic and pharmacodynamic characteristics. New experimental and computational models for predicting a drug’s solubility, bioavailability, distribution (e.g., across the blood–brain barrier), and elimination are being developed in the hope of eliminating poor candidates before expensive clinical trials are carried out.

Genetics/Genomics and Pharmacogenetics/Pharmacogenomics

The work of Gerrod and Mendel 100 years ago, and their many successors, led to an understanding of single gene aberrations and resulted in the fields of genetic science and medicine. Despite the profound nature of this work, genetic disorders, although at times devastating for those affected, usually involve only a small fraction of a population, with most humans having a robust genome that allow progression to advanced age in benign settings. Based on the global achievements of the Human Genome Project and allied advances, genomic medicine has now emerged, leading to an understanding that complex interactions of genes and the environment may promote or retard disease, including the neglected diseases considered in this paper (21). This is surely a point for further basic and translational research. Moving to available and new medicines to prevent and treat disease, the science of pharmacogenetics (22) and pharmacogenomics is having an increasing impact on the way medicines are used and leads to the idea of individually targeted therapy (23). Pharmacogenetics and pharmacogenomics can also help identify new molecular targets for new drug development (24). When specific genetic understanding is not available, analysis and interpretation of clinical data should take into account the possible influence of various intrinsic and extrinsic factors on a medicine’s effect, e.g., efficacy and safety at a particular dosage and dose regimen in different ethnic populations. In this regard, the ICH E5 guidance on *Ethnic Factors in the Acceptability of Foreign Clinical Data* is an excellent reference for regulatory decision-making (25). Perceived benefits may also have other effects that need to be weighed carefully. Further stratification of populations may identify smaller target patient populations and thus less revenue for innovators, potentially causing a relative increase in the price of treatments. Ethical considerations arise with pharmacogenetics and pharmacogenomics, and guidance regarding pharmacogenomic data regulatory submissions is emerging (26).

Computer Modeling and Other Information Technology Tools

Computer modeling of drugs and disease states is being explored for preclinical pharmacology and toxicology, using the science of pharmacometrics (27). Clinical trial designs can be optimized by 1) computer modeling and simulation to predict the possible outcome of the trials or 2) integrating available knowledge of a drug candidate early in development using the drug and a disease model. Mathematical and statistical models will “allow more complete integration of the available knowledge” using “integrated teams of medical officers and biostatisticians, clinical pharmacologists, and pharmacometricians” to review drug applications (28). Innovative tools for clinical trials may also include enrichment design, adaptive clinical dose finding, dose–response assessment in phase 3 trials, and better use of information technology to manage data. Several tools identified may be useful for drug or vaccine development in developing countries and could translate into decision-making tools for regulatory agencies.

Biomarkers and Surrogate Markers

Biomarkers and surrogate markers are used increasingly as a means to signal efficacy. The US Food and Drug Administration (FDA) has identified biomarkers as one of the key tool kits in the agency’s Critical Path Initiative (29, 30). Biomarkers and surrogate markers may be particularly applicable for neglected infectious diseases. As an example, careful studies have demonstrated the value of relying on CD4 counts and viral markers as a means of assessing efficacy of new medicines for HIV/AIDS and are now routinely applied. A genomic expression system can be a predictive safety tool for evaluating the impact of a new compound on an organ function. Advanced nonclinical screening methods may be predictive for demonstrating the efficacy of a product in humans. A number of biomarkers are useful as diagnostic tools for disease progression, drug effectiveness, or toxicity. The use of combinatorial biomarkers is a first step toward an effective systems biology approach to drug development. Quantitative biomarkers such as imaging biomarkers and surrogate endpoints may be employed in both animal and early human trials to indicate effectiveness. Imaging modalities such as magnetic resonance imaging, computed tomography, and positron emission tomography can be used not only in early development to assess drug distribution in the body but also in later development to monitor disease response.

Comparisons to Placebo versus Active Controls

Clinical trials in developed countries generally measure benefits relative to placebo, except when using placebo rather than current treatment would be unethical (as is the case during development of certain antiretroviral drugs). Drug regulators in countries with more constrained resources may choose to use current treatment as the comparator in order to restrict new drug approvals to drugs that are at least as good as drugs that are already available. However, clinical trials to prove superiority or non-inferiority may involve considerably more patients in trials and be technically more difficult to carry out and interpret. If this standard is adopted, it is important to consider differences among drugs in terms of risks and benefits for different patient subgroups: e.g., some patients may respond better to drug A while others respond to drug B. For this reason—for at least some subclass of patients—and to encourage competition it seems prudent to admit a new drug if its risk–benefit profile is at least as good as that of an existing drug for at

least some subclass of patients. Because in practice clinicians and patients must make decisions between drugs, doing clinical trials relative to current treatment seems desirable, and this is certainly the norm for postapproval studies. Greater flexibility to evaluate active-control trials and more willingness to encourage sponsors to study multiple doses during Phase 3 clinical trials has been proposed (31). In these and similar settings, the responsible regulatory authority should communicate to practitioners and patients/consumers how limited the information is in support of a risk–benefit profile.

Adaptive Trial Designs

Traditionally a clinical trial design is formulated, negotiated with a regulatory authority, then patients are enrolled, and the trial is carried out to its conclusion—unless adverse events require it to be stopped. Unfortunately 9 out of 10 candidates tested in clinical trials fail, most of them in Phase 2 studies that are decisive for further large-scale clinical studies for safety and efficacy (Phase 3) that will be presented to regulators for marketing approval. One promising approach is adaptive clinical trials, in which a small trial is carried out, the results are analyzed, and a better design is used in the next stage.

Bayesian Statistics

Bayesian statistics provide an alternative to the design, and especially the analysis, of clinical trials (32). The reasons for this are as follows: Bayesian statistical approaches allow the results from previous studies to be incorporated, formally, into the analysis of a new study. This approach also does not require power calculations to be undertaken. Rather, it permits the trialists to stop when sufficient data have been assembled to allow conclusions to be drawn. In addition, Bayesian statistics do not require subgroups to be prespecified, and they provide a more reliable approach to investigating equivalence as well as superiority. Three reasons are offered regarding why Bayesian statistics have not been adopted more widely: 1) Bayesian statistics approaches probability in a different way from conventional “frequentist” approaches; 2) the approach is technically demanding, and many statisticians lack the necessary expertise; and 3) modern Bayesian statistics require sophisticated computing techniques that would have been impossible to accomplish 10 to 15 years ago. WHO has been active in applying Bayesian statistics and has published a white paper on using Bayesian techniques to predict life expectancy and healthy life expectancy (33).

Subpopulation Studies

These studies allow segmentation of a clinical trial population based on their likelihood to respond to the therapy or to have an adverse reaction. If responders versus nonresponders or those likely to have an adverse reaction can be identified, regulators can allow researchers to plan a shorter, faster, less expensive clinical trial with increased chances of success. Diagnostic biomarkers are a way to achieve such segmentation. Modern microarray technology allows determination of patterns of single nucleotide polymorphisms from a cheek swab or blood sample, so such differences can be discovered quickly and fairly cheaply. CYP-450 enzyme polymorphisms can be detected to allow better understanding of patterns of metabolism and to select individuals likely to show efficacy and to avoid toxicity.

Information Management

Information technology approaches allow better understanding of an at-times overwhelming amount of data. For example, mammograms are now being saved for comparison with later scans and for assessing causes of clusters of similar cancers. Available microarray chips can scan an individual's entire genome, and depositing these data in a genetic/genomic or pharmacogenetic/pharmacogenomic information system may allow discovery of complex genetic patterns associated with disease and with successful therapies. Academic centers are putting patient records in electronic form to identify candidates for clinical studies and observe trends and new correlations of patient treatments and outcomes. Regulatory clinical data warehouses may allow cross-study analyses to help determine best therapies and to enable early warning of potential adverse reactions.

Technology to Combat Counterfeits

One emerging high-technology solution to the problem of counterfeit and substandard drugs appears to be radio frequency identification (RFID), a chip that can be enclosed in the package or bulk container and read with an RFID reader. It enables tracking of packages from the manufacturer, to middlemen, to the pharmacy, to the patient, and it can identify counterfeit or relabeled products, as well as material that has been tampered with. For sensitive materials it can even track temperatures to which the package has been exposed. Other science-based approaches may be useful, such as near infrared probes, symbology, enhanced detection methods, field testing, and many others as well.

Outcomes Studies/Pharmacoeconomics Studies

Registration of a new medicine, no matter how extensive discovery and development studies are, frequently relies on only a small number of patients, usually studied for relatively short durations. Increasingly, studies performed primarily after a medicine has entered clinical use may amplify understanding of its effectiveness (benefit in "real world" use). Beyond effectiveness studies, outcome studies focus on clinical, humanistic, and economic factors. As a special aspect of economic outcome studies, pharmacoeconomic studies identify, measure, and compare costs and consequences of the use of pharmaceutical products and services. Taken together, these approaches are used increasingly in support of payment decisions and to promote rational use of medicines and good health care delivery practices (34).

REGULATORY DECISION MAKING: SPECIAL NEEDS OF DEVELOPING COUNTRIES

New Medicines

For a new medicine, market approval ideally requires weighing evidence of benefit and risk. Because both the objective benefits and risks and the qualitative trade-offs between them may differ among countries—due to differences in disease prevalence, competing risks, and risk tolerance—each country (or groups of like countries) should make its (their) own decisions. Standards for collecting and presenting data should be coordinated to reduce burden on originator firms and regulatory authorities. Developed countries and regions sometimes offer their review capabilities to applicants who wish to provide

medicines to developing countries. For example, FDA has prepared a fast-track approach for fixed-dose combination products to treat HIV/AIDS, malaria, and tuberculosis (35). The European Medicines Agency has produced a Guideline that allows the Committee for Medicinal Products for Human Use, working with WHO, to provide a scientific opinion regarding medicinal products intended for markets outside the community (36).

However well-intentioned the efforts of drug regulatory agencies in developed nations, it is a thesis of this paper that regulatory and other experts from developing countries would do better to develop their own decision-making capability, perhaps through collaborative action, rather than relying on decisions from a developed country's regulatory authority. The latter can at times lead to inappropriate decisions if adopted by regulatory bodies in developing countries. For this reason, a developing country's regulatory authority should review the underlying data and evaluation made by other regulatory authorities but should also consider how conditions differ locally in making its final evaluation. Because no drug is perfectly safe, approval involves weighing benefits and risks. Defining evidentiary standards for benefit and risk is critical and itself involves trade-offs. Requiring that firms provide more evidence from large randomized clinical trials prior to approval reduces the risk of approving a drug that has rare side effects but increases costs of R&D and delays the launch date. Extensive requirements thus can reduce a firm's incentives for R&D and result in foregone benefits for consumers. Elements include:

Efficacy and Effectiveness

Although the traditional gold standard is efficacy in prelaunch randomized clinical trials, combining these efficacy data with observational (postapproval) effectiveness data, using statistical methods, may be preferable. This approach argues for relatively small preapproval randomized and other studies, combined with careful postapproval observational studies. Placing more weight on postapproval data for effectiveness information is particularly relevant when fast-track approval is appropriate, e.g., for drugs to treat life-threatening conditions for which no good existing treatment is available, which includes several major diseases in developing countries. Postapproval observational data entail only minimal cost to originator firms. For this reason, effects on R&D incentives are small and offer better evidence about effectiveness in actual use than do randomized clinical trials. Appropriate statistical techniques to combine data from different sources also may be very useful for drugs for which conditions differ between developed and developing countries or across developing countries. There is thus a need to combine evidence from different sources. The goal for developing countries should be to obtain the information most relevant to their country while avoiding requirements for the collection of large amounts of new country-specific data that will add to R&D costs and hence discourage research and development relevant to developing countries. Just how much country-specific or region-specific data should be required depends on the specifics of the drug–disease–country at issue (37).

Measurement of Risks/Adverse Events

To gain an understanding of risk, health authorities should measure the frequency and severity of adverse events optimally in both preapproval randomized clinical trials and in

postapproval observational data, combined via appropriate statistical methods. Because disease strains, prevalence, and co-morbidities can differ among subpopulations, country vs. region, and high vs. low risk, the best assessment should be chosen for the relevant population. Because requiring additional data usually raises costs, drug regulatory agencies should consider the costs vs. additional information gained.

Risk–benefit Trade-offs

Whereas the data on benefits and risks are objective, at least ideally, the willingness to accept a particular risk–benefit trade-off is necessarily subjective. Thus there is no single right decision, but rather the appropriate risk–benefit trade-off differs:

- across drugs for any country: e.g., a higher risk–benefit ratio is tolerated for drugs to treat life-threatening conditions for which there is no existing treatment, e.g., cancer;
- across countries for a given drug: e.g., countries with higher competing risk factors and lower life expectancy may be willing to tolerate higher risks relative to benefits than will countries with fewer competing risks.

Differences across countries in tolerance for risk and preferences for benefits are distinct from and in addition to differences across countries in the objective measures of benefits and risks that reflect differences in disease prevalence, disease strain, and co-morbidities. For a country-specific drug evaluation, it may be ideal to measure both benefits and risks in the same unit, e.g., Quality-adjusted Life Years (QALYs) or DALYs, so that benefits and risks are commensurate. With a common unit of measurement, a regulatory agency can easily assess whether the benefits outweigh the risks. Note that QALYs and DALYs implicitly assign equal weight to all individuals. In practice, if the benefits and risks accrue to different subpopulations, decision-makers may have to make interpersonal comparisons and may choose to weigh them differently. As an example using vaccines, rare but severe risks to a very few individuals may need to be weighed against benefits for the vast majority. Ideally, if subgroups at higher risk can be identified *ex ante*, they can be excluded from the population taking the drug or vaccine so that risks and benefits accrue to everyone equally, which avoids the need for interpersonal comparisons.

In most clinical trials, benefits and risks are measured in different clinical units. In such cases there is no rigorous and consistent way to compare risks and benefits: It is an apples to oranges problem. E.g., for drug A, how does one weigh an X% probability of reducing viral load against a Y% increase in the risk of liver toxicity; for drug B, how does one weigh a Z% probability of reducing pain against a W% increase in risk of stroke? Moreover, individual consumers differ in their willingness to accept benefit–risk trade-offs, but the role of a regulatory authority is to set a basic threshold that best reflects the average preferences of citizens in their country. In practice, regulatory agencies appear to try to use risk–benefit criteria that are reasonably consistent across drugs for a given indication or class, but these standards and the differences across drug/indication classes are not based on any analytic, *a priori* criteria, but rather they reflect prevailing medical/regulatory judgment.

Risk–benefit Trade-off Judgments

How might these risk–benefit trade-off judgments differ between developed and developing countries? Theory and evidence suggest that willingness to tolerate risk declines with income and increases with competing risks. In fact, these two are correlated. Higher-income countries spend more money on risk reduction from many sources, e.g., higher safety requirements for cars, roads, industrial and consumer equipment, and higher spending on health care generally (see, e.g., US FDA’s Drug Safety Initiative Web page, reference 38). Developing countries with more competing risks may be willing to accept drugs with higher risks, other things being equal. But developing countries also have more constrained resources and hence may require higher benefits to make a drug worth buying, which suggests a focus on life-saving drugs, with lower priority for life-style drugs or drugs with marginal clinical improvement. Thus if a developing country’s risk–benefit tolerance requires higher benefits but also toleration of higher risk, this is a further reason (in addition different objective measures of benefits and risks) why developing country regulatory authorities ideally should make their own evaluation of drugs rather than rely on regulatory decisions in developed countries. A frequently cited example is the Rotashield vaccine developed to treat rotavirus infections. Withdrawn from the US market because of rare but unacceptable toxicity (intussusception), this medicine might well have been deemed acceptable by practitioners and patients of developing countries (39). The American Society for Microbiology called on FDA to enhance interactions among industry, academia, and government as part of its Critical Path so the agency could do a better job of risk–benefit analysis, citing the Rotashield case: “thousands of infants died outside the US from rotavirus infection ... following a very small percentage of adverse events in the US” (40).

Cost-effectiveness in Regulatory Decision-making

Most developed countries separate the market approval decision—made by a regulatory authority on grounds of clinical risks/safety and benefits/efficacy—from pricing and payment decisions, often on grounds that include pharmacoeconomic studies such as cost-effectiveness. One reason for separating these decisions is that the market approval decision makes a drug available to those consumers who want to pay for it out of pocket, even if their social or private insurance plan deems that it is not cost-effective given budget constraints and hence decides not to reimburse for it. Such flexibility is appropriate, given the fact that there is no absolute standard of whether a drug is cost-effective. A cost-effectiveness analysis measures the drug’s costs relative to some measure of effects, e.g., cost per QALY. Whether that cost is *worth* paying is a subjective judgment about which individual consumers may differ, depending on their resource constraints, preferences, and other factors. Payers make a reimbursement decision based on their budget constraints and some estimate of a beneficiary’s willingness to pay, but individual consumers may differ in their budgets and preferences. If a developing country chooses to make cost-effectiveness an intrinsic and necessary condition for market approval—rather than a separate step that applies to reimbursement or availability in public hospitals and clinics—then it limits individual a consumer’s flexibility to make his or her own judgment about how to spend his or her money.

A cost-effectiveness analysis may use the same measure of clinical benefits/effectiveness as a risk-benefit analysis. Alternatively and preferably, the clinical units of efficacy are converted to QALYs or some other utility measure that permits comparison across therapeutic alternatives with different clinical outcomes. The cost side of a cost-effectiveness analysis is more comprehensive than is a risk analysis, and measurement is in money, not clinical units. Thus a full measure of the costs of using a drug includes not only the price of the drug but also any other direct medical costs (e.g., costs of administration, doctor visits) and cost offsets (e.g., reduced hospitalization), including any costs related to side effects. Costs and effects should be measured relative to an appropriate comparator, e.g., current treatment. Generally, the appropriate comparator (the utility values attached to clinical outcomes and the costs of medical and other inputs) differ among countries. Thus a developing country should not rely on the cost-effectiveness decisions of other countries with very different environments. At most, developing countries could use the raw data upon which such decisions were reached in other countries, then assign their own QALY values to outcomes and monetary values to medical and other inputs.

An important prior decision in doing any cost-effectiveness analysis is to adopt the most appropriate perspective. The “social” perspective includes all costs and benefits, regardless of to whom they accrue. The “private” perspective considers only those costs and benefits that accrue to the decision-maker, usually the payer. Although public payers sometimes consider only costs and benefits that accrue to their budget, as representatives of taxpayers they should more appropriately also consider costs and benefits that accrue to other departments of government and to taxpayers (41).

In evaluating cost-effectiveness of drugs for developing countries that may receive some subsidy from an international agency/donor, the donor agency may want to consider costs that accrue to it and to the developing country (a social perspective), but the developing country itself may appropriately take a more private perspective and consider only the costs that it will bear, net of subsidies or grants from donors. If the availability of subsidies is uncertain, two cost-effectiveness evaluations could be done, one without and one contingent on subsidies. Alternatively, a probabilistic estimate of in-country costs could be made.

Implications for Developing Countries

The main implications for regulatory decision-making with respect to new drug approvals in developing countries are that both the appropriate measures of risks and benefits may be country specific, and the preferred trade-off between risks and benefits may be country specific. The ideal is to use data submitted to other regulatory authorities to the extent possible but to consider modifications as appropriate for the country. The need for modifications to match country context is equally true for cost-effectiveness analysis.

Multisource (Generic) Medicines

Generics are by definition follow-on products with the same active ingredient and formulation as the originator drug. If the regulatory environment is well designed,

generics offer the potential for significant savings to consumers because generics do not incur the costs of research and development realized by originator drugs. In order to preserve incentives for research and development, intellectual property approaches must assure adequate returns to innovators. As part of World Trade Organization (WTO) agreements, the Trade-related Aspects of Intellectual Property Rights (TRIPs) provisions include a number of flexibilities for compulsory licensing (CL) and parallel imports (PIs), early working, government noncommercial use, and voluntary licenses on reasonable commercial terms—all of which should proceed separately from regulatory decisions for safety, efficacy, and quality. All of these require careful balancing between commercial and public health interests in ways that are still evolving. The focus here is on regulatory decision-making for generics, assuming that some reference version of the compound (usually the originator) has already been approved.² With pharmaceutical equivalence established, in many instances via definitional as well as scientific approaches, documentation of bioequivalence becomes critical. If copy products are permitted to be marketed without evidence of bioequivalence, patients will be at risk of consuming either ineffective or unsafe products, given that the exposure pattern documented for the reference product may be altered (see Figure 1). If consumers face uncertainty regarding equivalence, then price competition will not be robust. Rather, generics will tend to compete on the basis of brand as a proxy for quality, which will mute price competition (42).

The greatest savings from generics occur in countries where generic pharmaceutical equivalence and bioequivalence documentation, resulting in a conclusion of therapeutic equivalence, are required so that patients, physicians, payers, and pharmacies can readily substitute generics for originator products. Under such competition generics compete on price, and savings to payers and consumers are maximized without threat to patient health. With good documentation of therapeutic equivalence, pharmacists can be authorized to substitute generics even if the physician prescribes the brand (in countries/locations where a prescription is required). Obviously, in countries/locations where pharmacies typically dispense without a prescription, authorization of substitution by pharmacists may be moot. Still, having in place a requirement for therapeutic equivalence and authorization for substitution are important components of the regulatory framework for a healthy and competitive pharmaceutical marketplace. Informing patients and other decision-makers that they can be confident in the quality of generics is crucial if generics are indeed to provide savings to consumers without threat to health.

² The conditions under which CL should be permitted present an important but separate issue from that of standards for regulatory approval. But there is an important question of what standards a generic product should face if a country issues a compulsory license to generic producer before the originator product is approved in that country. If a CL generic is first to market, then that CL generic should face the same regulatory requirements for approval that the originator would have faced unless the regulatory authority of different countries is to be relied upon. Presumably the CL product would then become the reference to which other generics would be compared in pharmaceutical equivalence and bioequivalence studies, if the originator has not sought local regulatory approval. Having the CL as a reference is essential to facilitate entry for other generics, and hence achieve price competition, without which the CL generic may have a virtual monopoly—in which case the cost savings from CL are not realized.

Over-the-Counter (OTC) Medicines

In developed countries, societies distinguish regulatory requirements between drugs that are available only with a prescription and those that are available over-the-counter (OTC). Some countries have a third, “behind-the-counter” category. For OTC medicines, the standard is that they must be safe and effective under self-medication, which may require evidence that consumers can read and follow labels, in addition to evidence about the drug’s risks and efficacy when appropriately used. Because in some developing countries many nominally prescription drugs are in fact available OTC, regulatory agencies may want to consider risks and benefits of self-medication. For example, antibiotics and other products that may lead to resistance should receive special consideration and possibly restricted use in order to preserve their efficacy.

Widespread self-medication is a further reason why a developing country’s regulatory agency may want to consider evaluations from developed countries as a starting but not the end point in market approval decisions. Developed countries increasingly exclude OTC medicines from reimbursement by insurance plans. This is based on the principle that insurance should focus on coverage for catastrophic expenses that are unaffordable to consumers. In developing countries, even basic medicines may be unaffordable to consumers, and insurance coverage is much less widespread. To the extent that insurance or other third-party payment is available, it is still appropriate to conserve these limited funds for the most clinically important products and services, leaving consumers to pay for less essential medications.

ACCESS: SPECIAL CHALLENGES IN DEVELOPING COUNTRIES

At issue in any consideration of access to medicines is the specific impact of the regulatory framework on access and cost, especially in the context of incentives to develop new medicines for neglected diseases. Access to medicines has four dimensions—accessibility, availability, affordability, and acceptability.

Accessibility

Accessibility refers to the timely ability for a patient to reach a clinic or pharmacy and obtain a medicine in case of a severe illness. Accessibility is affected by regulation in general terms, for example rules for the establishment of health care facilities and accreditation. Although this factor is important, accessibility probably does not play a large role in the context of incentives for development of new medicines in developing countries.

Availability

Availability is a combined function of regulation allowing medicines into the market (covered in other sections of this paper), funding, and supply chain management. A poorly operating supply chain restricts potential sales of a drug and therefore can act as a disincentive for development of new medicines. National regulations have to address the

following dimensions in order to ensure availability of medicines through the supply chain:

- Allocate clear responsibilities within the administration and sufficient resources to fulfill the tasks related to medicines supply in the public sector;
- Define technical standards, e.g., for drug procurement, quality assurance, and compliance with Good Distribution Practices;
- Set the framework for licensing of private-sector professionals who make up the supply chain (importers, manufacturers, wholesalers, and pharmacists); and
- Enforce anti-corruption, anti-collusion, and other measures needed to address misuse, fraud, drug diversion, and marketing of illegal or counterfeit products.

Affordability

Affordability refers to the price of a medicine, with a lower price affording better access. From a manufacturer's perspective, however, the higher the price, the greater is the incentive to develop new medicines. This conflict can be overcome only if sufficient dedicated funding for new medicines to treat disease in resource-poor settings is made available (vide supra for suggestions on a global institute of health to promote basic and early translational research on medicines for neglected diseases). Regulatory frameworks influence the price of drugs in various ways. Therefore this aspect is the most relevant one among the four in this section. Various push and pull strategies, particularly for vaccines and rare diseases, have been developed or advocated and attempt to resolve issues wherein commercial interest may be low but clinical need is high.

International Norms

The TRIPs agreement has defined the circumstances under which governments can issue a compulsory license for an important medicine. Compulsory licensing, if used on a regular basis in larger developing countries to overcome patent barriers and develop generic versions of new drugs, will create a disincentive for the commercial development of medicines that have their main market in developing countries. This may be of no particular relevance in the near future, as long as the combined size of these markets remains too small to create a significant commercial incentive. In the middle term this may change, however, given the growth rate of major developing country markets. Compulsory licensing is not expected to play a role in noncommercial drug development ventures. These have typically made a pledge to offer the medicines in developing countries at a generic price level even if the compound is still patent protected.

National Regulation

Intellectual property rules set the framework for the protection of new medicines against early generic competition (see, e.g., reference 43); pricing and reimbursement regulations define import, ex-factory, wholesale, and retail prices, as well as reimbursement levels by health insurance systems. Such rules and regulations have a direct impact on market size and commercial potential for each medicine. The effect of these national regulations on the overall commercial incentive to develop a new medicine depends on the following:

- Size of the market—companies look at the key markets and their conditions first;

- Ability to protect a product against generic competition by means of patent laws or other forms of marketing exclusivity, such as ‘orphan’ drug regulations;
- Speed of passage through the regulatory process and transparency of the process that defines price and reimbursement level;
- Expected outcome of pricing and reimbursement negotiation process—does the company get a fair price and access to the entire market (defined by reimbursement level)?

Pharmacoeconomic studies, including cost-effectiveness comparisons, can be part of the regulatory criteria on a national level (vide infra for a discussion of the developed country approach). Some countries require pharmacoeconomic data in order to grant reimbursement or approve the price for a new drug. As an incentive for the development of new essential medicines, this aspect is usually less important. The diseases targeted by essential medicines are by definition important from a public health and economic perspective, so that effectiveness usually equals cost-effectiveness, in particular if the cost of medicines is subsidized by the manufacturer or a donor. Cost-effectiveness from the donor’s perspective is measured by comparing various ways of reaching the same health outcomes. However, such considerations are not related to regulatory factors.

In the absence of a significant commercial market for new medicines, including vaccines, other models of financial incentives are being debated. The basic idea is to create a mechanism that guarantees funding for purchasing essential new vaccines or drugs, based on a defined set of specifications, before these products are developed. A manufacturer who is successful in developing a product according to specifications can count on a profitable price. Donor funds are then made available up to the guaranteed level for the procurement of these products. This model raises several issues related to intra-institutional regulations and guidelines in organizations such as the World Bank, Global Fund, WHO, and others, such as:

- Ability to enter into binding agreements that include future funding commitments;
- Possibility to allocate funds to central purchasing pools or to use funds allocated to a country to pay directly to the supplier of a required product;
- Monitoring and execution of long-term agreements and arbitration in borderline cases; and
- Governance and legal issues in multipartner agreements.

Acceptability

Acceptability of a certain form of treatment is a function of knowledge, culture, education, and trust in systems. The last is most immediately affected by regulation. In many developing countries, civil society may have little confidence in the rigor of national drug quality control, which limits acceptance of low-cost generic drugs. In the absence of an objective way to judge the quality of a drug, patients prefer imported, branded products that are usually more highly priced. This can limit the market potential of a medicine if it is introduced in a version that appears cheap or inferior and thereby create a disincentive for the developing manufacturer.

Another, more important disincentive stems from the fact that in poorly controlled markets the potential for medicine misuse, unwanted effects, diversion, and fraud is much higher—all factors that mean a risk for a manufacturer’s investment and reputation. One possible regulatory step would be to upgrade quality enforcement in a market and to communicate actively about all measures taken in order to build trust in the system.

Taking the various factors together, the postapproval phase for a new medicine in a developing country is critical for its uptake and usage, i.e., its access. Weak regulatory frameworks and lack of enforcement can lead to various bottlenecks that constrain access. Development experts use the term *absorptive capacity* to describe a system’s ability to make use of incremental funding, commodities, or technology.³ Better postapproval regulation is an important factor in improving health systems and their absorptive capacity, which will attract donor funding and help grow markets. This will enhance the willingness of commercial enterprises or noncommercial partnerships to invest in the development of new products and solutions along the lines of the following paradigm:

*Better regulation → Improved health system capacity → More donor funding →
Larger markets and less risk → Incentive to innovate*

Global funding instruments that are able to make commitments into the future to buy innovative products are an important new incentive for innovators. But adaptations of the rules and guidelines governing major development institutions will be required to make them work.

CAPACITY BUILDING

Examples of the following inter- and trans-regional activities that promote capacity building are summarized briefly in Attachment 9, which provides examples of information sharing and harmonization of regulatory requirements:

- ICH
- Asia-Pacific Economic Cooperation
- Association of Southeast Asian Nations
- Gulf Cooperation Council
- Pan American Network for Drug Regulatory Harmonization
- The South African Development Community.

Beyond these approaches, specific global, regional, and national activities offer examples in which governmental-sponsored activities are yielding to more collaborative

³ Absorptive capacity is linked to the concept of sustainability. In reviewing British Prime Minister Tony Blair’s plan to sharply increase official development assistance to Africa in support of the UN Millennium Development Goals (Attachment 8), the Hudson Institute invoked the concept of absorptive capacity. Large new resource flows, the Hudson Institute noted, too often lead to high inflation, real currency appreciation, and rising domestic interest rates—all of which disproportionately affect the poor. The Hudson Institute notes, as does the present report, that success depends on long-term transregional educational/regulatory activities and capacity building (44).

approaches as a means of advancing the availability of good-quality, safe, and effective medicines. These are discussed in more detail in the following sections.

The WHO Pre-qualification Project

WHO's pre-qualification effort was established in 2001 as a service to facilitate access to medicines that meet unified standards of quality, safety, and efficacy for HIV/AIDS, malaria, and tuberculosis. From the outset, the project was supported by UNAIDS, UNICEF, UNPA, and the World Bank as a concrete contribution to the United Nations' priority goal of addressing widespread diseases in countries with limited access to quality medicines. Pre-qualification originally was intended to give United Nations procurement agencies such as UNICEF the choice of a range of quality medicines. With time, the growing list of medicines that have been found to meet the set requirements has come to be seen as a useful tool for anyone bulk purchasing medicines, including countries themselves and other organizations (45).

For instance, the Global Fund to fight AIDS, tuberculosis, and malaria disburses money for medicines that have been pre-qualified by the WHO process. Manufacturers who want their medicines to be included in the pre-qualified products list are invited to apply. Each manufacturer must present extensive information about the product(s) submitted to allow qualified assessment teams to evaluate its/their quality, safety, and efficacy. The manufacturer must also open its manufacturing sites to an inspection team that assesses working procedures for compliance with WHO GMPs. Alternatively, the inspections carried out by stringent regulatory bodies are recognized, and their work is not duplicated by WHO. The standards against which the assessment teams evaluate both the quality specifications of medicines and the manufacturing sites are based on the principles and practices agreed by the world's leading regulatory agencies and adopted by the WHO Expert Committee on Specification for Pharmaceutical Preparations. All product and manufacturing site requirements, standards used in evaluating the product and the profile of the inspection teams are outlined on the WHO Prequalification Project Web site (46). The site also includes the list of pre-qualified medicines and their manufacturers.⁴

European Certificate of Suitability

The procedure leading to a European Certificate of Suitability (CEP) is based on a Resolution of the Public Health Committee [Partial Agreement, Resolution AP-CSP (99) 4]. Under this official procedure, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate concerning the evaluation of the suitability

⁴WHO's Certification Scheme that yields Certificates of Pharmaceutical Products (CPPs), which replaced free sale certificates, is an earlier approach compared to WHO's Prequalification Project but still considered valuable. It is reliable if issued by credible authorities. Many innovator products are registered in developing countries based on a CPP issued by the European Medicines Agency or US FDA. The approach thus works well for first-entry manufacturers who have taken the time and expense to register a medicine with an advanced authority. Because many medicines to treat neglected diseases may come from countries where regulatory capability is much more limited, the WHO Prequalification Project represents an advance over the earlier approach. Even this capability, however, may be viewed as less than optimal, with some funding governments/agencies insisting on approval by an advanced authority.

of the monograph for the control of the chemical purity and microbiological quality of their substance according to corresponding specific and general monographs. This procedure is aimed at facilitating and simplifying exchanges between the partners to ensure that the quality of substances is guaranteed and that these substances comply with the *European Pharmacopoeia*. CEPs are recognized by 34 signatory states of the European Pharmacopoeia Convention and by the European Union. A CEP can be used by the manufacturers of pharmaceutical products in their applications for marketing authorization to demonstrate the compliance of the substance used with the monographs of the *European Pharmacopoeia* and Directives 2001/83/EC and 2001/82/EC.

USP Dietary Supplement Verification Program (DSVP)

Given limited regulatory oversight in the US for dietary supplements (some of which are botanical medicines in other countries), USP established a verification (certification) activity, working with participating dietary supplement and ingredient manufacturers to assure consumers that: 1) what's on the label is in fact in the bottle—all the listed ingredients in the declared amount; 2) the supplement does not contain harmful levels of contaminants; 3) the supplement product will break down and release ingredients appropriately into the body; and 4) the supplement has been made in accordance with applicable GMPs (47). USP's DSVP is analogous in some ways to EDQM's Certificate of Suitability and WHO's Pre-qualification Project. The core activity is based on general concepts of product certification (48).

EMERGING REGULATORY LANDSCAPES

Regulatory agencies consider information about the safety, efficacy, and quality of a medicine, and based on various kinds of risk–benefit decisions may allow—or not as the case may be—market access. Increasingly, civil societies take into account factors about a new medicine beyond safety, efficacy, and quality. For example, many countries engage in medical pricing/payment decisions that can be supported by outcomes studies, including pharmacoeconomic studies. In addition, societies are promoting ways to promote evidence-based quality of care and patient safety considerations, including safe medication use. Taken together, these factors influence research and development strategies for new medicines, perhaps in ways that now are poorly understood or not understood at all. Examples of societal approaches drawn from developed countries are described briefly in the following paragraphs.

Example for Registration—US FDA

The tasks and obligations of FDA are delineated in laws, regulations, and guidances that have developed over approximately 100 years. These standards for information and review arose over time from highly publicized negative events (e.g., the Elixir of Sulfanilamide disaster in 1938 resulted in a premarket safety notification requirement; the thalidomide disaster resulted in the 1962 efficacy standard and other regulatory requirements). A paradigmatic view of the quality, safety, and efficacy information needed for FDA's decision-making is summarized in Figure 1. The lower part of the figure depicts a drug substance, with amount expressed usually in terms of mass,

contained within a pharmaceutical dosage form. The drug substance enters the body typically through one of five routes of administration: oral, topical, mucosal, parenteral, or inhalation (49). Administered either once or repetitively, the medication creates an exposure pattern that can be expressed in terms of dose or through measures that reflect systemic or local absorption (e.g., area under the concentration–time curve and/or peak concentration). The exposure pattern results in the positive (efficacy) and negative (risks) effects of a medicine. The upper part of the figure depicts the positive and negative dose or exposure pattern in terms of a dose–response relationship for benefit and risk.

A registration decision is based on consideration of information in an application for benefit and risk relative to an exposure pattern, which is controlled by the quality attributes of the dosage form and its ingredients. Characterization of the drug substance and dosage form result in a private specification (tests, procedures, acceptance criteria) that must be met for batch release. Consistency (equivalence) between the clinical trial material used to document efficacy and safety and the marketed dosage form is critical to ensure that the risk–efficacy profile, defined prior to approval relative to a specified exposure pattern, is maintained after market access. An acceptable understanding of an exposure–response relationship can yield an understanding of the population optimal dose and therapeutic window. Carefully designed studies can also yield this information for the individual, but these studies are rarely done.

In response to demands from civil society, FDA has developed a number of ways to advance registration of important new medicines, including a classification system dividing new medicines into priority and standard medicines, an “orphan drug” approach, accelerated approval, and other approaches as well.⁵ Postapproval control for a new medicine in the US is a key issue of increasing focus and concern. This stems not only from recent findings about risk for widely marketed medicines but also the information needed to ensure continuing safety and efficacy of a medicine in the presence of postapproval change. This was addressed in the FDA Modernization Act legislation of 1997, which spoke to the information needed in postapproval filings depending on the type of change. The language of the legislation spoke to continuing documentation of “original” safety and efficacy in the presence of postapproval change. In practice, the approach could be viewed as requiring redocumentation of safety and efficacy for all postapproval changes in method of manufacture and components and composition. From a science and technical standpoint, the task is made easier by a risk-based approach that

⁵In response to demands from civil society, FDA has at times relied on small clinical trials to allow access, particularly when treatment effects are clear. As an example, an important clinical trial in support of market access for zidovudine studied only 282 patients, comparing 145 subjects receiving 250 mg of zidovudine every four hours versus 145 subjects receiving placebo. Based on clear clinical benefit outcomes for efficacy (19 placebo died/45 developed opportunistic infections, compared to 1 died/24 developed opportunistic infections for patients on zidovudine), as well as changes in weight and CD4 cell count favoring the active treatment arm, this single study strongly supported a conclusion that zidovudine decreased mortality and the frequency of opportunistic infections in subjects with AIDS or AIDS-related complex (50).

works to ensure continuing pharmaceutical equivalence and bioequivalence for all manufacturers—both first- and second-entry in the presence of postapproval change.

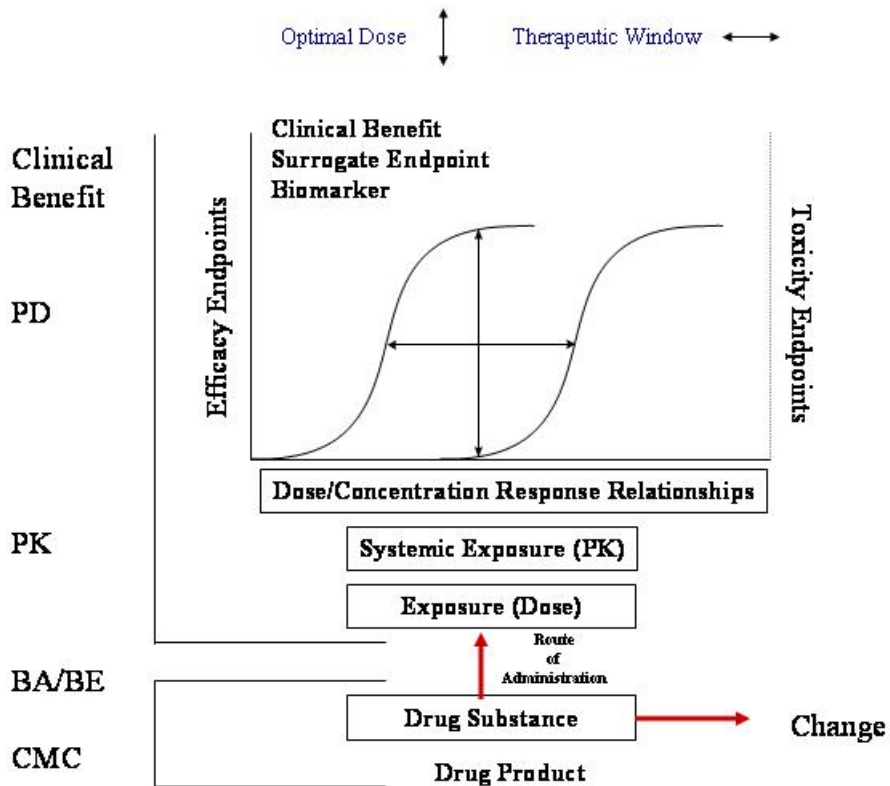


FIGURE 1

Example for Pricing: Australia’s Pharmaceutical Benefits Price Authority (PBPA)

PBPA is an independent nonstatutory body established January 1, 1988, with the objective of securing a reliable supply of pharmaceutical benefits at the most reasonable cost to Australian taxpayers and consumers (51). PBPA’s main mechanism for reviewing prices of pharmaceutical products supplied through the Pharmaceutical Benefits Scheme (PBS) relies on the advice of the Pharmaceutical Benefits Advisory Committee (PBAC) after comparison of the product to other relevant products. When this is not available, PBPA may turn to information comparing the gross margin on the cost of manufacture or similar factors. PBPA may also request additional data from applicants, including drug utilization data, so that relevant treatment costs can be independently calculated. The main mechanism to determine initial prices is the advice of PBAC arising from pharmacoeconomic (cost-effectiveness) information supplied by the sponsor and evaluated by PBAC. For new listings recommended by PBAC and approved by the Minister, the Authority recommends prices to be negotiated by the Department of Health

and Ageing. The prices set by the Authority cover not only subsidized products but also products listed in the Schedule priced below the maximum co-payment.

Examples for Quality of Care: The UK's National Institute for Clinical Excellence (NICE) and the US HEDIS Measures

NICE

Based on a number of advances in clinical understanding (transition from anecdote to evidence) and observations (moving away from differential patterns of treatment depending on area of residence), the United Kingdom's National Health Service added in 1999 a new component termed the National Institute for Clinical Excellence (NICE). NICE has the responsibility of advising clinicians about how to provide patients with the highest standard of clinical care (52, 53). It does so by 1) assessing clinical effectiveness and cost-effectiveness of medicines, devices, and diagnostic tools; 2) providing guidelines about management of medical conditions, again using clinical effectiveness and cost-effectiveness studies; and 3) assessing safety and efficacy of drugs and devices, including at times an appraisal of cost-effectiveness. Determinations may be expressed in terms of the size of an effect in response to an intervention; e.g., a medicine may be evaluated in terms of incremental cost per QALYs gained.

HEDIS Measures

Sponsored, supported, and maintained by the National Committee for Quality Assurance (NCQA), the Health Plan Employer Data and Information Set (HEDIS) is a set of standardized performance measures designed to ensure that purchasers and consumers have the information they need to reliably compare the performance of managed health care plans. The performance measures in HEDIS are related to many significant public health issues such as cancer, heart disease, smoking, asthma, and diabetes. HEDIS also includes a standardized survey of consumers' experiences that evaluates plan performance in areas such as customer service, access to care, and claims processing (54).

Examples for Patient Safety: The UK's National Patient Safety Agency (NPSA) and the US Joint Commission for the Accreditation of Healthcare Organizations (JCAHO)

NPSA

The NPSA is a Special Health Authority created to coordinate the efforts of all those involved in health care, and more importantly to learn from patient safety incidents occurring in the United Kingdom's National Health Service. As well as making sure that incidents are reported in the first place, NPSA aims to promote an open and fair culture in hospitals and across the health service, encouraging doctors and other staff to report incidents and "near misses." A key aim is to encourage staff to report incidents without fear of personal reprimand and to know that by sharing their experiences others will be able to learn lessons and improve patient safety (55).

JCAHO

In the US, the practice of medicine and pharmacy is controlled at the state rather than federal level. To develop approaches beyond the state level, national nonprofit voluntary organizations have arisen. One such organization is JCAHO, which accredits approximately 18,000 health care sites, including most US hospitals, nursing homes, and outpatient surgical centers. Accreditation is based on standards, which increasingly have focused on patient safety as a result of a series of Institute of Medicine reports indicating problematic safety practices, including safe medication use practices, in patient care in the US. On May 20, 2005, the Joint Commission's Board of Commissioners approved the 2006 National Patient Safety Goals (NPSGs). A partial list includes improving the accuracy of patient identification and the effectiveness of communication among caregivers, improving the safety of using medications, and eliminating wrong-site, wrong-patient, wrong-procedure surgery. Other goals emphasize the importance of reducing nosocomial infections, including influenza and pneumococcal disease in institutionalized older adults. Beginning January 1, 2006, all Joint Commission–accredited health care organizations will be surveyed for implementation of applicable NPSGs (56).

COLLABORATIONS IN DEVELOPING COUNTRIES: HOPE FOR THE FUTURE

Regulators, practitioners, and patients in developing countries have unique opportunities to work collaboratively with their counterparts in other countries and within their own countries to promote the availability of safe, effective, and good-quality medicines that are priced appropriately and rationally and are safely used. Collaboration should be directed toward action rather than just information exchange and harmonization. Collaboration and empowerment are important for at least the following reasons (see also 57):

- It is not true that developed countries have resolved questions and have available all needed approaches. Developed countries sometimes have subpopulations that receive health care at the level of some developing countries. Because of their special needs, creativity, and energy, developing countries and their regulatory personnel, however constrained, may create novel solutions that have been intractable for all nations.
- The general approaches to availability of good medicines, access to them, and their rational and safe use may involve multiple local authorities, for example a regulatory authority (like FDA), a pricing authority (like PBAC), an outcomes/pharmacoeconomics and evidence-based medicine authority (like NICE), quality of care approaches relying on HEDIS and similar measures, and a patient safety/safe medication use authority (like the UK NPSA and the US JCAHO). Even in countries with substantial resources, maintenance of these types of authorities is difficult and can become constrained by economic and political factors. The possibility of a smaller nation's creating these authorities alone—perhaps even small nations with good resources—is difficult to imagine.

- World demographic shifts are such that developing countries will be the ones with the largest populations and needs and, in consequence, the largest pharmaceutical and health care needs. Given that resources in these countries are likely to become even more constrained, developing countries might create regulatory and other environments that address these needs through collective action and a common will. The goal should be clarity about the needs of practitioners and patients rather than following customary approaches. As one group has pointed out, we must “avoid the culmination of current trend[s] in a double-standard system: the ICH standard for wealthy countries and the WHO standard for the others where[by] developing countries have everything to lose ...” (58).
- In a globalizing market, nations with limited resources become especially vulnerable to fraudulent and inappropriate commercial practices that do not support clear public health initiatives. Examples include counterfeit and substandard medicines, inappropriate internet communications, duplicitous marketing practices, and excessive prices. Approaches to identify, reduce, and eliminate these practices should benefit from collaborative understanding and action.

Collaborations for Discovery and Research and Development

A public–private partnership (PPP) is a research and development collaboration consisting of various organizations such as pharmaceutical companies, public research and academic institutions, international organizations, and small-sized specialized companies. PPPs utilize the expertise of the private sector in product research and development and specifications and the expertise of the public sector in the diseases and populations of interest and an understanding of the environment in which the product will be tested and used. Because resources and existing infrastructure are shared, risk is lowered for all involved. PPPs ensure that projects on product development for neglected diseases are viable, are adequately funded, and aim for accelerated progress.

The creation of PPPs has offered new hope for research and development for neglected diseases. With an array of new and improved interventions in the pipeline, civil societies throughout the world may be poised to mount significant attack on neglected diseases. PPPs currently support thousands of scientists from research institutes, academia, and pharmaceutical and biotechnology companies. They are advancing a robust product pipeline that focuses solely on the health needs of developing countries. These nonprofit initiatives also have stimulated and leveraged critical research capacity in countries hit hardest by neglected diseases, allowing affected countries to contribute to solutions in solving their own health challenges. Accomplishments to date include the registration of an antimalarial drug, a pipeline of more than 8 diagnostics, 34 new drug candidates, 28 microbicides, and 31 vaccine candidates addressing diseases such as HIV/AIDS, malaria, tuberculosis, pneumonia, and diarrheal diseases, as well as lesser-known diseases such as kala-azar and Japanese encephalitis. Twelve products currently are entering into late-stage clinical trials. Some of these could be available within the next five years. Philanthropic organizations have played a key role in launching and financing many of these partnerships. The health care industry has provided important contributions by

means of its technical and scientific expertise. Many of the projects have received public funding. Public support for public–private partnerships can take many forms but ultimately will require the raising and focused application of hundreds of millions of dollars of new funding for various part of the innovation value chain. The Pharmaceutical R&D Policy Project (PRPP) of the London School of Economics has observed that governmental incentives to advance research for neglected diseases largely have not been successful. PRPP asserts that the cause of such failures is a lack of empirical evidence about both the costs and effectiveness of these incentives and governmental programs. The result, then, is poorly formulated and targeted public research and development investment strategies (59). Examples of PPPs include:

- The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) that developed 67 disease control tools, of which 38 are used for international disease control initiatives (www.who.int/tdr/);
- Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development (TB Alliance), both of which managed to raise the public profile of malaria and tuberculosis and are developing drugs for these diseases (www.mmv.org/rubrique.php3?id_rubrique=15 and www.tballiance.org/);
- Drugs for Neglected Diseases Initiative (DNDi), which focuses on African trypanosomiasis, leishmaniasis, and Chagas’ disease (www.dndi.org/);
- Institute for One World Health (IOWH), which reformulates existing drugs and develops new compounds for leishmaniasis, malaria, Chagas’ disease, and diarrhea (www.oneworldhealth.org/); and
- Bio Ventures for Global Health (BVGH), which uses biotechnology to meet the health needs of people in LDCs (www.bvgh.org/).

Collaborations for Registration of New Medicines: Potential Opportunities

Working collaboratively, regulatory scientists can design early- and late-phase nonclinical and clinical trial protocols to assess medicines and other strategies to treat neglected and other diseases affecting their populations. The outcome would be a set of “off-the-shelf” protocols to guide a successful research outcome for medicines to treat a specified neglected disease under consideration by a PPP.

Efficacy

Collaborative work could focus on clinical trial designs to: 1) identify biomarkers and surrogate markers; 2) establish endpoints, expressed in terms of cure or a specified magnitude of effect; 3) indicate need for a comparator; 4) establish parameters to measure genetic/genomic and pharmacogenetic/pharmacogenomic factors; 5) assess the impact of other intrinsic and extrinsic factors on therapeutic outcomes; 6) promote accelerated approval approaches; 6) consider ethical issues, including poststudy requirements for treatment; 7) establish stopping rules based on unacceptable risk or lack of efficacy; and 8) identify needed postapproval studies.

Risk

Based on a preliminary understanding of the pathophysiology of a disease and the mechanism(s) of action of a drug, potential risks may be identified and ranked according to the likelihood of harm using standard risk-assessment approaches. Clinical trial designs can then be designed to assess the occurrence of these events, with a clear understanding of the limits of the planned clinical strategy to identify infrequent events. Authorization of new products may be accelerated if the drug sponsor agrees with the regulator to mandatory prospective pharmacovigilance plans before product launch.

Quality

Guidance documents in ICH and WHO generally provide a reasonable set of approaches to characterize the quality of ingredients and clinical trial dosage forms and to allow scale-up to marketed dosage forms. Developing country regulators, again working collaboratively with other partners, can carefully consider when to alter specific approaches depending on need. For example, for some infectious diseases, when treatment might be expected to be of short duration, focus on impurities in ingredients or a dosage form may not merit the same scrutiny as would be required for a medicine intended for chronic use.

Collaborative Action for a Scientific Opinion

Given some agreement on nonclinical and clinical approaches to guide R&D in the areas of safety, efficacy, and quality, a next logical step might be for developing country regulators to engage in joint reviews of information in a regulatory filing. Already some observers are discussing the possibility of “virtual centers of assessment in the EU” (60) and the possibility of collaboration to achieve a scientific opinion is already occurring in the area of quality. The WHO Prequalification Project is, in its fundamentals, an ingredient and dosage form review process analogous to a generic drug review. EDQM’s Certificate of Suitability achieves a similar evaluation for drug substances and excipients. In this context, regulatory collaborations to reach a scientific opinion about risk and benefit for medicines to treat neglected and other diseases in developing countries should be viewed as incremental rather than revolutionary. To assist in generation of a risk–benefit scientific opinion, regulators could develop decision-making toolkits based on national and regional needs, perhaps with input of representatives of civil society.

Collaborations for Multisource Interchangeable Medicines

Bioequivalence for pharmaceutically equivalence ingredients/dosage forms, and hence generic substitution, can be facilitated in several ways, with the goal being—within a nation, region, or even globally—a complement of well-manufactured multi-source products that are therapeutically equivalent to a specified first-entry (pioneer) product. Key elements to achieve this goal are: 1) careful post-approval change control for both pioneers and generics to ensure that both remain pharmaceutically equivalent and bioequivalent to their prior iterations in a market over time; 2) a well-selected and characterized global Comparator Pharmaceutical Product (global CPP) to support

bioequivalence studies by generic manufacturers.⁶ This product should be selected from a market with strong regulatory provisions to ensure availability of good-quality, safe, and effective new medicines with careful postapproval change control; 3) prospectively, multisource manufacturers should be required to document both bioequivalence and pharmaceutical equivalence to ensure therapeutic equivalence to the CPP after expiry of relevant patent/exclusivity provisions; 4) retrospectively, bioequivalence studies should be required both for new multisource products as well as already marketed similars as a means of reducing and eventually eliminating non-interchangeable multisource products from local and global commerce.⁷

WHO's update of its bioequivalence guidance will enhance reliance on in vitro dissolution as a means of documenting bioequivalence (66). This updated document relies on the biopharmaceutics classification system (BCS) and is coupled with techniques to allow comparison of dissolution profiles. With availability of this document and the availability of a global CPP, a world system of interchangeable pioneer and generic products may be envisioned.⁸ Features of such an approach would include: 1) practitioners and patients would be able to access medicines throughout the world with well-defined safety, efficacy, and quality—both for originator products and for interchangeable multisource products; and 2) generic manufacturers would have to conduct only one bioequivalence study for countries of the world, relying on the global CPP; and 3) international trade in medicines would be enhanced, with reduced concern about medicines crossing national borders (e.g., via Internet sales).

Collaborative Standards-setting Activities

Standards refer to a broad set of documentary and physical materials that allude to products, processes, and people. Standards are generated by a variety of public and private bodies and may be either voluntary or mandatory. When developed by rigorous science-based processes, with good transparency and allowance for public comment, standards become an important way to achieve many of the collaborative activities

⁶To assist countries and regions where the reference product may not always be readily identifiable, WHO prepared a document titled *Revision/Update of the Guidance on the Selection of Comparator Pharmaceutical Products [CPP] for Equivalence Assessment of Interchangeable Multisource (Generic) Products* (61). From a slightly different perspective, CMR International has prepared R&D Briefings for Southeast Asia and the Western Pacific; the Middle East and Africa; and Latin America that focus on the regulatory climate and the importance of what they term the Certificate of a Pharmaceutical Product (62–64).

⁷ Pioneer products may themselves lack a clear relationship, in terms of pharmaceutical equivalence and bioequivalence, to corresponding versions in developed countries where initial documentation of safety, efficacy, and quality first occurred. These pioneer products may themselves thus require some kind of documentation of bioequivalence and pharmaceutical equivalence.

⁸ For those countries with an internally defined CPP (e.g., the US with its Reference Listed Drug system), a three-way bioequivalence study might at times be needed to understand the relationship between the global CPP, the national CPP, and the generic test medicine. This type of approach has been used between countries (e.g., US and Canada) to allow marketing of an interchangeable generic when uncertainty exists about the quality and performance of the national CPPs.

discussed in this paper.⁹ Both ICH and WHO have developed a large number of standards to guide the development and approval processes for new and generic medicines. For developing countries, special care is needed to ensure active participation in collaborative standards setting. Product quality ingredient and product standards (e.g., a public specification) and sound GMPs coupled with adherence and conformity testing are critical to ensure the quality of new and generic medicines and to combat counterfeits. Noting that 27 manufacturers of generic anti-HIV drugs are expanding their production capacity in Asia, an editorialist in *The Lancet* recently called for the development of a regional government-run network of laboratories that could evaluate marketed drugs to test for counterfeit products (67). Such networks would depend on reliable, transparent public standards and sampling protocols.

DEVELOPING COUNTRIES: THE ROLE OF PRACTITIONERS AND PATIENTS

A positive regulatory decision to allow market access is just the start of the life cycle of a new medicine. At this point, other members of civil society who engage in the use of the medicine begin to gain a better understanding of its effectiveness, its risk profile, its value relative to cost in achieving defined therapeutic outcomes, and ways to use it safely. Key participants in this effort are practitioners and patients. Effective medicines use is significantly dependent on the transfer of all relevant information from knowledgeable practitioners to the benefactor (patients and consumers) of treatment in a manner understood, accepted, and respected by the latter. In developed nations, for example, pharmacists are expertly trained practitioners in the science behind and the use of medicines and associated patient care, and as such they are in an excellent position to fulfill this information-sharing task to its fullest extent. Nurses and physicians work with the patient to enhance the effect of medicine through nutritional and lifestyle improvements, increased adherence, and side effect management. Effective and efficient use of all health human resources in a concerted manner is the best method of ensuring the proper procurement, distribution, and dissemination of medicines.

A general approach may involve a collaboration of practitioners and patients supported by a drug information service that continuously abstracts the medical literature for information about new medicines. Multidisciplinary collaboration that draws on the specialized skills and knowledge of all caregivers in a concordant manner with patient feedback is imperative to creating a comprehensive compilation of data for use by all stakeholders. This information can then be converted into knowledge-based approaches for recommended usage and best practices. The approaches can be summarized in periodically updated compendia of drug information, with wisdom-based information, developed through an authoritative, credible, unbiased process, abstracted into key points and specific alerts to be delivered at the point of care. International bodies (including, but

⁹ After a 3-year study a Canadian group found that successful biotechnology innovation in Brazil, China, Cuba, Egypt, India, South Africa, and South Korea correlated positively with each country's levels of education, access to essential drugs, individual leadership, collaborative linkages, enterprise creation, intellectual property rights, and an entrepreneurial spirit (66).

not limited to, the World Medical Association, the International Pharmaceutical Federation, the International Council of Nurses, and the International Alliance of Patient Organizations) can help achieve these goals and can grow with suitable funding and commitment.

In the modern era, instructions for use of a medicine are provided by manufacturers via the package insert or comparable information. This information, itself at times extensive, is supplemented by thousands of pages of drug information that appear monthly in the biomedical literature, the popular press, and increasingly on the Internet. Various organizations throughout the world have attempted to consolidate this wealth of information into drug information compendia, translating drug information to knowledge. But the task of supplying reliable value-added information (off-label uses, safety, dosing, and other information) to supplement regulatory-approved labeling is a daunting one, given the wealth of information and the need to sensibly and reliably abstract it. Because information now frequently is an unreliable commodity from the Internet, the financial model to sustain provision of authoritative, unbiased, creditable, and frequently updated drug information is lacking. Even more important is the need for experts to translate drug information into wisdom—the standardized alerts and brief summaries needed to bring important and frequently updated information about health care and medication use to the point of care. For developing countries, the challenge and the need are especially great. Yet perhaps modern information technology and collaborative action can offer solutions. A general approach might involve a collaboration of practitioners and patients supported by a drug information service that continuously abstracts the medical literature for evidence-based, reliable information about new medicines. This information can then be converted into knowledge-based approaches for recommended usage and best practices. The approaches can be summarized in periodically updated compendia of drug information, with wisdom-based information developed through an authoritative, credible, unbiased process, abstracted into key points and specific alerts to be delivered at the point of care.

THE WAY FORWARD: A GLOBAL HEALTH CARE SECRETARIAT

Despite what now can only be described as a deeply challenged set of systems to treat neglected diseases in developing countries, much has occurred that offers hope. Opportunities relate to transnational collaborative activities, such as WHO's Pre-Qualification program and the EDQM Certificate of Suitability, that advance beyond information exchange and harmonization to collaboration for action. These initial efforts to move beyond national decision-making, which can be flawed and resource-constrained, set the stage perhaps for a truly global regulatory and practitioner/patient enterprise. By means of enhanced collaboration, public and private officials and regulators of developing countries may be in a remarkable position to advance basic research, discovery, drug development, registration, utilization, and related approaches for medicines (with allied activities) to prevent and treat diseases that have plagued humankind for centuries—and to develop medicines to treat other conditions as well. In the past several years, national, sub-regional, regional, trans-regional, and global

activities for collective action have appeared and offer hope. These not only have yielded needed registration and other standards but also have engaged regulators in the conduct of bilateral and multilateral conformity assessment activities. They have thus moved beyond information sharing and harmonization to yield useful results; i.e., they are action oriented.

The concluding theme of this paper is that regional and global collaboration efforts should be strengthened and, when possible, expanded and consolidated. Further consolidation is based on a vision of a collaborative global health care secretariat with multiple components, involving representatives from all countries, and yielding decisions suitable for national adoption. The components would focus on a) discovery; b) research and development; c) sound regulatory decision-making and, when appropriate, rapid registration decisions; d) optimal pricing/payment strategies; e) evidence-based health care delivery based on outcomes/pharmacoeconomic studies, f) quality of care and g) safe medicine use.

As a further proposal, this paper argues for close involvement of practitioners and patients throughout the overall process and urges for them a dominant role after registration. Specifically, it proposes a consortium of practitioners and patients to advance optimal health care, including pharmaceutical care, based on continually updated drug information. Independent, credible, authoritative practitioner and consumer experts would transform prospectively and retrospectively designed research studies and observational data into knowledge-based information monographs and wisdom-based brief summaries and alerts, following the paradigm of

data → information → knowledge → wisdom.

An overarching theme is the need for action. With sufficient (but not exorbitant) resources, a collective effort based on this shifting duality of inputs (regulators to the community and community to regulators) may promote, as overarching strategic objectives, rational use of medicines and good, cost effective health care delivery practices. An overall structure is shown in Figure 2. The secretariat is imagined to operate in close cooperation with the World Health Organization, relying on frequent and continuing input from governmental and practitioner/consumer experts from all countries of the world and in particular from developing countries. This input would yield science and policy decisions that would be suitable for national adoption, based on local acceptance and modification if needed.

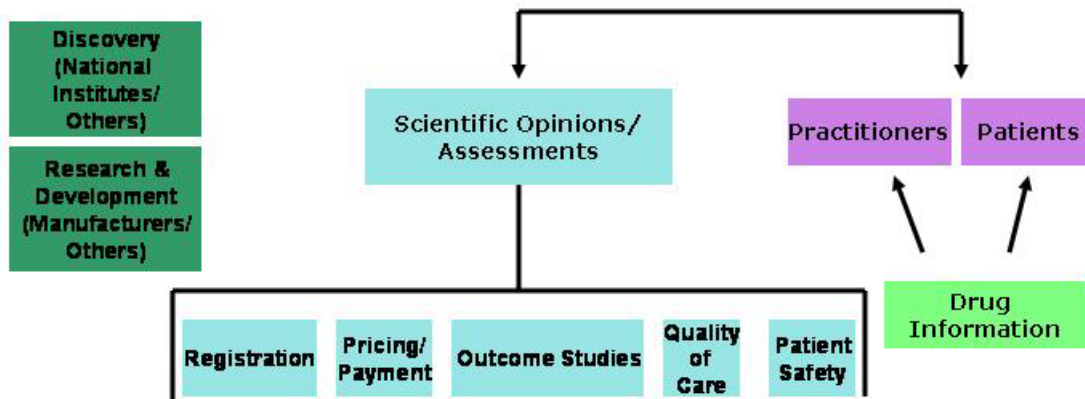


FIGURE 2

Such a secretariat could evolve over time into even stronger authorities and alliances, working to establish procedures that ensure transparency and trust and rely on advancing skills and shared values. Indeed, the vision perhaps leads to a world medicines agency with participants from experts from around the world, managed by a secretariat, and yielding scientific opinions on many topics suitable for national consideration and adoption. While not small, the expense of such a venture is almost certainly minimal compared to costs encountered today, which leave many if not all actors in civil societies at the mercy of fragmented, duplicative, and poorly coordinated approaches that are encumbered by inertia, misinformation, and perhaps even incompetence and corruption. A particular feature of the approach is that it consolidates and focuses the skills and wisdom of experts from developing countries themselves. Nonetheless, partnering with science and technical experts from developed countries is encouraged, so that skills and wisdom of all contributors are enthusiastically welcomed and shared.

REFERENCES

1. CIPIH. Terms of reference for Topic 5. Available at: www.who.int/intellectualproperty/studies/Study5Annexes.pdf. Accessed October 11, 2005.
2. WHO. Effective drug regulation: what can countries do? Available at: [whqlibdoc.who.int/hq/1999/WHO_HTP_EDM_MAC\(11\)_99.6.pdf](http://whqlibdoc.who.int/hq/1999/WHO_HTP_EDM_MAC(11)_99.6.pdf). Accessed October 17, 2005.
3. WHO. Effective drug regulation: a multicountry study. Available for purchase at: www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=503. Accessed October 17, 2005.
4. WHO. CIPIH Workshop. Available at: www.who.int/intellectualproperty/events/workshop/en/index.html. Accessed September 14, 2005.
5. International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Research and development for neglected diseases: lessons learned and remaining challenges. Geneva, Switzerland; IFPMA; 2004. Available at: www.ifpma.org/documents/NR1897/RD%20for%20Neglected%20Diseases_October04.pdf. Accessed September 23, 2005.
6. Danzon P. Selling life-saving drugs to poorer countries: at what cost? Available at: knowledge.wharton.upenn.edu/index.cfm?fa=viewArticle&id=649. Accessed September 16, 2005.
7. WHO's International Labor Office and International Council of Nurses. Public service reforms and their impact on health sector personnel—critical questions: a tool for action. Available at: www.icn.ch/en/index.htm. Accessed September 15, 2005.
8. Trouiller P, Folb P, Weerasuriya K. Legal and regulatory issues affecting drug development for neglected diseases: harmonization of technical requirements for registration of pharmaceuticals for human use. *Drugs for neglected Diseases working group, Médecins sans Frontières*. 2001;133–140.
9. Seiter A. Pharmaceuticals: drug regulation in low- and middle-income countries. Available at: siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1109774792596/HNPBrief_4.pdf. Accessed October 17, 2005.
10. WHO. Effective drug regulation: what can countries do? Available at: www.who.int/medicines/library/general/who-htp-edm-mac-11-99-6/who-htp-edm-mac-11-99-6.htm Accessed October 12, 2005.
11. WHO. Effective drug regulation: a multicountry study. Available at: www.who.int/medicines/library/qsm/eff-drug-reg/eff-drug-reg.shtml. Accessed September 15, 2005.
12. WHO. Health and the millennium development goals. Available at: www.who.int/mdg/publications/mdg_report/en/. Accessed October 17, 2005.
13. Behrens RH et al. Substandard and counterfeit drugs in developing countries. *Tropical Doct*. 2002;32:1–2.
14. Rozendaal J. Fake antimalarial drugs in Cambodia. *Lancet*. 2001;357:890.

15. Primo-Carpenter, J. *A Review of Drug Quality in Asia with Focus on Anti-Infectives*. Rockville, MD: USP; 2004. Available at: www.uspdqi.org/pubs/other/ANEReview.pdf. Accessed November 2, 2005.
 16. Primo-Carpenter, J. *A Matrix of Drug Quality Reports on USAID-assisted Countries by the US Pharmacopeia Drug Quality and Information Program*. Rockville, MD: USP; 2005.
 17. Department of Essential Drugs and Other Medicines, World Health Organization. Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs. Geneva, Switzerland; 1999. Available at: whqlibdoc.who.int/hq/1999/WHO_EDM_QSM_99.1.pdf. Accessed September 15, 2005.
 18. ICDRA. Eleventh international conference of drug regulatory authorities: progress report and recommendations. Available at: www.who.int/medicines/publications/druginformation/ICDRA11_recommendations.pdf. Accessed October 17, 2005.
 19. Anon. Safety and efficacy issues: the role of pharmacovigilance in medicines safety. *Who Drug Inf*. 2005;19(1):13–15.
 20. National Association of Boards of Pharmacy. Verified Internet pharmacy practice sites. Available at: www.nabp.net/. Accessed November 4, 2005.
 21. Guttmacher AE, Jenkins J, Uhlmann WR. Genomic medicine: who will practice it? A call to open arms. *Am J Med Genet (Semin Med Genet)*. 2001;106:216–222.
 22. Vogel F. Moderne Probleme der Humangenetik. *Ergeb Inn Med Kinderheilkd*. 1959;12:52–125.
 23. Council for International Organizations of Medical Sciences Working Group on Pharmacogenetics. *Pharmacogenetics: Towards Improving Treatment with Medicines*. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 2005.
 24. Anon. Pharmacogenetics: towards improving treatment with medicines. *WHO Drug Inf*. 2005;19(1):3–12.
- ADD CIOMS BOOK w/8b
25. ICH. Guideline E5: ethnic factors in the acceptability of foreign clinical data. Available at: www.ich.org/MediaServer.jserv?@_ID=481&@_MODE=GLB. Accessed October 12, 2005.
 26. FDA. Guidance for industry: pharmacogenomic data submissions. Available at: www.fda.gov/cber/gdlns/pharmdntasub.pdf. Accessed October 17, 2005.
 27. Gieschke R, Steimer JL. Pharmacometrics: modeling and simulation tools to improve decision making in clinical drug development. *Eur J Drug Metab Pharmacokinet*. 2000;25:49–58.
 28. Anon. FDA wants to be “model” agency: preparing for clinical trial simulations. *The Pink Sheet*. October 18, 2004:28.
 29. FDA. Innovation or stagnation: challenge and opportunity on the Critical Path to new medical technologies. Available at: www.fda.gov/oc/initiatives/criticalpath/whitepaper.html. Accessed October 17, 2005.
 30. Anon. Biomarker working group to explore development of Guidance. *The Pink Sheet*. November 15, 2004:29–29.
 31. Anon. FDA “Critical Path” may lead to changes in dosing, active-control trials. *The Pink Sheet*. December 13, 2004:31–32.

32. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Bayesian methods in health technology assessment: a review. *Health Technol Assess*. 2000;4(38):1–130. Available at: www.ncchta.org/execsumm/summ438.htm. Accessed September 15, 2005.
33. Salomon JA, Mathers CD, Murray CJL, Ferguson B. Methods for life expectancy and healthy life expectancy uncertainty analysis. Available at: whqlibdoc.who.int/hq/2001/a78510.pdf. Accessed October 17, 2005.
34. Motheral BR, Daniels CE, Cox ER. Pharmacoeconomics and outcomes research: evaluating the studies. *J Managed Care Pharm*. 2000;6(suppl):1–16.
35. FDA. Guidance for Industry. Fast track development programs—designation, development, and application review. Available at: www.fda.gov/cder/guidance/5645fnl.htm. Accessed September 15, 2005.
36. EMEA. Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community. Available at: www.emea.eu.int/pdfs/human/regaffair/557904en.pdf. Accessed October 12, 2005.
37. Mahmoud A, Danzon PM, Barton JH, Mugerwa RD. Product development priorities. In: Jamison D, Bremen J, eds. *Disease Control Priorities*. Washington, DC: Institute of Medicine; 2005: In press.
38. FDA. FDA’s new drug safety initiative. Available at: www.fda.gov/cder/drugSafety.htm. Accessed October 17, 2005.
39. Roberts L. Rotavirus vaccines’ second chance. *Science*. 2004;305:1890–1893.
40. Anon. FDA action plan should engage academia, government, industry—ASM. *The Pink Sheet*. August 16, 2004:12.
41. Creese A, Kotwani A, Kutzin J, Pillay A. Evaluating pharmaceuticals for health policy in low- and middle-income country settings. In Freemantle N, Hill S eds. *Evaluating Pharmaceuticals for Health Policy and Reimbursement*. Malden, MA: Blackwell Publishing; 2004:227–243.
42. Hill S, Johnson K. Emerging challenges and opportunities in drug registration and regulation in developing countries. Available at: www.dfidhealthrc.org/shared/publications/Issues_papers/ATM/Hill.pdf. Accessed October 17, 2005. See esp. section 4.
43. Eisenberg RS. The shifting functional balance of patents and drug regulation. *Health Aff*. 2001;19(4):119–135.
44. Adelman C, Norris J, Weicher J. *Analysis of “Our Common Interest: Report of the Commission for Africa” [A Multicountry Commission Chaired by Prime Minister Tony Blair in Preparation for the G8 Meeting July 2005]*. Washington, DC: Hudson Institute; 2005.
45. Anon. Prequalification of medicines. *Who Drug Inf*. 2005;19(1):35–39.
46. WHO. The WHO prequalification project. Available at: www.who.int/mediacentre/factsheets/fs278/en/. Accessed October 12, 2005.
47. USP DSVP. USP verified. Available at: www.usp.org/USPVerified/. Accessed October 12, 2005.
48. National Institute of Standards and Technology. *Definitions of Terms and Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements*. Gaithersburg, MD: NIST; 2000.

49. Marshal K, Foster TS, Carlin HS, Williams RL. Development of a compendial taxonomy and glossary for pharmaceutical dosage forms. *Pharm Forum*. 2003;29(5):1742–1752.
50. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med*. 1987;317:185–191.
51. Pharmaceutical Benefits Pricing Authority [Australia]. Policies, procedures, and methods used in the pricing of pharmaceutical products. Available at: [www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pricing-pbpamethods.htm/\\$FILE/pbpamethods.rtf](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pricing-pbpamethods.htm/$FILE/pbpamethods.rtf). Accessed September 14, 2005.
52. National Institute for Clinical Excellence. Developing clinical guidelines. Available at: www.nice.org.uk/page.aspx?o=114219. Accessed September 16, 2005.
53. Rawlins MD. NICE work—providing guidance to the British National Health Service. *N Engl J Med*. 2004;352:1381–1385.
54. HEDIS. The health plan employer data and information set. Available at: www.ncqa.org/Programs/HEDIS/. Accessed October 12, 2005.
55. NPSA. National patient safety agency. Available at: www.npsa.nhs.uk/. Accessed October 12, 2005.
56. JCAHO. Facts about the 2006 national patient safety goals. Available at: www.jcpatientsafety.org/show.asp?durki=9726&site=164&return=9335. Accessed October 12, 2005.
57. Hill S, Johnson, K. Emerging challenges and opportunities in drug registration and regulation in developing countries. Available at: www.dfid.gov.uk/pubs/files/dfidhilldrugs.pdf. Accessed October 12, 2005.
58. Trouiller P, Salmén R, Myhr K, Folb P, Weerasuriya K, Gray A. The globalisation of regulatory requirements and the development and availability of medicinal products in developing countries: quality, efficacy, and safety issues. *Drugs for neglected Diseases working group, Médecins sans Frontières*. 2000:141–154.
59. PRPP. Pharmaceutical R&D policy project. Available at: www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm. Accessed October 12, 2005.
60. Anon. “Virtual centers of assessment—the way forward for EU reviews? *Scrip*. September 7, 2005:2–3.
61. WHO. Revision/update of the guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. Available at: www.who.int/medicines/services/expertcommittees/pharmprep/QAS05_143_Comparator_Rev%201.pdf. Accessed October 13, 2005.
62. CMR International. *R&D Briefing 47: Assessing the Regulatory Environment and Its Impact on Patients’ Access to New Medicines—South-East Asia and the Western Pacific*. Epsom, Surrey, UK: CMR International Institute for Regulatory Science; 2005.
63. CMR International. *R&D Briefing 48: Assessing the Regulatory Environment and Its Impact on Patients’ Access to New Medicines—Middle East and Africa*. Epsom, Surrey, UK: CMR International Institute for Regulatory Science; 2005.

64. CMR International. *R&D Briefing 49: Assessing the Regulatory Environment and Its Impact on Patients' Access to New Medicines—Latin America*. Epsom, Surrey, UK: CMR International Institute for Regulatory Science; 2005.
65. WHO, Pan American Health Organization, Pan American Network for Regulatory Harmonization. Science-based criteria for bioequivalence in vivo and in vitro, bio-wavers, and strategic framework for implementation (Draft). Available at: www.paho.org/english/ad/ths/ev/BE-doct-draft-Eng.pdf. Accessed October 13, 2005.
66. Thorsteinsdóttir H, Quach U, Martin DK, Daar AS, Singer PA. Promoting global health through biotechnology. *Nature Biotechnol.* 2004;22(suppl):DC48–DC52.
67. Frost KR. Ensuring the safety of HIV/AIDS generics. *The Lancet.* 2005;365(suppl.):1290–1291.

ATTACHMENTS

ATTACHMENT 1

USP Advisory Panel (Revised September 14, 2005)

Mei Ling Chen, Ph.D., Associate Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration

Patricia Danzon, Ph.D. Professor and Chair, Health Care Systems Department, Wharton School of Management, University of Pennsylvania

Peter Gund, Ph.D., Sr. Solutions Scientist, Life Sciences Worldwide and Pharma R&D Solutions, IBM

Victoria Hale, Ph.D. Chief Executive Officer and Founder, Institute for OneWorld Health

Chris Hentschel, Ph.D. CEO, Medicines for Malaria Venture

Precious Matsoso, Director, WHO Technical Cooperation for Essential Drugs and Traditional Medicines

Carl Peck, M.D., Professor of Pharmacology and Medicine at Georgetown University School of Medicine, Founder and Director, Center for Drug Development Sciences (CDDS), University of California San Francisco

Sauwakon Ratanawijitrasin, Ph.D., Director, Pharmaceutical System Research and Intelligence Center, Faculty of Pharmaceutical Sciences, Chulalongkorn University

Sir Michael Rawlins, M.D., Chair of National Institute for Health & Clinical Excellence (NICE)

Andreas Seiter, M.D., Global Pharmaceutical Industry Fellow, The World Bank

Vinod Shah, Ph.D., Scientific Secretary, International Pharmaceutical Federation (FIP), Consultant, USP

Krisantha Weerasuriya, M.D. Regional Adviser, Essential Drugs and Medicines Policy (EDM), WHO South-East Asia Regional Office (SEARO)

Linda Carrier-Walker, Director of Communications and External Relations, International Council of Nurses



Stuart Walker, Chief Executive Officer, Center for Medicines Research (CMR) International Ltd.
Member of Regulatory Advisory Board of CMR International Institute for Regulatory Science

Stan Finkelstein, M.D., Chair Senior Research Scientist, MIT Sloan School of Management, Co-Director, Program on the Pharmaceutical Industry (POPI)

USP Staff

Nancy Blum, M.P.H., Director, Global Assistance Initiatives

Joyce Primo-Carpenter, M.D., Associate Director, Global Assistance Initiatives

Stefan Schuber, Ph.D., Director, Scientific Reports

Eric Sheinin, Ph.D., Chief Scientific Officer

Elizabeth Singh, Manager, Executive Administration

Roger Williams, M.D., Executive Vice President and Chief Executive Officer*

*To whom all correspondence should be addressed:

US Pharmacopeia
12601 Twinbrook Parkway
Rockville, ME 20852-1790
USA

Tel.: +1.301.816.8300

E-mail: rlw@usp.org



ATTACHMENT 2

International Health Expert Committee of USP's Council of Experts

CHAIR

Salomon Stavchansky, Ph.D.

Alcon Centennial Professor of Pharmaceutics
The University of Texas at Austin

VICE CHAIR

Andreas Seiter

Senior Health Specialist-Pharmaceutical Fellow
World Bank

MEMBERS

Anthony Boni

CTO
USAID

Denis D. Broun, M.D.

Managing Director
Management Sciences for Health

Laura Ceron, Pharm.D.

Adviser of Director
Ministry of Health, Department of Medicines-DIGEMID

J. C. Craft, M.D.

Chief Scientific Officer
Medicines for Malaria Venture

Prashant M. Dikshit, Ph.D.

Clinisearch Biotechnologies

Maurice N. G. Dukes, M.D.

Editor and Consultant
Meyler's Side Effects of Drugs

Enrique Fefer, Ph.D.

Independent Expert

Stan N. Finkelstein, M.D.

Senior Research Scientist
MIT/Harvard Medical School



José Aparcio B. Funck, Ph.D.

Consultant
Pontifícia Universidade Católica do Rio Grande do Sul

Joseph F. Galleli, Ph.D.

Senior Advisor, Biotech. Product Dev.
National Institutes of Health

Professor Roman S. Kozlov, M.D., Ph.D.

Deputy Director of Science
Institute of Antimicrobial Chemotherapy
Smolensk State Medical Academy

Howard Levy, Ph.D.

Medical Director
Eli Lilly and Company

Robert B. Myers, B.S.

President
Parenteral Drug Association

Kate K.T. Nguyen, Pharm.D.

Clinical Pharmacist
Coram Health Care

Iruka N. Okeke, Ph.D.

Assistant Professor
Haverford College

Andreas Seiter, M.D.

Senior Health Specialist/Pharmaceutical Fellow
World Bank

Andrew Walubo, M.D.

Professor
University of Orange Free State

ATTACHMENT 3

CIPIH Studies and Authors

No.	STUDY	AUTHOR
1	a. The Disease Burden on Developing Countries: Where Are the Real Research Gaps?	Colin Mathers, <i>World Health Organization (Australia)</i>
	b. What has been achieved, what have been the constraints and what are the future priorities for pharmaceutical product-related R&D to the reproductive health needs of developing countries	Peter Hall, <i>Consultant (UK)</i>
	c. Case study review of current volume and balance of the global research effort	Alyna Smith, <i>CIPIH Secretariat (Canada)</i>
2	a. The Cost of Research and Development: what are the implications for R&D relevant to the Health Needs of Developing Countries?	—
	b. From Prevention to Cure: Setting Priorities for Research and Development Part 1: Asking the Questions - How Donors Set and Influence Global Priorities	Charles Clift, <i>CIPIH Secretariat (UK)</i>

	c.	From Prevention to Cure: Setting Priorities for Research and Development Part 2: Conceptual Framework - Models for Moving Forward	Andrés de Francisco, <i>Global Forum for Health Research (Uruguay)</i>
3	a.	IP & innovation	Richard Kjelgaard, <i>WIPO (USA)</i> Anthony Taubman, <i>WIPO (Australia)</i>
	b.	A Review of IP and Non-IP Incentives for R&D for Diseases of Poverty. How Can We Incentivise Research to Get the Right Balance between Incremental Innovation and Breakthrough Innovation?	Adrian Towse, <i>Office of Health Economics (UK)</i> and Hannah Kettler, <i>Gates Foundation (USA)?</i>
	c.	Pharmaceutical Innovation and the burden of disease in developing and developed countries	Frank Lichtenberg, <i>Columbia University (USA)</i>
	d.	Intellectual Property Issues in R&D: Public-private Partnerships (PPPs)	Jon Merz, <i>Penn University (USA)</i>
	e.	Intellectual Property Issues: PPP Products	Warren Kaplan, <i>Boston University (USA)</i>
	f.	Intellectual Property Issues: US Universities	Various, <i>Duke University (USA)</i>

4	a.	<p>Global changes in research and development patterns in response to TRIPS</p> <p>The effect of intellectual property rights and price regulation on the arrival of new drugs on the market in poor countries</p>	Jenny Lanjouw, <i>University of California at Berkeley (USA)</i>
	b.	<p>The impact of product protection for pharmaceuticals on incentives for the creation of health care products & on access to new medicines: India Case Study</p>	Sudip Chaudhuri, <i>Indian Institute of Management (India)</i>
	c.	<p>The Use of Flexibilities in TRIPS by Developing Countries: Can they Promote Access to Medicines?</p>	Sisule Musungu, <i>South Centre (Kenya)</i> Cecilia Oh, <i>World Health Organization (Malaysia)</i>
	d.	<p>Economic Aspects of Access to Medicines after 2005</p>	Padmashree G. Sampath, <i>INTECH (India)</i>
	e.	<p>Tariffs on essential medicines in developing countries</p>	Müge Olcay, <i>CIPIH Secretariat (Turkey)</i>
5	a.	<p>How does the regulatory framework affect incentives for research and development?</p>	Roger Williams, <i>U.S. Pharmacopoeia (USA)</i>

	b.	How does the regulatory framework affect incentives for research and development? : developing countries' perspective	Precious Matsoso, <i>Medicines Control Council (South Africa)</i>
7		Taking the Temperature of Public-Private Partnerships for Product Development: How healthy are they and what is the prognosis for success?	Elizabeth Ziemba, <i>SHARED Inc.(USA)</i>
8		Other Incentives	Stephen Maurer, <i>University of California at Berkeley (USA)</i>
9		Traditional medicine & innovation	Bhushan Patwardhan, <i>University of Pune (India)</i> Weiyong Wu, <i>Shanghai Innovative Research Center of Traditional Chinese Medicine (China)</i>
10	a.	Health Innovation Systems in Developing Countries: Agenda & Strategies for Building National and Regional Capacity	John Mugabe, <i>NEPAD (Uganda)</i>
	b.	Product patents for pharmaceutical development in Japan and its implications for developing countries	Tomoko Saiki, <i>Tokyo Institute of Technology (Japan)/ University of Auckland (Japan)</i> and Reiko Aoki, <i>Hitotsubashi University (Japan)</i>
	c.	Biotechnology Capacity and Innovation Systems in Cuba	Halla Thorsteinsdottir, <i>University of Toronto (Iceland)</i>

	<p>d.</p> <p>Case Studies: Developing Innovative Capacity</p> <p>India</p> <p>China</p> <p>South Africa</p> <p>Brazil</p>	<p>Managed by Cathy Garner, <i>MIHR (UK)</i></p> <p>H R Bhojwani (<i>India</i>)</p> <p>TBA* (<i>China</i>)</p> <p>TBA (<i>South Africa</i>)</p> <p>TBA (<i>Brazil</i>) (*=<i>To Be Announced</i>)</p>
--	---	---

ATTACHMENT 4

Executive Summary:

A Proposal for a Regulatory Framework and Introduce Incentives for R&D
P. Matsoso et al.

Executive Summary

Terms of reference of the study

Review the ways in which the regulatory framework affects the incentives for, and costs of, R&D and the effect on access, particularly in respect of medical products for developing countries,

- Review the issues involved in the growth of regulatory requirements for the approval of new products, in particular as these affect the cost of R&D and the incentives for investment in R&D, particularly in respect of products of particular relevance to developing countries.
- Review the impact of international arrangements (e.g., ICH, the WHO prequalification project, WHO EDL) which have relevance for the approval of products, and access to them, in developing countries.
- Consider how the challenges posed by new medical technologies could be dealt with by regulatory authorities and the possible implications for developing countries.
- Make proposals for consideration by the Commission on possible changes in regulatory approaches, at both national and international levels, which could contribute to faster and more cost-effective regulatory procedures to facilitate the introduction of new medicines, vaccines, and other products in developing countries consistent with ensuring the quality, efficacy, and safety of medicines.
- Come up with practical proposals about how to strike an appropriate balance between risk and benefit in the construction and application of regulatory frameworks, recognizing that this balance may need to be different as between the developed and developing world.
- Finally, consider mechanisms to increase capacity for research (including ethical) review.

In response to these terms of reference, a proposal was made that the study will have three parts, each of which will be based on a review of existing literature combined with qualitative research.

Part one identifies particular regulatory challenges that may exist in relation to specific areas of R&D of relevance to developing countries, including the development of new formulations and delivery systems. Many of the regulatory challenges related to new technologies are those presented by vaccines and biologicals. Therefore, in this study successful vaccine regulatory approaches have been used as the basis for proposed regulatory models.

Part two outlines regulation within the global landscape, including recent trends towards international and regional harmonization of regulatory requirements, and what it means for developing countries.

Finally part three investigates the specific question of clinical trials, considering the interplay of economic, ethical, safety and scientific concerns on the part of industry, government, and patients.

ATTACHMENT 5

Drug Regulation and Incentives for Innovation: The Case of ASEAN

Sauwakon Ratanawijitrasin, Ph.D.
Pharmaceutical System Research & Intelligence Center
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Thailand

Public policies represent a government's intention and action put forth to achieve collective goals. Oftentimes, a public policy produces effects beyond its stated objectives. In addition, it may also interact with other public policies in ways that enhance or hinder them—with both intended and unintended effects. These phenomena, or their possibility, raise further policy issues for debate. The pharmaceutical sector is an area in which such issues arise at both national and international levels.

Consumer protection and promotion of pharmaceutical R&D are the two societal goals toward which public policies regularly generate extensive debates. Although a lot of new medications discovered have given great benefits to humanity, many of them have caused serious harm to those who use them. Consequently, although society needs continuous development of new medicines to combat diseases and improve health, society also demands protection from potential damage that the use of drugs might bring.

Drug regulation is the totality of all measures—legal, administrative, and technical—that governments take to ensure the safety, efficacy, and quality of drugs, as well as the relevance and accuracy of product information. Public policy restricts private-sector activities in order to attain social goals set by the state. To ensure that drugs are efficacious, safe, and of good quality, drug regulation imposes standards on pharmaceutical products, as well as the ways these products are discovered, made, distributed, and dispensed. Through legislation, administrative rules, and technical requirements, drug regulation exerts controls on how clinical trials, product assessment, manufacturing and importation process, quality control, promotion and advertising, and dispensing are to be carried out.

With reports of a number of tragic adverse events caused by use of drugs, especially in the latter half of the last century, more stringent controls have been imposed on the procedures for market authorization of drugs. These controls inevitably entail increased costs on the part of pharmaceutical businesses. Among the various activities that have to meet regulatory requirements, R&D of new drugs is the most costly. Although estimates vary regarding how much the pharmaceutical industry actually spends on R&D of new drugs vary and what proportion of the costs are borne by taxpayers through government research agencies and funds is an issue being debated, the notion that regulation adds to the costs of drug development both in terms of money and time continues. These costs, it has been argued, constitute disincentives for pharmaceutical firms to invest in R&D. In fact, arguments positing that drug regulation unnecessarily delays the development and

introduction of valuable new drugs and deprives patients of life-saving drugs have been around for decades.

Meanwhile, patent laws have been adopted in more and more countries, especially following the TRIPS Agreement, with the aim of rewarding innovations. Another set of debates questions the merit of intellectual property protection vs. the problems of access to drugs and the high prices of vaccines. Are these debates, which mainly take place in countries where new drugs are developed, also of policy significance in developing countries where R&D capabilities are generally much poorer? How does drug regulation affect incentives for research and development in the context of developing countries?

This paper was prepared for the World Health Organization's Commission on Intellectual Property Rights, Innovation, and Public Health (CIPIH) to address the issue of the impact of drug regulation on incentives for research and development of new drugs and vaccines.

ATTACHMENT 6

Pathogenesis and Treatment Options for Neglected Diseases

South American trypanosomiasis (Chagas disease)

South American trypanosomiasis occurs throughout Mexico and central and southern America. Its pathophysiology results in a spectrum of cardiac, gastrointestinal, or neurological damage collectively termed Chagas disease. Chagas disease is caused by *Trypanosoma cruzi* and is transmitted to humans through blood feeding arthropods, blood transfusion, or through vertical transmission. The overall prevalence of this infection is estimated at 16–18 million cases. Approximately 120 million people (about 25% of those living in Latin America) are at risk. The chronic form of Chagas disease affects a significant number of people, especially the poor, in Latin America. About 25 to 30% will develop irreversible organ damages, resulting in considerable morbidity and mortality and economic loss. In the past ten years, successful disease transmission control programs have been implemented. Medicines to treat the infection are nifurtimox and benznidazole, with a 50% cure rate for acute infections but little or no activity in chronic forms of the disease. They also have serious and frequent side effects, are unavailable to most people in endemic areas, and are expensive, thereby limiting their use. Vaccine treatment is not available.

African trypanosomiasis (African sleeping sickness)

An estimated 300,000 to 500,000 people in 36 countries in sub-Saharan Africa suffer from African trypanosomiasis, with more than 60 million at risk. This vector-borne disease is caused by *Trypanosoma brucei gambiense* and *rhodesiense*, parasites that are transmitted to humans by the tsetse fly (*glossina*). Sleeping sickness is difficult to diagnose because initial signs and symptoms are nonspecific, and the disease is fatal without treatment. Available medicines such as suramin and melarsoprol are difficult to use, associated with toxicity, expensive, and likely to promote resistance. A vaccine is not available.

Visceral leishmaniasis

Visceral leishmaniasis is endemic in 88 countries where 350 million people are at risk of infection. An estimated 500,000 new cases come from recurrent epidemics that occur every year in the rural areas of the Indian subcontinent (India, Nepal, and Bangladesh), Brazil, and Sudan. Kala-azar is caused by the parasitic protozoa of the genus *Leishmania*, transmitted to humans by sandflies. Different types of leishmaniasis have spread to other areas of the world in the past 10 years. Although pentavalent antimony (sodium stibogluconate) has been the medicine of choice for many years, it is difficult to administer, painful to the patient, and toxic to the point of death. Pentavalent antimony has lost its effectiveness in many parts of India. Alternative drugs like ambisome and miltefosine are costly and require prolonged treatment. A formulation of paromomycin is currently being registered in India for treatment of this disease. No vaccine is available.

Onchocerciasis (river blindness)

Onchocerciasis is an eye and skin disease caused by *Onchocerca volvulus*. It is transmitted to humans through the bite of a blackfly. After infection, the death of microfilariae is toxic to the skin and the eye, resulting in extreme itching and various eye lesions. After repeated years of exposure, these lesions may lead to irreversible blindness and disfiguring conditions sometimes named "leopard" skin and "lizard" skin. River blindness occurs in areas where blackflies breed near fast-running streams and rivers in the inter-tropical zones. About 90% of the disease occurs in Africa. It is also found in six countries in Latin America and in Yemen, where the disease is believed to be exported by the trafficking in humans. In some West African communities, about 50% of men over the 40 years of age had been blinded by this disease. In 1974, WHO launched the Onchocerciasis Control Programme that conducts larvicidal spraying over blackflies breeding sites. People infected with river blindness are treated with ivermectin, an effective drug that kills the microfilariae.

Schistosomiasis

Schistosomiasis is endemic in 74 LDCs with more than 80% of infected people living in sub-Saharan Africa. The infection is caused by the trematode flatworms (flukes) of the genus *Schistosoma*. *S. haematobium* is the most prevalent and widespread species in Africa and the Middle East. *S. intercalatum* occurs in 10 countries in the rainforest belt of Africa. *S. mansoni* is found in Africa and is the only species seen in Latin America. *S. japonicum* is restricted to the Pacific region including China and the Philippines. *S. mekongi* is found in limited areas of Laos and Cambodia. Schistosomiasis is transmitted to humans by infected snails that release the larval forms of the parasites (cercariae). These in turn cause infection after penetrating the skin. Urinary schistosomiasis is caused by *S. haematobium* and is associated with bladder cancer. In intestinal schistosomiasis (infection with *S. mansoni*, *S. japonicum*, or *S. mekongi*), progressive enlargement of the liver and spleen occurs with increased portal pressure. Intestinal damage also occurs as a result of fibrotic lesions around eggs lodged in tissues, which also is associated with increased portal pressure. Bleeding occurs and can be fatal. Prevention is achieved through snail control. Drugs used to treat snail fever are praziquantel and oxamniquine.

Leprosy

Leprosy is caused by the bacillus, *Mycobacterium leprae*. It is a chronic disease affecting mainly the skin and nerves, with symptoms that can take as long as 20 years to appear. Leprosy is not highly infectious. It is transmitted via infectious oral and nasal fluids during close and frequent contact with untreated patients. An estimated 755,000 new cases of leprosy were detected during 2001. Leprosy is still considered a public health problem in 14 countries in Africa, Asia, and Latin America. Intensive efforts are ongoing to reach the leprosy elimination targets in six countries: Brazil, India, Madagascar, Mozambique, Myanmar, and Nepal. Taken together, these countries account for 90% of the prevalence of the disease in the world. In the beginning of 2002, about 70% of the world's registered leprosy patients were found in India. Treatment provided at the early stages prevents disability and is curative. Treatment involves three medicines (Multi-

Drug Therapy/MDT advocated by WHO): dapsone, rifampicin, and clofazimine. This drug combination is easily administered, well tolerated and is curative.

Lymphatic filariasis (elephantiasis).

The parasitic worms *Wuchereria bancrofti* and *Brugia malayi* cause lymphatic filariasis. They are transmitted by mosquitoes and live almost exclusively in humans, where they lodge in the lymphatic system. At these sites, they remain for many years, producing millions of microfilariae (minute larvae) that circulate in the blood. More than a billion people in more than 80 countries are at risk of infection. More than 120 million have already been affected by it, with 40 million of these seriously incapacitated and disfigured. One-third of infected patients live in India, one third are in Africa, and most of the remainder are in South Asia, the Pacific region, and the Americas. In tropical and subtropical areas where lymphatic filariasis is well established, the prevalence of infection is continuing to increase. A primary cause of this increase is the rapid and unplanned growth of cities, which creates numerous breeding sites for the mosquitoes that transmit the disease. In its most obvious manifestations, lymphatic filariasis causes enlargement of the entire leg or arm, the genitals, vulva, and breasts due to lymphedema. In endemic communities, 10–50% of men and up to 10% of women can be affected. The filariae also cause internal damage to the kidneys and lymphatic system. Available medicines include diethylcarbamazine and albendazole. Transmission is interrupted by mass treatment in endemic areas.

Dengue fever

Dengue is a mosquito-borne viral infection that in recent years has become a major international public health concern. The Dengue virus is transmitted to humans through the bites of infective female *Aedes* mosquitoes. Dengue fever is a severe, flu-like illness that affects infants, young children, and adults but seldom causes death. Dengue haemorrhagic fever (DHF) is a potentially deadly complication characterized by high fever, hemorrhagic phenomena—often with enlargement of the liver—and, in severe cases, circulatory failure. During epidemics, attack rates are often 40–50% but may reach 80–90%. An estimated 500,000 cases of DHF require hospitalization each year with children affected disproportionately. Without proper treatment, DHF case fatality rates can exceed 20% but with good care can be reduced to less than 1%. Dengue fever is found in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban areas. DHF has become a leading cause of hospitalization and death among children in Asian countries. Dengue is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific; Southeast Asia and the Western Pacific are most seriously affected. Before 1970 only nine countries had experienced DHF epidemics, but this number had increased more than four-fold by 1995. Some 2.5 billion people—two fifths of the world's population—are now at risk from dengue. An estimated 50 million cases of dengue infection occur worldwide every year. In 2001, there were more than 609,000 reported cases of dengue in the Americas, of which 15,000 cases were DHF. This is more than double the number of dengue cases that were recorded in the same region in 1995. Not only is the number of cases increasing as the disease is spreading to new areas, but explosive outbreaks also are

occurring. In 2001, Brazil reported more than 390,000 cases, including more than 670 cases of DHF. No medicines are available for treatment, and a vaccine has not been developed. Maintenance of the circulating fluid volume is the core of DHF case management. Vector control through use of insecticides and environmental management remain the primary means of control.

Dracunculiasis (Guinea worm)

Dracunculiasis is caused by the parasitic worm *Dracunculus medinensis*. The worm migrates through the subcutaneous tissues of humans, causing severe pain especially when it occurs in the joints. When a person drinks contaminated water from ponds or shallow open wells, the larval sac (*Cyclops*) is dissolved by the gastric acid of the stomach, and the larvae are released and migrate through the intestinal wall. After 100 days, the male and female forms mate. The males become encapsulated and die in the tissues while the female move down muscle planes. After about a year of infection, the female worm filled with larvae emerges usually from the feet, causing an intensely painful edema, with the appearance of a blister and then ulcer accompanied by fever, nausea and emesis. While rarely fatal, dracunculiasis causes severe suffering and disability. It reappears every year during the agricultural season. In 2000, the 14 endemic countries in sub-Saharan Africa reported about 75,223 cases. Sudan reported 73% (about 54,890) of all cases. No medicines or vaccines are available to prevent or treat dracunculiasis.

HIV/AIDS

Acquired Immune Deficiency Syndrome (AIDS) is caused by human immunodeficiency virus (HIV). There are 2 different types of HIV: HIV-1 the most common type found worldwide, and HIV-2 found mostly in West Africa. HIV/AIDS has been identified in more than 200 countries and is spreading rapidly, especially in LDCs. Transmission occurs via direct contact with an infected person through sex, exchange of blood or body fluids, from mother to child, and in other ways as well. HIV infection affects the immune system. A deficient immune system makes the individual susceptible to opportunistic infections (e.g., tuberculosis and pneumonia) and to conditions such as cancer. The UNAIDS 2004 Report on the Global AIDS Epidemic warns that the number of people living with HIV has increased in every region of the world during 2003 with the following trends. The UNAIDS 2004 Report provided the following key trends in infection:

- 1.1 million people in Asia became infected with HIV last year alone—more than any previous year. The epidemic is expanding rapidly in this region, with sharp increases in HIV infections in China, Indonesia, and Viet Nam. With 60% of the world's population, Asia's fast-growing epidemic has global implications.
- India, with an estimated 5.1 million people living with HIV has one in seven HIV-positive people worldwide. This represents the largest number of people infected outside of South Africa.
- An estimated 25 million people are living with HIV in sub-Saharan Africa. There appears to be stabilization in HIV prevalence rates, which appears to be due to a rise in AIDS deaths and a continued increase in new infections.

- In Latin America, approximately 1.6 million people are living with HIV, and the epidemic tends to be concentrated mainly among populations at increased risk of HIV exposure, such as injecting drug users and men who have sex with men. Low national prevalence is disguising some serious epidemics. For example, in Brazil—the region’s most populous country and home to more than one in four people living with HIV—national prevalence is well below 1%. However, in some cities, infection levels above 60% were reported among injecting drug users.
- Eastern Europe and Central Asia continue to have expanding epidemics. An estimated 1.3 million people are living with HIV. Russia, with more than three million injecting drug users, remains one of the worst-affected countries in the region. But women account for an increasing share of newly diagnosed cases of HIV—up from one-in-four in 2001 to just one-in-three one year later. The epidemic’s most striking feature is the age of those infected. More than 80% are under 30. Condom use is generally low among this group. By contrast, in North America and Western Europe, only 30% of infected people are under 30.
- Infections are also on the rise in the United States and Western Europe. In the US, an estimated 950,000 people are living with HIV, up from 900,000 in 2001. Half of all new infections in recent years have been among African Americans. In Western Europe, 580,000 people are living with HIV, compared to 540,000 in 2001.

The UNAIDS 2004 Report estimates the financing needed to combat the epidemic. It argues that although global spending on AIDS has increased 15-fold from US\$300 million in 1996 to just under US\$5 billion in 2003, this amount is less than half of what will be needed by 2005 in developing countries. The report says that according to newly revised costing estimates, an estimated US\$12 billion (up from US\$10 billion) will be needed by 2005 and US\$20 billion by 2007 for prevention and care in low- and middle-income countries. The estimated US\$20 billion would provide antiretroviral therapy to just over six million people (over four million in sub-Saharan Africa), support for 22 million orphans, HIV voluntary counseling and testing for 100 million adults, school-based AIDS education for 900 million students, and peer counseling services for 60 million young people not in school. Approximately 43% of these resources will be needed in sub-Saharan Africa, 28% in Asia, 17% in Latin American and the Caribbean, 9% in Eastern Europe, and 1% in North Africa and the Near East. Only 7% of people in developing countries have access to antiretroviral treatment and only 20% of people worldwide has access to HIV prevention services.

Malaria

Malaria is a life-threatening parasitic disease caused by the Plasmodium species that are transmitted to humans through infected Anopheles mosquitoes. The four types of human malaria are: *P. vivax*, *P. malariae*, *P. ovale*, and *P. falciparum*. *P. vivax* and *P. falciparum* are the most common, and *P. falciparum* is the most deadly. *P. falciparum* malaria is most common in Africa south of the Sahara and causes an extremely high mortality in this region. An estimated 40% of the world's population, most of whom live in the world’s poorest countries, is at risk of malaria. This infection is also found throughout the tropical and sub-tropical regions of the world and causes more than 300

million acute illnesses and at least one million deaths annually. Ninety per cent of deaths due to malaria occur in Africa south of the Sahara, and this involves mostly young children. Malaria kills an African child every 30 seconds. Children who survive may suffer from learning impairments or brain damage. Pregnant women and their unborn children are especially vulnerable. Malaria parasites destroy red blood cells, causing anemia, and clog capillaries that carry blood to vital organs such as the brain, resulting in cerebral malaria. If there are no drugs available for treatment or in the presence of parasite resistance to these drugs, then the infection can progress rapidly to become life-threatening. Widespread resistance of the malaria parasites to conventional antimalarial drugs, such as chloroquine, sulfadoxine–pyrimethamine (SP), and amodiaquine, has contributed to increasing malaria mortality and morbidity. Multidrug-resistant *P.falciparum* malaria is widely prevalent in Southeast Asia and South America and occurs increasingly in African continent.

Tuberculosis

Tuberculosis is a contagious disease caused by the bacillus *Mycobacterium tuberculosis*. Infection occurs primarily by inhalation. If left untreated, a person with active tuberculosis will infect on average between 10 and 15 people every year. Overall, one-third of the world's population is currently infected with tuberculosis, and 5–10% of people who are infected with TB bacilli become sick or infectious at some time during their life. The largest number of cases occurs in the Southeast Asia Region, which accounts for 33% of cases globally. However, the estimated incidence per capita in sub-Saharan Africa is nearly twice that of the Southeast Asia, at 350 cases per 100,000 population. An estimated 1.75 million deaths resulted from TB in 2003. As with cases of disease, the highest number of estimated deaths is in the Southeast Asia Region, but the highest mortality per capita is in the Africa Region, where HIV has led to rapid increases in the incidence of TB and increases the likelihood of dying. Drug resistance is an increasing problem. Strains that are resistant to a single drug have been documented in every country. Strains resistant to all major anti-TB drugs have emerged. Drug-resistant TB is caused by inconsistent or partial treatment, poor compliance by patients, wrong treatment prescribed by health care professionals and health workers, or questionable quality of drug supply. Multidrug-resistant (MDR) tuberculosis is one form of TB wherein the bacillus is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. Rates of resistance are high in some countries, especially in the former Soviet Union, and poses a challenge to control efforts. WHO and its international partners have formed the Directly Observed Therapy (DOTS)-Plus Working Group, which develops global policy on the management of MDR-tuberculosis.

ATTACHMENT 7

Challenges of Drug Regulation in Small Countries

Drug regulation involves a combination of scientific, personal health, public health, and commercial imperatives. In developed nations, the scientific component of drug registration carries a preponderance of evidence in favor of registration, but the sophistication of this information and frequently its public inaccessibility tend to diminish its usefulness for reviews by drug regulatory authorities (DRAs) and LDC civil societies.

Drug registration benefits civil society. In some parts of the developed world, a strong pharmaceutical industry contributes to the national economy and therefore must be considered in drug registration activities. These considerations are not important in LDCs, which typically do not have a well-developed pharmaceutical industry, although some LDCs may wish to promote economic advance by promoting a local pharmaceutical industry.

The model of drug registration often is transplanted from developed-world countries to LDCs with little modification. One aspect of this model is the requirement for toxicology studies. It is extremely unlikely that a country of 10 million people (possibly even 15 million) in the developing world would have a toxicologist capable of evaluating the preclinical toxicology section seen in an innovator's drug dossier in developed nations. For example, Sri Lanka, with a population of 18 million, does not have such a toxicologist. It should also be noted that there are at least 60 countries in the developing world that have population less than 15 million.

This brings us to the question of how there could be some guidance from a developed country's DRA, which does have expertise in evaluating toxicology. It should be possible for the DRA of an LDC to draw up a list of Reference Drug Regulatory Authorities (RDRAs) and specify that only medicines (note here it is the chemical substance and not the product) that have been approved in these RDRAs that will be considered for registration. If any substance that is not registered in these RDRAs is submitted to the DRA of an LDC, then extra justification would be required. Theoretically there will be drugs for tropical diseases not prevalent in the developed world (and therefore not registered in those countries) submitted for registration in the developing world. This becomes problematic for DRAs in LDCs when one considers how infrequently developed nations approve new drugs for conditions such as malaria vis-à-vis new products to treat e.g., hypertension, so-called life-style drugs, or products that are designed for life-long treatment in a target population.

Sri Lanka includes as a RDRAs those in Canada, the US, United Kingdom, Netherlands, Scandinavia, Australia, and New Zealand. Note that France and Switzerland were not included. This was because there was good evidence that the Swiss authorities sometimes register newly approved products for export only; this is not stated in the drug's approval

certificate and is a strategy so that Swiss manufacturers can show a registration certificate to the country of export, which is a requirement in DRAs of most countries in the developing world.

Practically this has meant the number of new chemical entities being submitted in the developed world has decreased, and in LDCs there is a high index of skepticism regarding substances that are not registered in the RDRA. An example is registration of amoxicillin with a lactobacillus on the grounds that there would be a decrease in adverse effects. This lactobacillus is considered a probiotic, and there is enormous literature on the topic of probiotics, but the most important fact is none of these probiotics have been registered as a drug in the RDRA.

Transparency in the DRAs of the developing world sometimes is minimal. For example, in Sri Lanka recently there have been many registrations on “exemption certificates,” which are basically letters of “no objection” to a product being imported into the country. This is a mechanism for circumventing full registration procedure. Although this can be used in a very small minority of situations, it has been used so extensively in Sri Lanka that the number of these exemption certificates was equal to valid registrations. Because there was no transparency, this went unnoticed until the recent discovery of a contaminant in an exemption certificate drug, which highlighted the problem of lack of transparency and full accountability.

Conflicts of interest concepts are almost never applied in the DRA of an LDC. It is common for pharmaceutical companies to try to identify the clinician who has been given the dossier to evaluate and then to try to influence the evaluator. There is no requirement for the evaluators in the DRA to declare any conflicts of interest. Conflict of interest generally does not involve ownership of stock in pharmaceutical companies but mainly funding of conferences abroad for clinicians and sometimes payments for lectures.

DRAs in the developing world on most occasions are a subsidiary arm of the Ministry of Health, which is at the third or even fourth level of the governmental hierarchy. This is unlike the situation in the US, where the Commissioner of FDA reports directly to the Secretary of Health and Human Services. This has implications for the functioning of DRAs. Officials rarely get a chance to talk to the top administrator for the health service and are under the influence of mid-level bureaucrats. In addition, DRA personnel are frequently considered only as civil servants and thus transferable in an LDC in the absence of a defined career structure, e.g., the head of the DRA may have begun a career as the head of the maternity and child services and may later be promoted to be head of laboratory services. The technical officers in the DRA, such as pharmacists and drug analysts are also exposed to transfers, though some MOH may understand the need to maintain pharmacists and other health care personnel in the DRA.

It is not entirely lack of resources that afflicts DRAs but lack of will, too. For example good drug information is available in the *British National Formulary*, which is available on CD, and therefore updating can be done easily. However, unless the head of DRA

pushes for this resource and makes it available to DRA staff, then its information will not be of use.

At times members of LDCs themselves are unaware of the onus that can be associated with an application for registration. For example in Sri Lanka, when it was requested that drug companies making application for new chemical entities submit any articles on the drugs from a list of medical journals, the DRAs may be tasked with this responsibility, which belongs more properly to the applicant. Some evaluators also seem to be unaware of differences between an independent refereed journal article and a sponsored supplement. Drug application dossiers may be full of sponsored supplements, and the information in them sometimes is taken with the same credibility as that from independent refereed medical journals.

The “Summary of Product Characteristics,” which is a kind of product information leaflet (PIL) is very often neglected by the DRAs of LDCs. These PILs can serve a useful function of providing good drug information. If PILs are vetted properly and then approved, the prescribers and the pharmacist could see them as good sources of information. Vetting them is not too much of a problem because there are several sources of independent drug information against which they can be compared. Often drug information centres are unavailable in the developing world due to lack of funds. In these settings, PILs can be a very convenient method of transferring information from pharmaceutical companies. However assessors in LDC DRAs may not examine PILs as part of the application review.

The lack of approved product information also leads to the question of drug advertisements that make various claims that are more extensive than what is allowable. DRAs that have very few resources do not consider monitoring drug advertisements an important part of their function, and often this area is abused. Drug advertisements are very potent sources of information/misinformation and often are responsible for the irrational use of drugs.

There is also the question of the function of the DRA. Traditionally it is to ensure quality, safety, and efficacy of medicinal products, as is the case in most developed countries. However, many developed countries do have a fourth hurdle—cost—implemented in their drug approval process, e.g., the Pharmaceutical Benefits Scheme in Australia. When DRAs in developing countries attempt to look at cost, there may be protests that cost-effectiveness analysis is not the traditional function of DRAs. This may be true, but cost is part of the chain in access of medicines to the public.

One of the aspects of the regulation of medicines in the developing world is the difficult situation regarding nutraceuticals and cosmeceuticals. One of the common problems regards dehydroepiandrosterone (DHEA), which in some nations is not considered a medicinal product and therefore is not registered by the DRA. However if DHEA is imported into a country by means of an open license and then many efficacy claims are made, frequently the DRA cannot regulate DHEA because it is not registered as a

pharmaceutical product. To dignify DHEA as drug would mean giving it credibility that is undeserved; however leaving it open means that there can be enormous abuse by advertisements. This same thing does occur with nutritional products which have claims regarding diabetes and other diseases. An example of this is Liv.52, which is manufactured by an Indian company as a hepatotonic.¹⁰ It may be legally marketed as a dietary supplement in the United States if it makes no claims to modify the “structure or function” of the body, and if these ingredients were marketed in the US before October 1994 or FDA was informed 75 days before marketing and did not take negative action on the basis of believing that the product was dangerous (i.e., if it does not violate the US Dietary Supplement Health and Education Act [1994] because it is not advertised in the US as a medicinal product). It is then recycled back to countries in South Asia as “registered by US FDA” and is advertised as a medicine with defined indications to treat liver failure, alcoholic cirrhosis, etc. Unless the DRA knows that it is a nutritional supplement and not a medicine, there is potential both for confusion and possible failure to safeguard public health.

One could make further points about the deployment of “technology for technology’s sake” in pharmacopeial standards. If a drug is 99% pure and has been used for a long time without any problems, what would be the point in raising the purity to 99.5%? Absent further clinical studies is there any demonstrated advantage in decreased side effects or improved efficacy? Knowing that bioavailability can easily vary over range of 20%, what is the effect of increasing purity by 0.5%, especially if this affects the cost and/or availability of the product in LDNs? The public health relevance of such science for the sake of science is extremely dubious. However, for some manufacturers there may be adverse cost implications, and therefore if the barrier is raised there may be problems for manufacturer of the 99% pure drug product and therefore a loss of an affordable drug to the population.

Some have argued in favor of setting lower quality limits for drugs that are used in developing countries. Consider, however the situation of an Abbreviated New Drug Application that was submitted to FDA for a rectal formulation of artesunate used in the treatment of cerebral malaria. During the review an unidentified contaminant was identified. What might be the consequences of a delay of two years in trying to identify the contaminant? If rectal artesunate is shown to be effective and if reliable data could show how many lives it could save (say, for example 50,000 per year), then one could assert that a delay of two years would have cost 100,000 lives. The question, rather, should be asked whether there were indications that this unidentified contaminant had the

¹⁰ According to the Total Herbal Care Web site, the contents and alleged functions of Liv.52 are: Capers (*Capparis spinosa*)-hepatic stimulant; Chicory (*Cichorium intybus*)-increases bile secretion; Black Nightshade (*Solanum nigrum*)-hepatoprotective; Arjuna (*Terminalia arjuna*)-regulates cholesterol biosynthesis; Negro Coffee (*Cassia occidentalis*)-hepatic tonic; Yarrow (*Achillea millefolium*)-hepatic stimulant; and Tamarisk (*Tamarix gallica*)-hepatic stimulant. Available at www.totalherbalcare.com/product_info.php?products_id=1. Accessed 24 August 2005. Cf. Liver Support.com, which lists the same ingredients and assertions for its LIV.52 product at www.liversupport.com/Liv52.htm. Accessed 24 August 2005.

potential for serious adverse effects or if it was simply a regulatory requirement that there be “no unidentified substances in the formulation.” If there were no strong reasons to suspect that this unidentified contaminant would have major adverse effects, then the population in certain LDCs was not well served by regulators’ taking two years to identify the substance. This and similar situations will be interesting to watch and may be a “lesson to learn.” For comparison, consider the relatively small therapeutic benefits that COX-2 inhibitors have demonstrated vs. their risks. One wonders whether regulation was served but not public health during the regulatory reviews of these drugs. Coxib dossiers certainly must have had the state of the art scientific expertise necessary to identify every molecule that was in the formulation, but was the scrutiny of the clinical evidence as exact? Examination of the clinical evidence for the artesunate would show it to be a significant therapeutic advance, and perhaps the pharmaceutical dossier may therefore need to be evaluated at a different risk–benefit level.

Others have suggested, however, that improved regulatory systems in LDCs can be leveraged to better advantage.¹¹ According to this view, four main drivers determine pharmaceutical R&D:

- Medical need,
- Scientific opportunity,
- Market assessment and regulatory concerns, and
- Available resources.

In the context of LDCs, scientific opportunities abound because of the large number of diseases for which no adequate treatment exists. In addition, because many of these diseases disproportionately affect younger populations pharmaceutical companies can explore reformulating existing products for pediatric use. Market assessment requires pharmaceutical manufacturers to evaluate the regulatory environment, practices, and capabilities of DRAs in developing nations. Regulatory barriers, and thus disincentives for pharmaceutical development include but are not limited to regulatory delays, backlogs, and uncertain time lines, along with the absence of clear and reliable guidelines. Lack of appropriate technology hinders the work of DRAs and may impair communications with market applicants. Finally, uncertain regulatory environments and unpredictable regulatory requirements create further deter pharmaceutical companies, which may seek more appropriate ways to allocate their drug-development resources.

DRAs in developing nations have themselves to consider a number of problems facing the marketplace they at least nominally regulate. Public distrust in DRAs, distributors, and manufacturers can arise from the appearance of substandard medicines on the market. In some LDNs unauthorized drug outlets, smugglers, and counterfeit drugs erode the public’s trust in and support of the DRA. No less serious is public perception that a DRA either leaves loopholes in the drug regulatory system or ignores specific areas of unmet medical need. Both the public and potential drug manufacturers will be discouraged by

¹¹ Matsoso MP. *How can regulatory systems best be improved to promote R&D and improve access to new treatments?* Available at www.who.int/intellectualproperty/events/ThemeDMMatsoso.pdf. Accessed August 31, 2005.

any perception that a DRA distorts the market (e.g., by withholding or unfairly distributing pharmaceuticals). Finally, pharmaceutical companies, DRAs, and the public at large will not tolerate the real or perceived exploitation of clinical trial subjects, especially if the public perception is that the clinical trial does not meet acceptable standards or that the resulting product will be unavailable because of unaffordable postapproval prices or because of lack of distribution in the nation that hosted the clinical trial.

Solutions are available for DRAs in developing nations need not be overly burdensome. In one model, an LDC can strengthen its DRA by viewing the latter as a public health safeguard with sufficient managerial, administrative, and operational autonomy. This will necessitate a critical mass of staff for key regulatory functions. The latter include proactive steps to ensure registration of high-priority products, followed with due pharmacovigilance and steps to ensure that GMPs are respected. A proactive DRA can also serve an important public health function by mounting educational programs, monitoring clinical trials, and making the public aware of counterfeit or substandard drugs.

These tasks may seem daunting when resources are limited, but harmonization (e.g., regional adoption of standard regulatory practices and environments) and partnerships can help conserve valuable resources at the same time that they build regional capacity. For example, LDNC can collaborate on important activities such as developing regulatory networks and pooling resources and expert knowledge to deal with regional and sub-regional health challenges. An example of the latter would be collaborative clinical trials to develop vaccines, biologicals, and other products. LDCs also can work with well-established regulatory bodies in areas such as training and participating in regional or global initiatives. No single strategy will be appropriate for every country, disease, or drug, but collaborative work can yield positive, long-lasting results.

ATTACHMENT 8

UN Millennium Development Goals*

Goal 1: Eradicate Extreme Poverty and Hunger

Goal 2: Achieve Universal Primary Education

Goal 3: Promote Gender Quality and Empower Women

Goal 4: Reduce Child Mortality

Goal 5: Improve Maternal Health

Goal 6: Combat HIV/AIDS, Malaria, and Other Diseases

Goal 7: Ensure Environmental Sustainability

Goal 8: Develop a Global Partnership for Development

*See www.un.org/millenniumgoals/

ATTACHMENT 9

The International Conference on Harmonization (ICH)

The Global Cooperation Group (GCG) of ICH was formed on 11 March 1999 as a subcommittee of the ICH Steering Committee. Its purpose is to make available information about ICH, ICH activities, and ICH guidelines to any country or company that requests the information. GCG will respond to regulatory authorities or pharmaceutical companies that request information. GCG consists of representatives from the ICH Steering Committee and from five non-ICH regional harmonization initiatives: APEC (Asia-Pacific Economic Cooperation), ASEAN (Association of the Southeast Asian Nations), GCC (Gulf Cooperation Council), PANDRH (Pan American Network for Drug Regulatory Harmonization), SADC (Southern African Development Community). The GCG's mission statement is *to promote a mutual understanding of regional harmonisation initiatives in order to facilitate the harmonisation processes related to ICH guidelines regionally and globally, and to strengthen the capacity of drug regulatory authorities and industry to utilise them*. ICH has been criticized at various times for exclusion of representatives of developing countries, lack of accountability, and for other reasons as well. (Web: www.ich.org/cache/compo/276-254-1.html)

Asia-Pacific Economic Cooperation (APEC)

APEC was established in 1989 and is the premier forum for facilitating economic growth, cooperation, trade, and investment in the Asia–Pacific region. Its purpose is to further enhance economic growth and prosperity for the region and to strengthen the Asia–Pacific community. APEC is the only intergovernmental grouping in the world operating on the basis of nonbinding commitments, open dialogue, and equal respect for the views of all participants. Unlike the World Trade Organization or other multilateral trade bodies, APEC requires no treaty obligations among its participants. Decisions made within APEC are reached by consensus, and commitments are undertaken on a voluntary basis. Since its inception, APEC has worked to reduce tariffs and other trade barriers across the Asia-Pacific region, creating efficient domestic economies, and increasing exports. Key to achieving APEC's vision are referred to as the Bogor Goals “of free and open trade and investment in the Asia-Pacific region by 2010 for industrialised economies and 2020 for developing economies.” These goals were adopted by leaders at their 1994 meeting in Bogor, Indonesia. APEC also works to create an environment for the safe and efficient movement of goods, services, and people across borders in the region by means of policy alignment and economic and technical cooperation. APEC's scope of work includes three broad areas known as APEC's Three Pillars:

- Trade and Investment Liberalisation,
- Business Facilitation, and
- Economic and Technical Cooperation.

The outcomes of these three areas enable APEC members to strengthen their economies by pooling resources within the region and achieving efficiencies. Tangible benefits are also delivered to consumers in the APEC region by increased training and employment

opportunities, greater choices in the marketplace, cheaper goods and services, and improved access to international markets. (Web: www.apecsec.org.sg/apec.html)

Association of Southeast Asian Nations (ASEAN)

The Association of Southeast Asian Nations or ASEAN was established in 1967 by five original Member Countries, Indonesia, Malaysia, Philippines, Singapore, and Thailand. Brunei Darussalam joined in 1984, Vietnam in 1995, Laos and Myanmar in 1997, and Cambodia in 1999. The ASEAN Declaration states that the aims and purposes of the Association are to accelerate the economic growth, social progress, and cultural development in the region through joint endeavors in order to strengthen the foundation for a prosperous and peaceful community of Southeast Asian nations and to promote regional peace and stability through abiding respect for justice and the rule of law in the relationship among countries in the region. (Web: www.aseansec.org/)

Gulf Cooperation Council (GCC)

GCC was established as a cooperative network of six Member States to effect coordination, integration, and interconnection in all fields among the six member states: the United Arab Emirates, State of Bahrain, Kingdom of Saudi Arabia, Sultanate of Oman, State of Qatar, and State of Kuwait. Deep religious and cultural ties link the six states, and strong kinship relations prevail among their citizens. The GCC represents a practical answer to the challenges of security and economic development in the area and is also a fulfillment of the aspirations of its citizens towards some sort of Arab regional unity. The GCC Charter states that the basic objectives are to effect coordination, integration and interconnection between Member States in all fields, strengthening ties between their peoples, formulating similar regulations in various fields such as economy, finance, trade, customs, tourism, legislation, and administration, as well as fostering scientific and technical progress in industry, mining, agriculture, water, and animal resources, establishing scientific research centers, setting up joint ventures, and encouraging cooperation in the private sector. (Web: www.arab.de/index.htm)

Pan American Network for Drug Regulatory Harmonization (PANDRH)

PANDRH is an initiative to support the processes of drug regulatory harmonization throughout the Americas. It has three main components: the Pan American Conference on Drug Regulatory Harmonization (the “Conference”), the Steering Committee, and Working Groups on themes defined as priorities by the Conference. The Pan American Health Organization (PAHO) serves as the Secretariat for all three components of PANDRH. Financing for its activities is sought from pharmaceutical industry associations, professional associations, governments, conference registration fees, PAHO contributions, nongovernmental organizations (NGOs) and other sources, as identified. The mission of the Conference is to promote drug regulatory harmonization for all aspects of quality, safety, and efficacy of pharmaceutical products as a contribution to the quality of life and health care of the citizens of the Member Countries of the Americas. Participants in the Conference are regulatory authorities from each of PAHO’s Member States, along with representatives from regional and national pharmaceutical industry associations, consumer groups, academia, professional pharmaceutical associations,

regional economic integration groups, global drug harmonization initiatives, and other interested groups. The Conference meets every two years, and its goals are to examine global regulatory systems, develop and adopt proposals for technical/regulatory harmonization, review existing medicinal drug regulation requirements and guidelines for specific issues, and identify and discuss medicinal drug regulation implementation issues. Between Conferences, the PANDRH Steering Committee facilitates advancement by coordinating, promoting, facilitating, and monitoring harmonization processes in the Americas. The Committee achieves this mission in a variety of ways, including organizing meetings, workshops, and other related activities to carry out the recommendations of the Conference and establishing study groups on regulatory topics identified by the Conference. The Steering Committee also is responsible for preparatory activities related to subsequent Conferences and for convening meetings and determining methods for reaching consensus. It establishes Working Groups and assigns specific tasks to each based on the recommendations of the Conference. Steering Committee members represent diverse geographic regions in the Americas, are nominated by the Conference, and serve four-year terms. With only two exceptions, its members should be regulatory authorities from PAHO Member States. The Steering Committee meets annually. (Web: www.paho.org/)

The South African Development Community (SADC)

SDAC has been in existence since 1980, when it was formed as a loose alliance of nine majority-ruled States in Southern Africa known as the Southern African Development Coordination Conference (SADCC), with the main aim of coordinating development projects in order to lessen economic dependence on the then-apartheid South Africa. The founding Member States are: Angola, Botswana, Lesotho, Malawi, Mozambique, Swaziland, United Republic of Tanzania, Zambia, and Zimbabwe. The transformation of the organization (SADCC) from a Coordinating Conference into a Development Community (SADC) took place on 17 August 1992 in Windhoek, Namibia when the Declaration and Treaty was signed at the Summit of Heads of State and Government. This event provided SADC legal character. The Member States are Angola, Botswana, the Democratic Republic of Congo, Lesotho, Malawi, Mauritius, Mozambique, Namibia, South Africa, Swaziland, United Republic of Tanzania, Zambia, and Zimbabwe. The objectives of SADC as stated in Article 5 of the Treaty remain relevant (listed below), but Member States underscore the need to ensure that poverty alleviation is addressed in all SADC activities and programs with the ultimate objective of eradicating it. HIV/AIDS is a major threat to the attainment of the objectives of SADC and therefore is accorded priority in all SADC programs and activities. Article 5 objectives are to:

- Achieve development and economic growth, alleviate poverty, enhance the standard and quality of life of the people of Southern Africa and support the socially disadvantaged through regional integration;
- Evolve common political values, systems, and institutions;
- Promote and defend peace and security;
- Promote self-sustaining development on the basis of collective self-reliance and the interdependence of Member States;
- Achieve complementarity between national and regional strategies and programs;

- Promote and maximize productive employment and utilization of resources of the Region;
- Achieve sustainable utilization of natural resources and effective protection of the environment;
- Strengthen and consolidate the long-standing historical, social, and cultural affinities and links among the people of the Region. (Web: www.sadcreview.com/)