

Global Pharmaceutical Development and Access: Critical Issues of Ethics and Equity

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ABSTRACT

The article presents global data on access to pharmaceuticals and discusses underlying barriers. Two are highly visible: pricing policies and intellectual property rights; two are less recognized: the regulatory environment and scientific and technological capacities. Two ongoing transitions influence and even distort the problem of universal access to medications: the epidemiologic transition to an increasing burden of chronic non-communicable diseases; and the growing role of biotechnology products (especially immunobiologicals) in the pharmacopeia. Examples from Cuba and Brazil are used to explore what can and should be done to address commercial, regulatory, and technological aspects of assuring universal access to medications.

KEYWORDS Biotechnology, biological products, clinical trials, drug costs, economics, pharmaceutical, pharmaceutical preparations, intellectual property, patents, access to health care, world health, Cuba, Brazil

INTRODUCTION

Access to medications is part of the wider issue of the right to health, which in turn is part of the global debate on equity and human rights. Approaching the issue from an ethical perspective is more complex than from a legal perspective, since it means going beyond individual convenience to assume a commitment of larger scope: with the community, the nation, and humankind. According to the ethical theory of consequentialism, an action is ethical or not depending on its consequences. Our analysis should then focus on the consequences of the behavior of current global systems of research, manufacturing, distribution and use of medications; and on what we can do to modify these consequences to achieve better population health and equity.

There are ethical issues related to access to existing medications, and also related to scientific research on new medications.

THE FACTS

The human right to health is recognized in many international instruments, such as the founding documents of WHO, the Alma Ata Declaration and several treaties on human rights. Article 25.1 of the Universal Declaration of Human Rights (1948) states: "Everyone has the right to a standard of living adequate for the health of himself and of his family, including food, clothing, housing and medical care and necessary social services". Over 100 countries include health provisions in their constitutions.[1,2] Access to essential medications is also included in the UN's Millennium Development Goals.

Nevertheless, empirical data show that in most countries, access to medications is far from universal.

Deep concerns about access to medications have appeared in the specialized literature since the 1990s. In 2001, the World Health Assembly endorsed a resolution calling for development of standardized methods for measuring and monitoring pharmaceutical prices, resulting in the launch of the WHO's Health Action International Project on Medicine Prices and Availability.[3–5] The first draft of its manual was published in 2003. Since then, more than 50 studies using the manual have been conducted on the affordability and availability of essential medications, and on the special and more complex case of medications for chronic diseases.

Availability is assessed through retail pharmacy surveys; affordability by comparing medicine prices with the average daily wage of an unskilled worker in the public sector.

Although carried out in countries with widely diverse characteristics, and including various types of medications, most of these studies shared these common results:

- In low- and middle-income countries, medication prices are high, especially in the private sector, reaching in some cases 80 times the international reference price.
- Availability in low- and middle-income countries can be low, particularly in the public sector. A study published by WHO found that mean availability of essential medications was 35%. Low availability in the public sector drives users to migrate to the private sector, where prices are high.
- Treatments are often unaffordable (e.g., requiring over 15 days' wages to purchase 30 days of treatment). This problem is especially serious for chronic diseases needing long-term treatment.
- Average per capita spending on pharmaceuticals in high-income countries is 100 times that in low-income countries. WHO estimates that 15% of the world's population consumes over 90% of global production of pharmaceuticals (by value).
- In low- and middle-income countries, because of high prices, medications account for 25% to 70% of total health care expenditures, compared to less than 15% in high-income countries.
- Government procurement systems can be inefficient, buying expensive brand-name medications instead of more economical generics.

Do we have a problem? It is obvious that the answer is yes. Independently of the specifics in each country and the need for more precise data, the inescapable conclusion is that there is a huge gap between discourse on the right to health and the reality of broad access to medications. To overlook this fact, or to recognize it passively, constitutes an ethical problem in itself.

Low-income countries are not the only ones failing to achieve universal health care coverage.[6,7] It is a global issue. In the 1970s,

a California minimum-wage worker could insure his/her family of four for 15% of his annual income; in 2005, the same worker had to pay 101% of his/her income to purchase the same coverage.[8]

In addition to access to available medications, there is a second dimension of the problem related to priority setting for scientific research on new pharmaceuticals. According to some estimates, less than 10% of the world's biomedical R&D funds are aimed at addressing the problems responsible for 90% of the global disease burden. This disparity has been termed the 10/90 gap. [9] It means that research efforts primarily concentrate on new products for long-term treatment of non-communicable diseases of adulthood, especially in high-income countries. Only 1% of new medications developed in the 25 years up to 2004 were for tropical diseases and tuberculosis, which together account for over 11% of the global disease burden.[3]

THE MOST VISIBLE CAUSES

The roots of the problems described above are socio-economic and political. We live in a world that is very far from fair. This inequity is revealed in nutrition, employment, housing, wages, and almost all dimensions of human life. Life expectancy, a broadly encompassing health indicator, shows wide disparities among countries (and within countries), related to an also huge divide in wealth reflected in Gross Domestic Product (GDP).

Inequity in access to medications is just one component of this larger problem, and its ultimate solution will mean confronting the formidable economic and political challenges of our time—a discussion beyond the scope of this article.

This paper will focus on more specific causes of inequitable access to pharmaceuticals related to medications and research policies, particularly the impact of policies on medications pricing (related to concentration of the pharmaceutical industry) and intellectual property and patents.

Systems for distribution and financing of medications vary widely from country to country, and no policy can be applicable everywhere. Nevertheless, price studies have found some inadmissible distortions that should be corrected.

Notably, there is an inverse correlation between the proportion of price patients pay out of pocket and the country's GDP.[10] That is, in poorer countries patients must pay a higher fraction of the price of a given medication, while patients in richer countries receive greater support from the public purse.

Although prices in the public sector are often lower than in the private sector, in many countries prices to patients in the public sector are significantly higher than public procurement prices. Such large margins suggest that some public facilities may be generating income through pharmaceutical sales.

The second causal factor of high prices and low access to medications is the impact of intellectual property agreements. This situation is relatively novel and is the expression in the pharmaceutical arena of neoliberal economic policies imposed in the 1980s and 1990s.

Since then, such agreements have constituted a continuous process and been the subject of permanent debate, in which three milestones can be distinguished:

- In 1980, the Patent and Trademark Law Amendments Act (Bayh-Dole) in United States allowed universities to obtain patents from research carried out with public funds, and to sell these to the private pharmaceutical industry.
- In 1995, the World Trade Organization (WTO) was born, and it enforced the Trade Related Intellectual Property Agreements (TRIPS), which established standards of patent protection for pharmaceuticals.
- In 2001, the WHO Ministerial Conference released the Declaration on TRIPS and Public Health (Doha Declaration) which affirmed that TRIPS agreements “*can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health, and in particular, to promote medicine access for all.*”[11]

In 2004, WHO created a Commission on Intellectual Property Rights, Innovation and Public Health, which in turn commissioned 22 studies to expand the knowledge base on the issue. [12–14] These concluded that intellectual property does not provide effective incentive for innovation in developing countries.

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The polemics around patents continue, and although there is growing awareness of the inadequacy of the current global system for supporting innovation in new medications, practical results have been very limited.

We are witnessing a collision of pressures: on one side, several governments and international organizations insist on the implementation of the Doha Declaration recommendations for more use of flexible options included in the TRIPS agreements—such as exemptions of patentability, compulsory licensing, and exhaustion of rights. On the other side, the big pharmaceutical manufacturers in rich countries and their political allies are trying to undermine these options through bilateral or regional trade agreements, known as TRIPS-Plus or WTO-Plus. Provisions in these agreements further narrow circumstances in which a compulsory license can be justified—virtually nullifying such opportunities—and extend periods of data exclusivity, enabling large pharmaceutical companies to prevent or delay generic competition.

The brutal fact is that in many countries, interest in maintaining standing as a preferred trading partner committed to intellectual property protection has thus far prevailed over commitment to access to medications.

One of the most consistent findings of all medicine pricing studies is the large gap between originator companies' brand prices and those of generic versions, a difference that prevails even after patent expiration.

A study of 15 pharmaceuticals in 36 countries found price ratios between originator products and generic products on the order of 300% in Africa, 200% in the Americas, 287% in Europe, 221% in Southeast Asia, and 304% in the Asia-Pacific region. In some countries these ratios are even higher.[15]

Special Article

The two phenomena discussed so far—medication pricing structure and intellectual property—are in turn a consequence of pharmaceutical industry concentration and its market-driven nature.

Over 90% of the value of the world's pharmaceuticals is produced in high-income countries. More than 70% is produced in just five countries, and more than 45% by the top ten companies. The fraction of the pharmaceutical market in the hands of these top ten increased from 27.5% in the 1980s to 45.7% by the year 2000.[3]

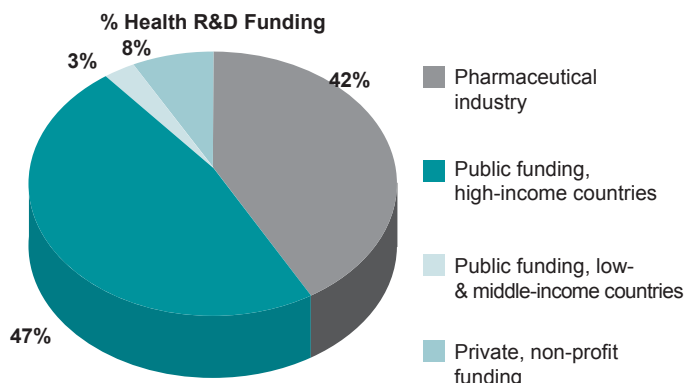
At the same time, the pharmaceutical market is far from being a "free market" whose "invisible hand" optimally determines investments and prices. Effective demand, or ability to pay, is also highly concentrated in high-income countries. It has been estimated that 15% of the world's population in these countries consumes 90% of medications, and the trend towards further market concentration continues: the US share of the pharmaceutical market increased from 18% in 1976 to 52% in the year 2000.

Medication expenditures occur mainly in the private sector and this became more pronounced in the 1990s—for all countries and income groups—when governments' participation in pharmaceutical expenditures decreased from 42.9% to 39.2%. Paradoxically, the bias is even greater in middle- and low-income countries, where 74% of medication expenditures are in the private sector, compared to 58% in high-income countries.

This "market failure" in the pharmaceutical industry is also evident in allocations of investments for scientific research, which do not follow real demand—as determined by health impact—but rather effective demand.

Most medical research is done in high-income countries: 12 countries concentrate 80% of research spending. Moreover, medical research financing has been moving towards the private sector. In the United States, more than 60% of pharmaceutical research and more than 70% of clinical trials are financed by the private pharmaceutical industry, and the trend continues. This is the root cause of the 10/90 gap denounced by the Global Forum for Health Research, explaining why investment in R&D is directed mainly towards drugs for central nervous system, metabolic, neoplastic and cardiovascular diseases (Figure 1).[16]

Figure 1: Concentration of Global Health Research and Development



Source: World Health Organization: *The World Medicines Situation*

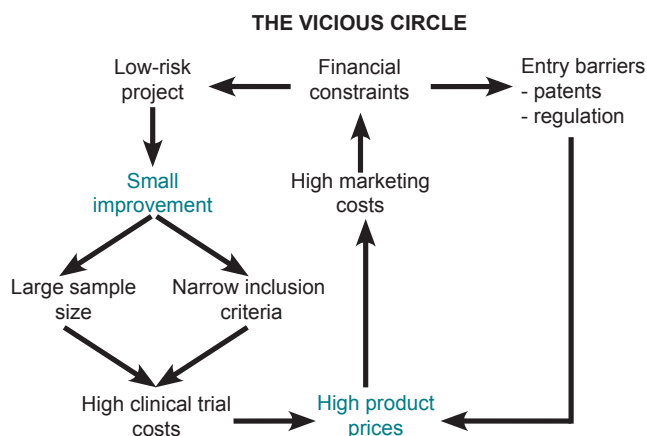
Another consequence of the concentrated and market-driven character of the pharmaceutical industry is decline in innovation:

while research spending tripled in the 1990s, output of new drugs actually declined.

The pharmaceutical industry has sold the public the idea that innovation is stimulated by competition and that the high prices guaranteed by patents are essential to its funding. However, a closer look at the financial structure of the pharmaceutical sector shows that marketing, not research, is the biggest expenditure.

Driven by competitive pressures for short-term profits, research projects increasingly favor low-risk, incremental innovations on already existing products. Then a kind of vicious circle emerges in which such innovations produce small improvements in clinical trials (Figure 2). But to achieve statistical significance, these trials must be carried out in homogenous populations with narrow inclusion criteria, a very expensive undertaking. This cost is later passed on in the form of higher prices. Market penetration with small medical improvements also requires a big marketing investment, another cost recovered through higher prices.

Figure 2: The Vicious Circle



Consequence: long-term high costs for minor improvements in highly-selected populations.

The absurd result of the repetitive operation of this vicious circle is that we get increasingly more expensive drugs with less innovation and thus less health impact. In epidemiological terms, limited access to these expensive products also contributes to minimal population-wide impact.

The issue of drugs with high prices and minimal clinical impact is quite evident in some recent anticancer drugs, such as Cetuximab for lung cancer, which has annual treatment costs of \$80,000 per patient and, according to the clinical trials, produces a survival advantage of 1.2 months; or Erlotinib for pancreatic cancer, which costs \$15,000 a year per patient, for a survival advantage of 10 days demonstrated in the clinical trial.[17]

LESS VISIBLE CAUSES

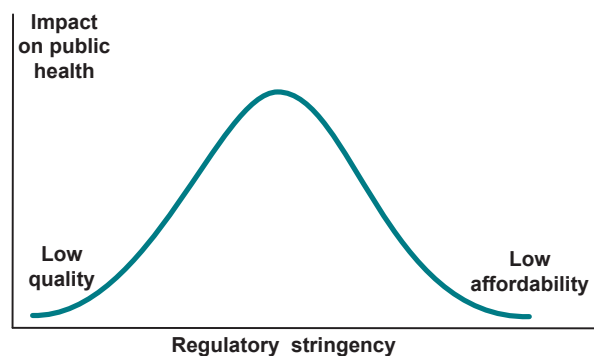
WHO has explicitly recommended that governments avoid taxing medications, stimulate generic competition, avoid use of expensive brand-name products in the public sector, and, when patents become an obstacle to medication access, use compulsory licensing and other provisions in local laws in accordance with the Doha Declaration.[12]

Thorough and coherent implementation of these recommendations is in itself a tremendous challenge for many countries at political, legal and administrative levels. But even if we were able to topple the first access barrier of inadequate pricing policies, and the second barrier thrown up by intellectual property provisions; there would still be two more barriers, which have been less frequently discussed until now.

The third barrier is related to the regulatory environment. The trend towards continuous increments in regulatory standards for medications is relatively recent: it was only in 1962 that proof of efficacy was required, driving the adoption of the current drug approval process.

No one will object to concerns for pharmaceutical safety and efficacy, particularly from an ethical perspective. However, beyond a certain threshold, regulatory standards also operate as protectionist barriers, limiting manufacture and innovation to those companies with an operational volume large enough to absorb costs (including the practice of passing the latter on in higher prices, further reducing affordability of new medications) (Figure 3).

Figure 3: Regulatory Stringency and Public Health Impact



Understandably, this is a delicate topic, but from a population health perspective, the relation between regulatory stringency and the public health impact of medications is revealed as a bell-shaped curve: when regulatory stringency is too lax, limited public health benefit results due to low product quality; when it is too tight, limited benefit results from high prices that impede access. Population health requires both quality *and* coverage.

At what point is an optimal balance achieved between safety and efficacy, on the one hand, and access, on the other, to achieve higher public health impact? This is a scientific problem, not only a legal one. Unless countries are able to build domestic scientific capacities, they will not be able to formulate their own strategies to address this complex issue and will not be in a position to protect their own populations.

The problem is even more complex for biological products, particularly for immunobiologicals. Before the emergence of biotechnology, expiration of pharmaceutical patents allowed more affordable generic versions of the same quality to enter the market.

In the United States, the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) of 1984 reduced regulatory barriers to generics, waiving the need to repeat clinical trials, if physical-chemical comparability can be demonstrated. But the landscape gets complicated with biological products that are com-

plex molecules produced inside living cells, a process which could introduce a variety of contaminants, and for which final product tests could have limited value as predictors of clinical efficacy.

The response was the doctrine that “the process is the product.” Rigorously implemented, the consequence would be that no process is strictly identical to any other, and that therefore generic biologics cannot exist. This is tantamount to a patent in perpetuity. The fourth barrier comes from limited scientific and technological capacities in many countries, making them unable to manufacture pharmaceuticals or to build their own regulatory strategy, let alone innovate. The problem of scientific capacity in developing countries is twofold: first, the volume of scientific activity, and second, its relation to the economy. To approach one without the other is an exercise in futility.

According to the 2010 UNESCO Science Report,[18] developing countries, with a share of 41.8% of the world’s GDP, contribute only 23.8% of global R&D investment. With 81.7% of the world’s population, they contribute 37.9% of scientific researchers and produce 32.4% of scientific publications. This is the volume problem, and there is vast literature that speaks to it. But it is even more important to recognize that a substantial part of this limited R&D remains unconnected to the economic structure of society. It is not easy to find unbiased indicators to demonstrate this relationship. But if we take patents, for example, the North–South divide is even more prominent: developing countries, although they produce 32.4% of scientific papers, own only 4.5% of patents.

Scientific capacity is increasingly needed not only for its own sake, but also to use science and to translate it into technology. As the pharmaceutical industry transits to a biological pharmacopeia, both manufacturing technology and regulatory decisions will be more deeply science-based, and in many countries the lack of scientific capacity could operate as a guarantee of monopoly even more efficient than intellectual property.

TRENDS: EPIDEMIOLOGIC TRANSITION

During the last few decades, with the exception of some African countries in which life expectancy has decreased due to the AIDS epidemic, the burden of non-communicable chronic diseases of adulthood has been increasing worldwide.

Globally, more than 35 million deaths each year (60% of all deaths) are due to chronic diseases, and 80% of these occur in middle- and low-income countries where these diseases also affect people younger than in the developed nations.[19] The trend is especially evident in Latin America, where most countries are experiencing a demographic transition towards a more aged population.

In Cuba, the first three causes of death are now cardiovascular diseases, cancer and stroke; together they account for 83% of mortality. Some 18% of the Cuban population is now over 60 years old, and if the trend continues, this figure will be 29% by 2030. Cancer is already the first cause of potential years of life lost.

When patients pay the greatest share of a medicine’s price out of their own pockets, a drug for a chronic disease is a significant economic burden for families, especially considering the addi-

tional load represented by the long-term use of such medicines. According to a WHO study in several countries, one month of asthma treatment consumes an average of 1.4 days' wages with generic drugs and 3.3 days with originator products.[20] Hypertension treatment with captopril requires 2.3 days' wages even with the generic drug. In some countries, chronic asthma or diabetes treatments can consume more than 10% of income.

TRENDS: BIOLOGICAL PHARMACOPEIA

Until the 1980s, the scope of biological products in the pharmacopeia was rather narrow, mostly limited to vaccines and blood derivatives. The biotechnology revolution changed this picture, permitting production of biological molecules with the same level of purity, reproducibility and scalability of chemically-synthesized drugs.

Biotechnology products occupied 10% of the pharmaceutical market in 2002. Their share is now 18%, predicted to reach 23% by 2016. This widening of biologicals' market share is even more evident when we look at the 100 top-selling drugs: biotechnology drugs were 15% of these in 2002, but jumped to 31% in 2010, and are forecast to be 48% by 2016.[21]

The dominance of biotechnology is particularly evident in some therapeutic areas. Among 633 biotechnology medications included in a 2008 survey by the Pharmaceutical Research and Manufacturing Association of America, 254 (40%) were for cancer treatment, including 109 monoclonal antibodies and 63 vaccines. By 2016 it is predicted that four of the five top-selling oncology drugs will be biologicals; and that all five top-selling antirheumatic products will be biologicals (Figure 4).

How will the increasing role of biotechnology drugs influence access to medications? It will worsen the situation, and not only because of patents.

Historically, once patents expire in the classic pharmaceutical industry, generic versions of medications appear with much lower prices,

often 20% of the original producer's price, due to the entrance of many manufacturers. But this will not occur for biotechnology drugs, at least not to the same extent, because manufacturing technologies are more complex and the regulatory environment is fuzzier.

At the time of this Symposium, the polemics about "biosimilar" monoclonal antibodies continue to heat up. In the next few years, patents will expire for five monoclonal antibodies, each one with sales over five billion dollars.[20]

The intellectual property barrier will fall, but the regulatory barrier will hold as long as current patent owners succeed in pressing their claims that chemical comparability cannot be 100% assured for complex molecules, not even with identical gene sequences, and that therefore clinical trials must be repeated. The current position of patent owners—echoed by developed countries' regulatory agencies—requires head-to-head clinical trials to compare biosimilar monoclonal antibodies with the original product. This stance can make the very concept of biosimilar antibodies unviable by making clinical trials unaffordable, especially for manufacturers in developing countries. The few monoclonal antibody manufacturers able to perform these expensive clinical trials will again pass on costs in the form of higher prices. Patents will expire, but oligopoly control of prices will possibly continue.

Furthermore, the technology barrier will remain. When biotechnology appeared in the 1980s, the first recombinant products were expressed in bacteria or yeast cells. This changed first with recombinant erythropoietin and later with monoclonal antibodies, all demanding genetic engineering and fermentation in mammalian cells. Currently, more than half of biotechnology products in clinical research require mammalian-cell technology.

This technology exists today on an industrial scale in fewer than ten countries. If we estimate that one third of oncology biopharmaceuticals currently in clinical trials will make it to the market, this could mean about 40 biotechnology products in the therapeutic arsenal of an oncology hospital in ten years' time—as many cytostatics as we have today.

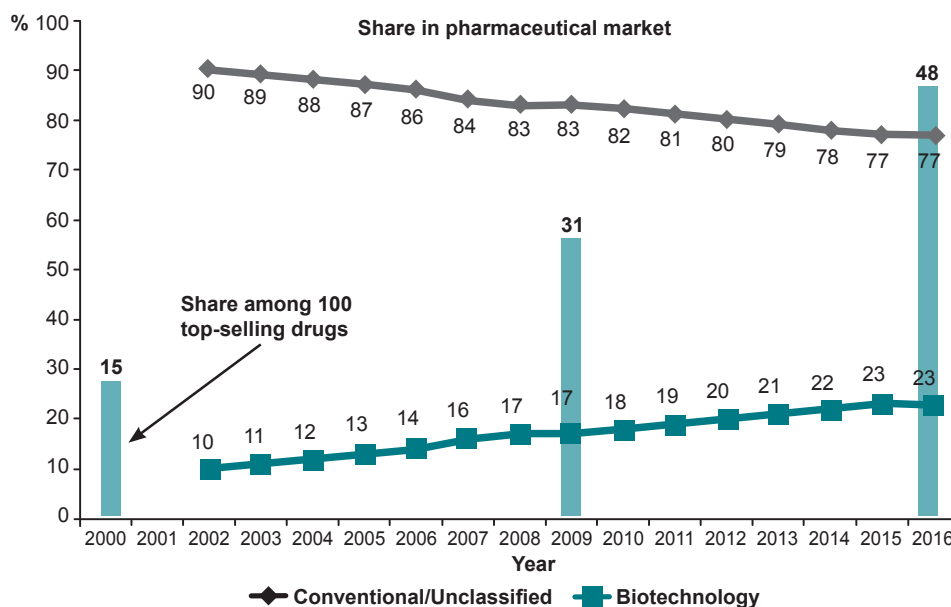
At dosages currently used for anti-tumor monoclonal antibodies (one to five grams per patient, and even more if the antibodies are used chronically), demand will reach several tons of monoclonal antibodies of therapeutic quality. There is no manufacturing capacity in the world for this.

WHAT CAN AND SHOULD BE DONE

Can we do something? Yes, we can—and there are tangible examples in Cuba and in Brazil.

In Cuba, 585 (67%) of 868 pharmaceuticals listed as essential are produced domestically. Medical attention is free and drug prices are quite low. But we also had to address the

Figure 4: Biotech Share in the Pharmaceutical Market



Source: EvaluatePharma 2010

challenge of biotechnology products: the most efficient policies for production and access to generic drugs may not work so well for biologics because of technological and regulatory complexities.

Over the last three decades, Cuba has been preparing its scientific and productive infrastructure for biotechnology.[22] Through formidable government investments, several research-and-production organizations have emerged, constituting what is known today as the Western Havana Scientific Pole: a complex of institutions with over 12,000 employees, including more than 7000 scientists and engineers. It provides the public health system with 12 vaccines, more than 40 biopharmaceuticals (including recombinant interferon, erythropoietin, and monoclonal antibodies), and diagnostic systems for screening of over 30 diseases. These organizations are currently carrying out some 90 research projects and clinical trials with the participation of 65 hospitals.

Brazil has also implemented a generic medicine policy and has had to fight patent, regulatory and technological barriers along the way.[23] There are 2792 generic medications registered in Brazil, 90% domestically manufactured. The volume of generics has been growing, from 233 million units distributed in 2007 to 330 million in 2010. Generics are 25% of all medications sold in Brazil, but there is more potential, since we see that the share of generics is 50% in the United States and 45% in Europe.

In 1996, a new law guaranteed free access to antiretroviral therapy in Brazil. National industries currently manufacture eight antiretroviral drugs. Based on its manufacturing capacity, Brazil was in a strong position to negotiate prices with multinational companies. In 2000, faced with Merck's refusal to reduce the price of an antiretroviral, the Brazilian government raised the possibility of issuing a compulsory license to manufacture the product. The US government filed a complaint against Brazil at the WTO. But Brazil had broad public support and the United States withdrew the complaint in 2001.

In 2007, the first compulsory license was effectively imposed for the antiretroviral drug Efavirenz, used by 75,000 patients. This strategy has saved more than one billion dollars; moreover, it demonstrated that the model of free access, generic production, strong price negotiation, and compulsory licensing, can work.

In 2009, a joint declaration by Brazil and India criticized the European Union's policy aiming to restrict the entrance of generic drugs.

Since 2004, Cuba and Brazil have undertaken joint projects in biotechnology: among the most important are production of recombinant erythropoietin and peginterferon, as well as development and supply to Africa (at WHO's request) of a meningitis vaccine. Illustrative of impact is that the distribution of erythropoietin for kidney failure patients in Brazil increased by a factor of four as a consequence of this joint work.

But beyond specific products, what has emerged is a new model of cooperation, with the participation of all three main actors in both countries: research-production institutions, regulatory agencies and public health authorities.

The model illustrates three features necessary to successfully approach medication access in the biotechnology era. In particular, the model:

1. Includes development of technological and scientific capacities (including clinical research).
2. Is based on regional, not just national, strategies, to achieve sufficient scale to absorb costs of technology development and high quality standards.
3. Aims at broad coverage, in order to maximize impact on population health indicators.

Universal access to medications is not an economic operation, although it should be economically viable: it is a health intervention and an ethical imperative. Population-wide coverage and impact on health indicators are goals that go beyond satisfying demand. From this perspective, significant results from clinical trials and the technical and economic viability of the manufacturing operation are no more than intermediate steps towards the more important ultimate goal: to improve population health. [24,25]

...a closer look at the financial structure of the pharmaceutical sector shows that marketing, not research, is the biggest expenditure.


Implementing universal access to medications and evaluating this strategy by its impact on population health indicators also means integrat-

ing pharmaceutical supplies into complex health interventions—preventive as well as diagnostic—assuring their rational and appropriate use.

In the coming years, the battle for universal access to medications will be fought largely in the field of non-communicable chronic diseases using the tools of biotechnology. This new landscape of aging populations, chronic diseases and biotechnology drugs will demand an approach to universal therapeutic coverage very similar to the successful one used for vaccines against infectious diseases: political will; clear pre-established goals and evaluation through impact on health indicators; wise stewardship capabilities; and a strong science component. Gone are the days when we can sharply separate public health (hygiene, prevention, epidemiology) from clinical services. New times demand much more integrated strategies, in which therapeutics increasingly become population-wide interventions.

What should be done, for example, to guarantee full access by all cancer patients to modern antitumor monoclonal antibodies? There are more than 100 therapeutic antibodies in clinical trials. This trend, although reflecting scientific progress, implies a risk of making "modern therapy" equivalent to "unaffordable therapy."

To handle this contradiction we need regional approaches in Latin America, building a regulatory environment appropriate to our population health needs, developing manufacturing capacities, and integrating new biopharmaceuticals into comprehensive therapeutic guidelines for optimal use of new products within cancer control programs.

The challenge is formidable, to be sure, as is the work ahead. But it can be done, and we can do it. 

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