

LOCAL PHARMACEUTICAL PRODUCTION AS MEANS TO IMPROVE ACCESS TO ESSENTIAL MEDICINES IN DEVELOPING COUNTRIES

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ABSTRACT

In many developing countries, there is lack of essential medicines for main diseases that affect the population. The countries generally do not have the capacities to manufacture their own drugs, and usually depend on medicines developed and produced in wealthy countries to meet local needs. Multinational pharmaceutical companies are reluctant to produce drugs solely for the developing country diseases because of the low purchasing power. Weak infrastructure for industry and technology, shortage of researchers and limited financial resources are among the reasons for lack of adequate pharmaceutical production in poor countries. There are global initiatives to increase accessibility to medicines for some neglected diseases and the international community is encouraging local production of pharmaceuticals as a possible means to make medicines available in developing countries. Nonetheless, some developing countries are able to produce pharmaceuticals locally, primarily generics that cover some percentage of local drug need, while few others are able to produce and export finished products and active pharmaceutical ingredients (APIs) mainly to other developing nations. The article explored issues of access to quality medicines and local production of pharmaceuticals in developing countries and the factors influencing this industry.

Keywords: Essential medicines, Pharmaceutical production, Developing countries, TRIPS, India.

INTRODUCTION

Pharmaceuticals are all products related to pharmacy, including starting materials (active pharmaceutical ingredients and excipients), finished dosage forms, and biological and other specific products¹. Providing safe, effective and affordable essential drugs and supplies is one of the elements of health for all indicators set by World Health Organization (WHO) in Alma Ata in 1978 and revitalized in 2008. It is estimated that about 30 percent of the world's population lack regular access to essential medicines and that in the poorest parts of Africa and Asia, the percentage is more than 50 percent²⁻⁴. Even if medicines are available, there are usually barriers to accessibility such as high price, inferior quality, and non-functioning health systems.

Access to treatments for infectious diseases, which are the main cause of morbidity and mortality in developing countries, and the supply of medicine to cure other diseases, is difficult or not available at all⁵. Drug development and production is mainly carried out in developed countries. The vast majority of medicines developed and produced in developed countries are for prevalent diseases, such as diabetes, cardiovascular diseases and cancer. Although non-communicable diseases are emerging as health problems in developing countries, infectious diseases remain the leading causes of fatality, particularly the "neglected" in poor countries in Africa and Asia, including parasitic diseases leishmaniasis, human African trypanosomiasis, lymphatic filariasis and many others. Infectious and parasitic diseases account for only five percent of the disease burden in high-income countries⁶, but represent about 50 percent of the developing countries' burden of disease⁷. Despite this, anti-infective agents, especially for tropical diseases, do not get enough attention in the leading pharmaceutical companies' agenda, except for HIV/AIDS, a pandemic which also disproportionately inflicts people in the developing world. Studies have shown that, out of 1,556 new active substances developed between 1975 and 2004, only 21 were intended for treating neglected tropical diseases including tuberculosis and malaria⁸.

Pharmaceutical production capacities to produce generic and off-patent drugs differ across developing countries. While few countries can undertake research and development activities for drug discovery, some are in a position to export locally produced generics (or still patented drugs before 2005) and APIs to other developing countries. Making drugs available and accessible to the world's poor through the encouragement of local drug production remains a

suitable option. Medicines can still be obtained at reasonable prices, but there are diseases that are still not in multinational pharmaceutical companies' plans and there is need for local players from developing countries to fill the gap. In today's globalized world, discussing drug production will certainly involve economic issues, technology acquisition, trade and patent rules, beside many other difficulties (e.g. trade barriers). All these issues need to be overcome before production lines are set up in existing manufacturing plants or plan to establish new production facilities. The article explores issues of access to quality medicines and local production of pharmaceuticals in developing countries and the factors influencing this industry. Examples of pharmaceutical production capacities in developing countries, the effect of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement, and key challenges facing drug manufacturing in the developing world are also discussed.

Availability of essential medicines in developing countries

Multinational pharmaceutical companies- the main drug developers and manufacturers are profit oriented and are concerned mainly with development of drugs that have the potential to attract and sustain high profit returns. The drugs developed are usually for diseases that affect affluent people in high-income countries, from where most of these companies originate. New drug development does not necessarily match the global disease burden⁶. Table 1 depicts the leading therapy classes of pharmaceuticals sold globally in 2008. This focus on health aspects that bring high profits has created a large disparity in access to affordable medicines between the developed and developing world⁹. The disparity is also noticeable in other health technology products, but pharmaceuticals usually constitute a considerable share in healthcare expenditure and are a major cost factor. In some developing countries, expenditure on drugs accounts for as high as 60 percent of total expenditure on health¹⁰, and in most cases paid out-of-pocket, which exacerbates accessibility for the poor.

Owing to inadequate drug availability for poor people's diseases, multinational pharmaceutical companies have launched donations or discounted drug prices to specific disease control programmes, mostly for the neglected tropical diseases. Examples are drugs for onchocerciasis, trachoma, schistosomiasis and Chagas disease. Specific disease programmes involving pharmaceutical companies and the international community partners (governments, donors, NGOs, philanthropies) are public-private partnerships (PPPs) intended to

make medicines available where they are most needed. Other partnerships- product development public-private partnerships (PDPs) are created to undertake research and development (R&D) for vaccines, diagnostics and drugs for neglected diseases of the developing world. Some PDPs examples are Global Alliance to Eliminate Leprosy (GAEL); Mectizan® (ivermectin) Donation Program (MDP); the International Vaccine Institute (IVI) for research and technical assistance for vaccines needed in developing countries; Drugs for Neglected Diseases Initiative (DNDi) to develop drugs for

malaria, visceral leishmaniasis, African trypanosomiasis and Chagas disease; Medicines for Malaria Venture (MMV) to develop and deliver new affordable antimalarial drugs; and the WHO programme for the capacity building of local manufacturing and prequalification of medicines. It is hoped that such projects will bring new solutions to some infectious diseases whose infectious agents have acquired resistance to available drugs (e.g. malaria, tuberculosis, leishmaniasis) or the drugs are not available in safe or suitable dosage forms (e.g. African trypanosomiasis).

Table 1: Leading Therapeutic Classes in 2008 by Global Pharmaceutical Sales

	2008 rank	2008 Sales (US\$ million)	% Growth 2008
Oncologics	1	48,189	11.3
Lipid regulators	2	33,849	-2.3
Respiratory agents	3	31,271	5.7
Antidiabetics	4	27,267	9.6
Acid Pump inhibitors	5	26,525	0.6
Angiotensin II antagonists	6	22,875	12.6
Antipsychotics	7	22,853	8.0
Antidepressants	8	20,336	0.6
Anti-epileptics	9	16,912	9.7
Autoimmune agents	10	15,933	16.9
Platelet aggregation inhibitors	11	13,633	10.3
HIV antivirals	12	12,234	11.9
Erythropoietins	13	11,459	-13.9
Non-narcotic analgesics	14	11,161	3.6
Narcotic analgesics	15	10,606	8.8

Source: IMS Health (www.imshealth.com)

On the other hand, many multinational pharmaceutical companies have also outsourced manufacturing activities to developing countries or contracted local manufacturers (contract manufacturing) to manufacture their products. Of course, such moves are informed by economic motives, such as the need to reduce production costs, but they still end up helping developing countries to build their own capacities and expertise in pharmaceutical production, in addition to reducing drug prices. Many leading multinational pharmaceutical manufacturers of antiretroviral (ARV) drugs (e.g. Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, and Roche) are allowing local manufacturers in developing countries to produce and sell generic versions of their products¹¹. There have also been calls and suggestions from some international health community members to draw more attention to the lack of medicines in developing countries. Médecins Sans Frontières (MSF), which launched in 1999 the -Access to Essential Medicines Campaign- to raise international awareness of the access to medicines crisis¹², has argued that development of generic drugs is a less costly and more sustainable method of supplying necessary drugs than donations¹³. Similarly, WHO has stressed that, donor countries should not only provide good-quality medicines to developing countries, but also local capacity-building, as the only sustainable solution¹⁴. Therefore, local production of pharmaceuticals to improve access to medicines is now encouraged as a measure to make medicines accessible to the poor¹⁵.

Local pharmaceutical production in developing countries

Pharmaceutical production is "the value added at each stage of the manufacturing process, whether it is the manufacturing of active ingredients in bulk from basic chemicals, the preparation of finished new medical entities, or the repackaging of imported generic ingredients to make finished branded or unbranded generic products"¹⁰. In monetary terms, over 90 percent of global pharmaceutical production takes place in a few high-income countries¹⁰, although the industry is globalizing in order to improve stocks of raw materials to be used in global production and also to improve skills and research capability¹⁶. The experience of developing countries with pharmaceutical production entails the lack of ability to independently produce the drugs that they need¹⁷. Where research and development of new chemical entities is far

beyond the ability of developing countries, some production options are easier and feasible. Developing and producing pharmaceuticals is a complex process, starting from basic research for new molecules (natural, semi-synthetic or synthetic) up to the formulation and manufacturing of the finished product. It is a time and resource-consuming process that usually requires screening and trying thousands of drug candidates before identifying the potential molecule, which after years of research may fail during clinical trials¹⁸. This makes the development of new chemical entities almost exclusively developed countries' business. Even in developed countries variation exists in capabilities, the level of R&D and the know-how leaving developing countries very far behind. In 2004, only ten of 188 countries in the world had well established pharmaceutical research and production capacity⁴. In the developing world, until March 2006 only one pharmaceutical manufacturing plant in the whole of Africa was accredited by the WHO¹⁹. Figure 1 shows global pharmaceutical market share by region in 2008. Although the use of monetary values rather volume may not give the real picture of production and consumption¹⁰, developing drug specifically for small markets is not a favorable option.

Since the 1970s some pharmaceutical industries in developing countries have been developing new production processes of generic medicines still under patent elsewhere in the world¹². Until recently, most developing countries had weak intellectual property rights protection or did not have any patent right at all. The capacities of local manufacturers differ widely with regard to the products manufactured. Those with well established R&D capabilities are outsourced by big international pharmaceutical companies²⁰. At least 10 of the largest pharmaceutical companies outsource aspects of medicinal chemistry to developing countries¹⁸, and until 2007 more than 50 licences have been granted by research-based companies to generic manufacturers in developing countries²¹. Increased competition from generic companies and the reduction of production costs are among the reasons for large pharmaceutical companies to open branches in different parts of the world.

The drug market in developing countries is very small compared to developed countries- it is only about one percent of the global pharmaceutical market²². This discourages both drug development (by big pharmaceutical companies) and the establishment of

domestic local production, which in most cases is privately financed. In Africa, the African Union (AU) has been raising the issue of local pharmaceutical production of generics, encouraging countries in the continent to set their objectives to support local production of

essentially needed medicines^{19,23}. Of-course, the lack of access to essential medicines in Africa is more severe than in other parts of the world, including access to drugs for HIV, malaria and tuberculosis.

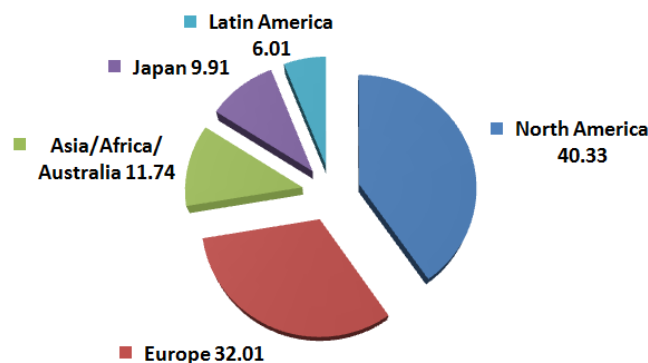


Fig. 1: Global Pharmaceutical market 2008 (\$ billion) by region (% share)

Source: Data from IMS Health (www.imshealth.com).

In the Middle East, Turkey is one of the largest pharmaceutical producers, importing less than one percent of the drugs needed locally and producing both finished products and APIs for local use and export²⁴. Egypt is among the largest pharmaceutical markets in the region and has started its pharmaceutical production early in late 1930's²⁵, manufacturing 90 percent of its medicine needs²⁶. Saudi Arabia on the other hand, imports about 85 percent of its pharmaceutical consumption and is the biggest market in the Gulf region²⁶. Jordan is almost a net exporter of pharmaceuticals. Jordanian pharmaceutical companies are all branded generic manufacturers, satisfying about 30 percent of local demand and exporting 70-80 percent of local production, primarily to Arab countries²⁷. Latin American countries such as Argentina and Brazil have developed strong pharmaceutical and chemical industries²⁸. Pharmaceuticals produced in Argentina and Brazil account for 55 percent and 25-40 percent of the domestic drug consumption respectively²⁸. In Asia and the developing world in general India and China are exceptions. The two countries are source of cheap generic medicines and APIs to the poor countries and have well established pharmaceutical industries. India is also a preferred destination for outsourced drug production and clinical trials. In the field of research in tropical and other diseases, China and India, on the one hand, and Malaysia and Thailand, on the other hand, have contributions to drug studies for malaria and leishmaniasis¹⁷. Both Malaysia and Thailand are newly industrialized economies (tier two)²⁹.

Taking developing countries as a group, China, India, Brazil, Thailand, South Korea, Malaysia, South Africa and Argentina are in a position to establish domestic research-based pharmaceutical industries, or at least contribute to global pharmaceutical R&D efforts^{4,6,10,30}. The capabilities of some manufacturing plants and R&D activities in these countries are well recognized, as generic drugs manufacturers are concentrating mainly on medicines for

communicable and tropical diseases²⁰. For instance, Malaysia hosts the regional training centre for quality control of pharmaceuticals of the Association of Southeast Asian Nations (ASEAN) countries³¹. The centre is also a WHO collaborating centre in the regulatory control of pharmaceuticals. In the global active pharmaceutical ingredients (API) market, China and India are in the lead. In 2005, China and India API industries were the world's first and third largest respectively, supplying sophisticated APIs including still patented products³². Pharmaceutical advancement in the two countries, especially India, has helped many poor countries to import APIs at reasonable prices to produce cheap drugs or to buy cheaper generics from Indian and Chinese manufacturers.

Drug manufacturers in developing countries are either wholly locally owned, generic manufacturers operating globally or locally, subsidiaries of multinational companies, having partly local and partly multinational ownership, or small-scale local manufacturers, with few NGO drug production^{28,33}. Few manufactures are able to undertake research to develop new chemical entities, while fewer are even able to engage in biopharmaceutical research activities. The majority, however, are only small-scale producers. Thus, it is important to mention that, developing countries cannot be considered as one entity, as many differences exist between countries with regard to infrastructure, economic status, existing health care and regulatory systems, and the role of private and public institutions. Pharmaceutical manufacturers of some developing countries have the capacity to produce pharmaceuticals that cover a wide range of specialties and account for a reasonable percentage of the essential medicines needed locally. At the same time, such countries export not only to developing countries, but also to industrialized countries (Table 2). The mentioned exporters remain the main sources of cheap medicines and APIs for other developing countries and are able to tap into the developed countries' markets.

Table 2: Pharmaceutical Exports from Low- and Middle-Income Countries, 1998 (US\$ million)¹⁰

Exporter	Exports to industrialized countries	Exports to developing countries	Exports to developing countries as percent of total
China	1079	592	35.4
India	288	576	66.7
Mexico	304	410	57.4
Argentina	25	277	91.7
South Korea	85	204	70.6
Brazil	64	183	74.1
Colombia	10	173	94.5

Pharmaceuticals alone may not solve the chronic health and healthcare problems existing in developing countries, but can play

an important role if made available and affordable. This is because drugs commonly make a significant part of total health expenditure

in any health care system, and in developing countries, the share is even bigger. Middle-income and newly industrialized developing countries need to provide guidance and support to least developed ones to build local pharmaceutical production. Till now there are strong signs of such support. Generic companies in India, Brazil and Thailand have offered assistance to low- and middle-income countries to produce ARVs locally through technology transfer via South-South collaboration³. However, Kaplan and Laing (2005)³⁴ argue that, a research agenda based on evidence and not relying just on post-hoc case studies should be created to test assumptions about local production of pharmaceuticals. There are many obstacles to overcome in most developing countries before a meaningful local production could become a reality. The extent to which most developing countries' manufacturers are capable of producing good quality drugs to meet local needs and the ability to engage in R&D to develop new chemical entities for local diseases is yet to be determined.

India: pharmacy of the developing world

A modern Indian pharmaceutical industry, as in many other developing countries has emerged in last four decades. In 1972, patents for pharmaceutical products were disallowed and only one production process could be patented (for a maximum of seven years), a measure that enabled the growth of many APIs and generics manufacturers^{32,35}. By 2005, the Indian pharmaceutical industry was the world's 13th largest in terms of value and the 4th largest in terms of volume²⁰. The industry is also one of the most advanced among the developing countries, providing generic medicines to many poor countries that have no manufacturing capacities or cannot afford the high prices of branded medicines^{15,30}. Two thirds of the drugs produced are exported, making India the main supplier of medicines to developing countries³⁰. Indian manufacturers of generic HIV/AIDS medicines have already entered the markets of sub-Saharan Africa¹⁶. The availability of Indian generics to treat HIV/AIDS and other illnesses has helped developing countries to bargain the prices of medicines with other manufacturers³⁶. In fact, many of the generics imported from India are cheaper than are those manufactured locally in other countries. No doubt that, the rise of Indian pharmaceutical industry has benefited both the Indian people and other populations in the developing world.

The reputation gained by the pharmaceutical industry in India through years of dedication has led to the emergence of Indian pharmaceutical giants like Ranbaxy, Cipla, Dr Reddy's, Sun, Biocon and many others. However, after the introduction of the TRIPS agreement, the Indian pharmaceutical industry as a leader in the developing world has to embark on a new era. After TRIPS, and as from 2005, India must respect patents on pharmaceuticals, and its law must meet international intellectual property rights standards. Despite the new conditions, Indian local pharmaceutical majors are gaining more grounds internationally, focusing on generics and APIs marketing in developing countries²⁰. Moreover, India's good infrastructure for industry and research has attracted multinational pharmaceutical companies to outsource manufacturing activities to the country. In 2009, GlaxoSmithKline (GSK) announced a partnership with India's Dr. Reddy's to manufacture and supply drugs to GSK for co-marketing in Africa, the Middle East, Asia-Pacific, and Latin America³⁷. In the same manner, Pfizer announced partnership with Aurobindo Pharma and Claris Lifesciences of India. India is also in a position to outsource activities to other countries.

As for research and development of new drug molecules, Indian firms have capacities comparable to those of big multinational pharmaceutical companies with growing R&D revenues³². These firms will benefit from the intellectual property protection rules and new drug discoveries will be rewarded. Patent protection may provide an incentive for Indian researchers to scale up R&D activities to develop drugs for developing country markets³⁸. Indian scientists will also benefit from the increasing outsourcing of clinical studies by multinational companies to the country³⁸⁻⁴⁰. Lower trial costs and diversity of patient are among the reasons to choose India for clinical trials, however, there are concerns about ethics and

regulation of trials³⁹. Finally, the Indian pharmaceutical industry in the light of the accumulated experience and expertise supported by intellectual property protection is able to compete in the international market⁴¹.

TRIPS and local pharmaceutical production

Internationally, the exclusivity of production is protected by World Trade Organization (WTO) agreements on TRIPS¹³. Additionally, Patent protection for chemical and pharmaceutical products is especially important since the actual manufacturing process is often easy to imitate without incurring much cost⁴². In January 1995, the TRIPS agreement established global minimum standards for the protection of intellectual property, including a minimum of 20 years patent protection on pharmaceuticals⁴³. Before the TRIPS agreement, many developing countries had no patent protection for pharmaceutical products, without which a research-based pharmaceutical industries business is not feasible^{42,44}. According to TRIPS, countries (mostly developing countries) were given until 2005 to comply with the agreement. Least developed countries (LDCs), on the other hand, would have a grace period until 2016 to comply with the agreement.

The TRIPS agreement came about as a result of pressure by the multinational pharmaceutical industry and industrialized countries to strengthen patent rules in the developing world³⁸. That means developing countries will not be able to produce cheap generics as easily as before, with a possible increase in prices of medicines and the possibility of limiting access to medicines for most of the world population. Developing countries in particular have voiced their concerns out. Later, in 2001, the Doha Declaration on TRIPS offered permission to developing and other countries in the form of compulsory licence (CL) to take the measures necessary to make essential medicines available to their people in the case of emergencies and epidemics to safeguard the public health. According to WTO, a CL is when a government itself produces or allows someone else to produce the patented product or process without the consent of the patent owner. As per Article 5(c) of the Doha Declaration, a national emergency or other public health crisis would include those relating to HIV/AIDS, tuberculosis, malaria and other epidemics⁴⁵.

Many developing countries took steps to amend their laws to comply with the TRIPS agreement as of 2005. However, this does not mean that they have moved smoothly into TRIPS era, easily accepted the situation, or not facing problems with implementation. After the initial objections by developing countries (which led to the Doha Declaration), there were many conflicts between power nations and the WTO on the one hand, and countries failed to comply with TRIPS in 2005 and thereafter, on the other. In South Africa and Brazil, for instance, there is the challenge of setting up a national intellectual property infrastructure and at the same time fulfilling the medicinal needs of the increasing mortality from AIDS⁴⁶. The case of Thailand explains how the TRIPS agreement and the Doha Declaration are interpreted in different ways. In 2006, Thailand issued a compulsory licence for imported (from India) and locally produced generic versions of Merck's ARV drug efavirenz and in 2007 for another AIDS drug Kaletra[®] produced by Abbott Laboratories and an anti-clotting agent Plavix[®] produced by Sanofi-Aventis (in Thailand)^{30,47}. The pharmaceutical companies concerned, especially in the case of Plavix[®], which is a non-infectious disease drug, did not accept these actions. Abbott withdrew the registration application for Aluvia[®], the new heat-stable form of Kaletra[®], and threatened to withhold all new medicines from the Thai market⁴⁸. Another dispute occurred in Malaysia in 2003 over the high prices of ARVs from patent- holding companies. In 2004, Malaysian ministry of health issued a contract to a local company to import generic versions of patented ARV drugs zidovudine, didanosine and a combination of lamivudine and zidovudine from Cipla (India)⁴⁹. As a result, patent holders GSK and Bristol-Myers Squibb lodged complaints against the Malaysian government's movement. The Indonesian government, on the other hand, used the option in TRIPS to produce generic ARVs since 2004, importing raw material from India, while providing remuneration to the patent holders⁵⁰. Brazil also issued a compulsory licence for efavirenz in 2007³⁰.

Although the TRIPS agreement posed many challenges to developing countries in pursuing the provision of essential cheap medicines to local population, governments are aware of the obligations and rights to protect national public health. However, the use of compulsory licence is not always a straightforward process and countries must negotiate with the patent holders to agree terms and pay royalties. Fortunately, there are the pharmaceutically advanced developing countries which can provide assistance to other countries to make use of the exceptions stipulated in the Doha Declaration. Developing countries can also manufacture and export medicines to other developing countries under CL. In the near future, a number of blockbuster drugs will be going off-patent, giving

an opportunity for developing countries to produce generic versions of these drugs with the hope of improving access to medicines and reducing treatment costs.

Challenges to local pharmaceutical production

The main challenges facing the global pharmaceutical industry in general are presented in Figure 2. In addition to the time expended, costs incurred and the high failure rates for new drug candidates, multinational pharmaceutical companies face price challenges from generic manufacturers. For pharmaceutical industries in developing countries that mainly manufacture generic drugs with little or no R&D activities the challenges are different. Some of the challenges are:

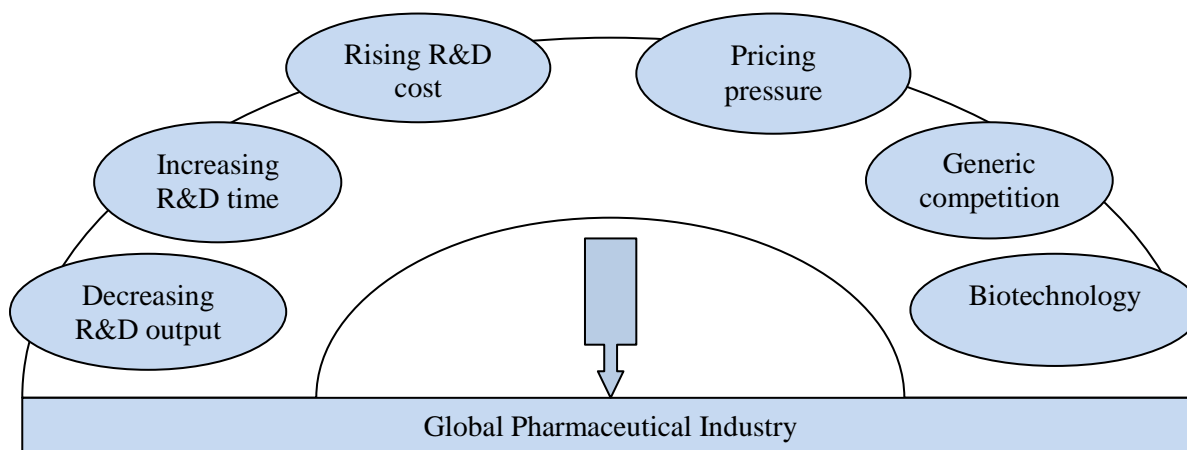


Fig. 2: Global pharmaceutical industry challenges²⁰

• Stewardship and regulatory systems

Pharmaceuticals are products that need special technical manufacturing capabilities throughout the whole process, following comprehensive guides of good manufacturing practice (GMP). There must be a body to regulate and supervise such activities, which is usually a public institution. Medicines as such are special commodities; their production, distribution and marketing require adequate control and supervision¹⁶. According to WHO GMP guidelines, manufacturers of the pharmaceutical products are responsible for the overall operations having an impact on the quality of the medicines, including active APIs. Beside pharmaceuticals, there are other related products (e.g. nutraceuticals, health supplements), which have physiological effects or therapeutic claims are becoming popular among consumers and need to be regulated to protect public health⁵¹. This puts additional work load on pharmaceutical regulatory bodies. Without effective regulation and strict adherence to GMP guidelines, manufacturing process will fail, allowing sub-standard and counterfeit medicines to appear in the market. This is particularly true of developing countries¹⁹. Moreover, the adoption of national lists of essential medicines and policies is effective for improving medicine access and rational use and many countries have adopted such lists.

Shakoor et al (1997)⁵² analyzed 96 samples of chloroquine and selected antibacterials from Nigeria and Thailand; they found that 36.5 percent of the samples were substandard to pharmacopoeial limits due to poor manufacturing. Substandard and low quality medicines may have direct effects on health, lead to microbial resistance, or increase the overall cost (when substituted with expensive alternatives) and duration of treatment. In 2001, WHO launched a prequalification programme for medical products to facilitate access to medicines of unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. The programme inspects pharmaceutical plants and quality control laboratories (QCLs) in addition to providing training and capacity building for pharmaceuticals in developing countries. Prequalification training courses were held in South Africa, Egypt, Ukraine, Morocco, Tanzania, Estonia, China and Senegal in 2007⁵³.

Adherence to GMP is facing difficulties in developing countries which lack the resources to assure the quality of imported APIs, manufacturing processes, finished products and premises' conditions. The shortage of trained professionals and the expertise, quality laboratories, and financial resources hampers innovation and the development of new chemical molecules. To produce a new drug, only one out of every 250 new compounds used in preclinical testing and only one in five to one in ten used in clinical trials ever receives FDA approval¹⁸. Additionally, synergy of collaboration between the government, academia, and the medical profession and consumer groups in the pharmaceutical industry does not exist in developing countries⁵⁴.

Beside the problem of sub-standard medicines, which could be attributed to inadequate regulatory supervision and control, counterfeiting is another issue in drug industry. Counterfeits and substandard medicines are estimated to be at more than ten percent of the global medicines market and as high as 25-50 percent in developing countries⁴. Out of 771 reports of counterfeit medicines received by WHO between 1982 and 1999, 48.4 percent were from the Western Pacific region, with most (51.2 percent) labeled as anti-infectives⁵⁵. Many manufacturing facilities in developing countries are not accredited by recognized international bodies such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the WHO and have weaker local supervision and control over manufacturing processes. Regulatory systems are often unstable, lack transparency and are unable to ensure continuous control over pharmaceutical manufacturers. Failure could occur at the very beginning, when importing APIs and other ingredients, which may simply be fraudulent or adulterated. The result is production of poor quality or fake medicines. Therefore, local consumers are skeptical about medicines produced locally and prefer the branded counterparts. In fact, the attitude of consumers in developing countries is always biased towards exported branded medicines even though they are more expensive than locally produced counterparts, because of the lack of trust. At a time, only 20 percent of the 191 WHO member states have well developed drug regulations, about 50 percent have different levels of regulation

capacity and the remaining 30 percent have very weak regulations if any⁵⁶. Only in the presence of strict and transparent regulatory measures, will locally produced pharmaceuticals gain the trust of local consumers and then find their way into international markets.

• The effect of TRIPS

Although supporters of the TRIPS agreement argue that developing countries will have a chance to build their own capacities to innovate and develop medicines in the post-TRIPS era, there still is a long way to go for most of the countries. The vast majority of drug companies in developing countries cannot afford the costs of R&D for developing new chemical entities, assuming they have the technical capacity and the know-how. Developing a new drug from basic research is a complex, risky, capital-intensive and time-consuming activity^{13,57}. It takes about eight years of clinical testing, and twelve to fifteen years in total for the drug to reach the market⁵⁸. Pharmaceutical industries in poor countries may prefer to continue the imitation of off-patent medicines rather than try to engage in any research activities. In such case, manufacturers should be able to adhere to GMP and maintain good quality laboratories to produce generics that are reasonably priced. But since copying and imitation are now restricted by TRIPS, they can only produce unpatented or off-patent medicines, making local production less likely to meet local needs, and it may also be non-profitable. A clear picture can be drawn from 2016 onwards when LCDs have to comply with TRIPS.

• Level of investment

Drug research and development is almost exclusively the preserve of the private sector, and is driven by profit prospects rather than public health needs⁵⁹. Therefore, despite governments' efforts to establish public drug manufacturing facilities, still most (over three quarters) of the pharmaceutical expenditures are from private investment²⁸. The size of pharmaceutical markets in developing countries is too small to attract private sector investment in drug development⁶⁰. While building a pharmaceutical plant needs a lot of investments, the cost of R&D for new drugs is far beyond the capacity of the companies in developing countries. The cost of bringing a new drug to the market ranges between US\$500 million and US\$800 million (based on year 2000 dollars)^{13,18}. The international community understands that, for local production to be economically viable, certain pre-requisites must be met. At least an effective regulatory framework, political stability, conducive economic conditions, the capacity to reach quality standards, and delivery capacity need to be in place⁶¹. After all, investments in local medicine production will be efficient only if locally produced pharmaceuticals are cheaper than the imported ones³⁴. Not forgetting the stiff competition in developing country markets between locally manufactured and imported generic or branded drugs.

If pharmaceutical production is to be a private investment, as is mostly the case, profits and amount of returns on investment will be the main concerns for investors. Developing countries that have weak industrial infrastructure must import technology and raw materials (APIs and packaging materials) from industrialized or other developing countries with advanced pharmaceutical industry. Such materials may be subject to import taxes and other fees, which could discourage private investment in the sector. Then the government role is to create an environment conducive to the growth of the industry by giving incentives (e.g. tax waiver).

• Market size and competition

Multinational pharmaceutical companies are generally not in favor of the small markets business. The same is true of drug development. In most African countries, for example, drug consumer markets are very small, making local production at national level technically and economically nonviable^{60,62}. In addition, in the small markets, local drug producers must compete with multinational pharmaceutical companies that have many marketing strategies, and are able to reduce prices at one hand and compensate elsewhere. Local manufacturers do not have such an option, as any reduction in price will affect their business.

Other challenges to local manufacturing are related to political and economic instability, development and health policies. Nonetheless, developing countries differ widely in the level of development and the type of challenges they face. Middle-income and newly industrialized countries are able to overcome many of the challenges and take confident steps in pharmaceutical production.

CONCLUSION

There are still gaps in access to essential medicines in developing countries. Despite the challenges that pharmaceutical industry in the developing world faces, its role in making essential medicines available is tangible. Some middle-income countries became industrialized, while others are progressing fast economically and are acquiring technology to improve their pharmaceutical industry. These countries share the same disease profile with other developing countries, and could use their advanced pharmaceutical technology to address diseases neglected by multinational companies. The lack of infrastructure for research and industry, the lack of reliable national regulatory systems, limited financial and human resources and small consumer markets are the main problems that hinder the establishment of local production of pharmaceuticals in poor countries. Technology, experience and knowledge sharing between developing countries will be effective in the pursuance to establish local pharmaceutical industries. Assisting existing pharmaceutical plants to adhere to GMP and the training of professionals will help to produce good quality products.

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