

# INVESTMENT IN PHARMACEUTICAL PRODUCTION IN THE LEAST DEVELOPED COUNTRIES

A Guide for Policy Makers  
and Investment Promotion Agencies



**United Nations Conference on Trade and Development**

***Investment in Pharmaceutical Production in the  
Least Developed Countries***

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and Investment Promotion Agencies**

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## Foreword

The United Nations Millennium Development Goals put considerable emphasis on access to medicines in developing countries, especially the least developed countries (LDCs). Even while great strides are being made to improve such access through philanthropic efforts of individuals, foundations and corporations, as well as through the impressive capacity of some of the larger developing countries, such as Brazil, China and India, to produce high-quality medicines at low cost, a significant proportion of the world's population remains without regular access to affordable, quality medicines. The local production of pharmaceuticals in developing countries has long been considered a possible avenue to meet the pressing need to step up efforts to ensure greater access to medicines. Most pharmaceutical firms in the poorer countries will, however, be unable to contribute to this objective without foreign direct investment and technology transfer.

This publication is intended to be an overview of important trends affecting the local pharmaceutical production in developing countries and a guide for policymakers, investment promotion agencies and investment negotiators in developing countries that are considering supporting local pharmaceutical firms as a means to help address their important health imperatives. The information contained in this publication is based on the engagement of UNCTAD with developing countries in their efforts to encourage the expansion of local pharmaceutical production capacity.

In 2005, the UNCTAD Commission on Investment, Technology and Related Financial Issues made the following recommendation:

"UNCTAD should, within its work programme on investment, technology transfer and intellectual property, assess ways in which developing countries can develop their domestic productive capability in the supply of essential drugs in cooperation with pharmaceutical companies."<sup>1</sup>

In 2006, UNCTAD initiated technical cooperation projects with the support of the German Ministry for Economic Cooperation and Development and the Department for International Development of the United Kingdom of Great Britain and Northern Ireland to provide advice and training on flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) related to public health for developing countries that are interested in supporting greater access to medicines and the local production of pharmaceuticals. In 2008, UNCTAD was named as a stakeholder on issues of local production of pharmaceuticals, technology transfer and intellectual property in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the World Health Organization (WHO). Beginning in 2009, UNCTAD, in cooperation with WHO and the International Centre for Trade and Sustainable Development (ICTSD), launched a project supported by the European Union (EU) to identify the main challenges and obstacles of the local production of pharmaceuticals in developing countries and related technology transfer. The role of UNCTAD in this project was to conduct a series of case studies on local pharmaceutical production in different regions, using different business models. This guide therefore puts together a wealth of experience in one publication, examining the complexities and

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<sup>1</sup> See [http://www.unctad.org/en/docs/c2122\\_en.pdf](http://www.unctad.org/en/docs/c2122_en.pdf) (para. 9(c) of the 2005 Agreed Recommendations).

dynamics of developing productive capacity in this field, with particular reference to LDCs.

This publication is not intended to be a step-by-step guide that in any way guarantees foreign direct investment and technology transfer into the local pharmaceutical sector. Rather, it aims to provide a better understanding of the state of current global pharmaceutical production and the role that developing country production plays in it. It also examines the range of policy instruments that would enable developing countries to increase their chances of attracting the interest of investors in this unique sector. In this regard, the tools that should be employed in any specific circumstance will necessarily differ from case to case.

A handwritten signature in black ink, appearing to read 'S. Panitchpakdi', with a stylized flourish at the end.

Supachai Panitchpakdi  
Secretary-General of UNCTAD

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## Abbreviations

EU	European Union
GSPA-PHI	Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property
ICTSD	International Centre for Trade and Sustainable Development
IFMPA	International Federation of Pharmaceutical Manufacturers Association
LDCs	Least developed countries
R&D	Research and development
TRIPS	Trade-Related Aspects of Intellectual Property
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNIDO	United Nations Industrial Development Organization
WHO	World Health Organization
WTO	World Trade Organization

## ***Executive Summary***

The global pharmaceutical sector has changed greatly in the last 10 to 15 years. The expiration of patents on some of the blockbuster drugs has meant that the large research and development (R&D)-based transnational corporations in the developed world, which had relied on the sales of these drugs for their profitability, have had to re-examine their business models and adjust accordingly. Many of them have undergone a significant re-organization of their operations. Some firms are forming alliances with major generic manufacturers, both in developed countries and the larger developing country markets. Other are acquiring smaller biotechnology firms with patent applications in the pipeline, while still others are expanding into related fields such as diagnostics and other areas.

Meanwhile, developing countries that have heretofore not had to offer patent protection on pharmaceutical products are finding that they must now offer such protection for new chemical entities as part of their commitments under the TRIPS Agreement of the World Trade Organization (WTO). These countries, such as India, had developed a large generic medicines industry based on, inter alia, their ability to reverse engineer medicaments patented elsewhere, and have been important players in providing other developing countries with generic medicines. Now, however, these large generic firms in China and India are becoming increasingly interested in selling their medicaments to developed country markets, and are beginning to partner with R&D-based transnational corporations in the sector.

The backdrop to these changes from an LDC perspective is, however, that much of their population still lacks access to much needed medicines, despite impressive gains in the availability of certain medicines in the last decade.

The above-mentioned changes in the pharmaceutical industry are impacting LDCs in two important ways. First, the larger generic pharmaceutical manufacturers in developing countries have in a number of instances begun to examine the possibility to engage in foreign direct investment in LDCs to produce medicines while they are increasingly aiming at selling their own output in more profitable developed country markets. Second, LDCs are in a good position to take advantage of the fact that, unlike other developing countries that are Members of WTO, they are exempt from having to offer patent protection on pharmaceutical products until at least 1 January 2016, and perhaps longer if WTO Members are able to agree on a further extension of the waiver granted to these countries from having to comply with the TRIPS Agreement.

In order to have a serious chance at benefiting from the current changes and attracting foreign direct investment in the pharmaceutical sector, however, a number of important prerequisites need to be met, many of which are lacking in LDCs. It therefore may not make sense for all LDCs to aspire to be scaling up their local production of medicines. Furthermore, they will want to ensure that such efforts go beyond a mere industrial policy, and that the push to support the local production of pharmaceuticals through foreign direct investment and related technology transfer will address real public health needs in the relevant country and/or region. Finally, such countries will need to have an effective promotion strategy that appeals to potential investors.

This guide outlines these recent trends, the basic prerequisites for the local production of pharmaceuticals and the key points that policymakers and investment negotiators,

especially from investment promotion agencies, will need to keep in mind in efforts to support this important sector. The Executive Summary highlights those points below.

*With respect to why government support is important:*

- ⇒ Investment in the pharmaceutical sector will not come on its own, especially for LDCs; concerted efforts led by government will be necessary for countries that seek to attract foreign direct investment and technology transfer.

*It is important to have a unified and coherent position among key stakeholders on important objectives at the outset of any such efforts:*

- ⇒ Because the institutional framework for the regulation, the manufacture and distribution of pharmaceuticals is fragmented; key government ministries and agencies will need to agree on the rationale and strategy for promoting local production through improved coordination and policy coherence.

*With respect to which medicines should be produced locally, and for whom:*

- ⇒ A decision to support the local manufacture of pharmaceuticals should also address the question of which medicines should be produced locally.
- ⇒ From a public health perspective, development gains are greatest if local production increases the supply of good quality and affordable essential medicines, of which there is a shortage, as well as for other poverty-related, tropical and neglected diseases.
- ⇒ The drug regulatory authority is an important source of information with regard to which drugs would be good candidates for local production from a public health perspective.
- ⇒ Local firms may also need to produce drugs other than those identified in order to be sustainable in the long run.
- ⇒ With respect to the question of whom the medicines should be produced for, government purchases are important in the LDC context, as there are generally no insurance systems and individuals are frequently unable to purchase needed medicaments out of pocket.

*With respect to lowering the cost of medicines:*

- ⇒ It is not always cheaper to manufacture medicines locally than to import them; however, that is not necessarily a reason to abandon the idea of producing medicines locally.
- ⇒ Some LDCs may not be able to rely on their current import sources, as exporter countries may become more interested in targeting more lucrative markets in the Member countries of the Organisation for Economic Co-operation and Development.
- ⇒ Building the domestic capacity to produce active pharmaceutical ingredients is one means to try to reduce the absolute cost of production and achieve security of supply.
- ⇒ There are a number of avenues through which the out-of-pocket cost to the consumer could be held to a minimum, such as the availability of public insurance or government purchases, though this may not have an impact on the absolute cost of production.

*With respect to maximizing technology transfer gains:*

- ⇒ Technology transfer needs to be part of any foreign direct investment in the local production of pharmaceuticals, especially in LDCs.
- ⇒ There is often an inherent tension between the transferor of technology and the recipient country of technology transfer, with the former seeking to limit technology transfer to the target firm and the latter seeking widespread diffusion of the technology into the economy.
- ⇒ Policies affecting technology transfer need to strike a balance between onerous protections that would stifle any hope of spillover effects and an absence of protection for undisclosed proprietary knowledge.
- ⇒ In-built partnerships with local universities and research institutes in investment deals could help nurture the human resource base upon which the long-term success of the investment relies and could potentially be a good strategic asset for conducting research on local diseases and finding possible cures.

*Both health policies and industrial policies are important, but:*

- ⇒ Pursuing local pharmaceutical production as part of an industrial policy is not necessarily the same as pursuing local pharmaceutical production as part of a health policy, though the two policies can be complementary.
- ⇒ Coherence of policies is critically important if policymakers wish to leverage pharmaceutical production to meet public health needs, as the dynamics and proponents of the respective policies within a country are different.

*With respect to the potential domestic partners for the investment:*

- ⇒ The drug regulatory authority will often have important information concerning the firms within its jurisdiction and their potential to be partners with foreign investors in the local production of pharmaceuticals.
- ⇒ The field of potential partners need not be limited to existing producers; distributors often have a network through which to sell products, which can potentially be attractive to investors.

*With respect to the targets for potential investors:*

- ⇒ Most LDCs will need to focus their efforts on attracting generic manufacturers rather than the big R&D-based pharmaceutical companies in developed countries.
- ⇒ Recent investment activity in this sector with respect to LDCs has been on a South–South nexus, featuring generic firms from Brazil, China and India.
- ⇒ The government can also be a potential investor, and may be influential in steering the product offering of the local firm towards certain medicaments that meet public health needs.

*LDCs have an edge in one important respect:*

- ⇒ The ability to legally produce generic equivalents of medicines that are on-patent elsewhere is a competitive advantage unique to LDCs.
- ⇒ The legal regime needs to ensure that LDCs interested in supporting local production can make use of this competitive advantage.

*However, that edge alone is unlikely to be sufficient to convince potential investors:*

- ⇒ Those LDCs interested in supporting local pharmaceutical production need to show investors certain basic requirements to support an industry are in place.
- ⇒ Countries need to build their human resource base in relevant fields such as pharmacy, chemistry and management.
- ⇒ Countries also need to be able to deliver the appropriate infrastructure.
- ⇒ A well-functioning drug regulatory authority is essential for countries that are considering supporting local production.
- ⇒ Some LDCs may wish to negotiate in order to channel donor assistance towards these activities.

*LDCs will need to show that there is market potential:*

- ⇒ LDCs are inherently not a market of choice for pharmaceutical investors, generic or otherwise. Efforts should be made to show that a market where local ventures could potentially be profitable exists.
- ⇒ One way this can be done is through advance purchase commitments by the government, with preference to local manufacturers within reasonable limits.
- ⇒ Another means to show the existence of a market is to pursue a regional market, for example, by harmonizing drug regulations and related intellectual property standards.

*Investment promotion agencies have an important role to play in communicating the efforts of a country in local production to potential investors, and to negotiate an interesting set of incentives.*

- ⇒ LDCs will need to inform potential investors that the prerequisites for pharmaceutical production are being met – investment promotion agencies have a particularly important role to play in this task.
- ⇒ A range of investment incentives may be employed to support the case for specific investments in local production of pharmaceuticals.
- ⇒ The decision on which incentives should be utilized differs from case to case and should be weighed carefully in terms of the full cost of the incentives and the benefits of the investment, both with regard to health and economic gains.

## ***Chapter 1***

### ***Developing Countries and Pharmaceutical Production – the Present Reality***

Significant strides have been made over the past 10 to 15 years to ensure greater access to medicines by developing countries. Recent advances in providing greater access to certain treatments, such as antiretrovirals used to treat the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in developing countries, have been impressive. According to the 2010 Millennium Development Goals Report of the United Nations, those receiving such treatments expanded from an estimated 400,000 worldwide in 2003 to approximately 5.2 million people by the end of 2009.<sup>2</sup> According to WHO, the number of people with regular access to essential medicines increased from 2.1 billion to about 4 billion between 1997 and 2002.<sup>3</sup> There remains, however, a significant gap in access for nearly 2 billion of the world's population, many of whom live in LDCs. The efforts of poorer countries to obtain philanthropic donations and/or import inexpensive generic versions of medicaments to meet the needs of their populations appear to be falling short, albeit for a variety of reasons.

The WHO 2008 Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) recognizes the potential contribution of the local manufacture of pharmaceuticals in developing countries to help tackle this situation. This landmark document acknowledges that a local pharmaceutical industry may contribute to meeting the goal of greater access to medicines.<sup>4</sup> Few developing countries have, however, been able to develop capacity in manufacturing pharmaceuticals in the absence of the support of, inter alia, foreign firms and technology transfer. In the light of this reality, the present guide is intended for policymakers, investment promotion agencies and investment negotiators in developing countries, and in particular LDCs that are interested in developing a local pharmaceutical industry through appropriate investment and related policies.

For the purposes of this paper, pharmaceutical production shall refer to the production of medicines based on modern chemical and biological processes, as opposed to traditional medicines. Local production shall mean the manufacture of pharmaceuticals in a developing country, whether by a locally owned firm, by a joint venture or by a foreign firm.

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<sup>2</sup> United Nations (2010), p. 45.

<sup>3</sup> WHO et al (2011) and WHO (2002). See also, Timmermans, K. (2006).

<sup>4</sup> Sixty-first World Health Assembly, document WHA61.21 of 24 May 2008, Annex, element 4.1, para. 34, (available from [http://apps.who.int/gb/ebwha/pdf\\_files/A61/A61\\_R21-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf)). Element 4.1 of the Plan of Action calls upon Member States to promote the “transfer of technology and the production of health products in developing countries”.

## **A. Basic terminology**

Before examining the state of pharmaceutical production in developing countries, a number of terms are defined at the outset to guide policymakers who may not be familiar with the sector.

- A **generic** drug refers to a medicine that is chemically equivalent – bioequivalent – to an originator drug, and has the same medical effects on the human body as the originator drug. A generic version of a drug can be produced legally only if there is no patent protection for the originator drug in the country where the drug is being produced. This can happen either after a patent expires or is otherwise invalidated in a country, or where there is no patent for the originator drug in that country in the first place. Normally, generic competition lowers the price of a drug, since no single firm has the power to exclude others from producing it.
- A **new chemical entity** refers to candidate molecules that are developed in the early stages of drug development that address a biological target. New chemical entities need to be synthesized and tested in laboratories and through human clinical trials before they can be approved as medicines by the local drug regulatory authority (see below). Pharmaceutical companies involved in R&D often seek to obtain patent protection over new chemical entities.
- **Biologics** refer to the class of biologically based products used in medicine, such as vaccines, monoclonal antibodies and various blood products. The molecular structure and technology for producing biologics tends to be more complex when contrasted with pharmaceuticals that involve small molecules. Most biologics involve some form of extraction from a biological agent. For example, vaccines refer to biological preparations that are designed to improve immunity to certain medical conditions. Vaccines<sup>5</sup> may be based on killed micro-organisms (such as influenza) or attenuated, meaning that they contain live viruses (such as yellow fever).
- A **patent** is the grant of an exclusive right to exclude others from making, using, selling or importing an invention (whether it is a product or a process)<sup>6</sup> for a specified period of time, typically 20 years for WTO Members. Patents are granted by a national patent office if an invention meets the respective criteria of novelty, inventive step and industrial application.
- An **active pharmaceutical ingredient** refers to the chemical substance in the medicine that is biologically active. Active pharmaceutical ingredients are distinguished from **excipients**, which refer to the components of a drug that are not biologically active, for example, gelatin capsules, that are combined with the active pharmaceutical ingredient to produce the final drug in the form of tablets, injectables and the like.

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<sup>5</sup> In the area of biologics, the development of generics is much more complex than in the case of chemical drugs because of the often unpredictable behaviour of biological products in the human body. For this reason, regulatory authorities in many countries will not authorize the distribution of vaccines upon a showing of bioequivalence.

<sup>6</sup> Patent law formally distinguishes between products (such as machines, manufactured goods or composition of matter) and processes (also termed methods).

- According to WHO, **essential medicines** refer to drugs that satisfy the priority health care needs of the majority of the population and should therefore be available at all times in adequate amounts and in appropriate dosage forms.<sup>7, 8</sup> Each country maintains its own list of essential medicines, while WHO has published a model list of essential medicines to which developing countries often refer. Essential medicines can be contrasted with **lifestyle medicines**, which is a general term used to refer to medicines used to treat non-life threatening and non-serious conditions, particularly those prevalent in more affluent societies.
- **Formulation** refers to the process by which active pharmaceutical ingredients and excipients are combined to make the final pharmaceutical product.
- The **drug regulatory authority** refers to the public authority that regulates, inter alia, medicines in the country. It authorizes the marketing of drugs for distribution and consumption in a country after it is satisfied that the medicament was produced having met applicable health and safety standards, including clinical trials or, in the case of generic medicines, bioequivalence.
- For purposes of this paper, **technology transfer** refers to the transfer of all components of technology, both codified (in terms of blue prints, hardware, machine parts and plant technologies) and tacit (know-how and skills) that are essential to enhance the capacity of the organizations in the recipient country to produce pharmaceutical products. This transfer may occur on an intra-firm basis, through licensing from one firm to another or through official development assistance. It may also occur informally, as when highly skilled staff moves from one firm to another.
- An **investment promotion agency** is an agency with the mandate to promote investment into a given geographical region. In many cases, it is a government agency (though it need not necessarily always be a governmental body). It can function as a one-stop shop for investors and is often responsible for coordinating promotion strategies for specific sectors.

## **B. Understanding pharmaceutical manufacturing**

This section outlines the pharmaceutical manufacturing process for policymakers who may not be familiar with the industry, as well as for investors and financiers. Broadly speaking, pharmaceutical manufacturing encompasses a wide range of activities from drug development – R&D – to the packaging and distribution of the final product, that is, the medicine. A detailed examination of each step in the manufacturing process is beyond the scope of this paper.

Drug discovery is the process of developing new drugs. It involves both basic research to identify new chemical entities and more advanced applied research, including the synthesis of the new chemical entity into a candidate drug, and live animal and human clinical trials on that drug. More broadly, R&D in the pharmaceutical sector need not

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<sup>7</sup> See [http://www.who.int/topics/essential\\_medicines/en/](http://www.who.int/topics/essential_medicines/en/) (accessed on 9 February 2011).

<sup>8</sup> From 2002 onwards affordability criteria has been changed from a condition to a consequence of selection. Before 2002, expensive medicines were often not included on the model list because their inclusion was seen as unrealistic. Under the new definition, a cost-effective medicine can be selected even if the price is high, and the fact that it is considered essential then implies that it has to become available and affordable.



necessarily focus exclusively on new medicaments – it could, for instance, also focus on combining existing medicaments into a single dosage form, such as in combination therapy of antiretrovirals to treat HIV and AIDS; it could involve the adaptation of existing medicaments to local climate conditions through incremental innovation (for example, how to make a medicine more heat- or humid-resistant); it could involve finding new modes for drug delivery (injection, topical or oral); or it could also involve the reverse engineering of an originator drug that, while it has been patented elsewhere, is off patent in the country seeking to manufacture its generic equivalent.

Once a drug has been developed, the developer applies to the national drug regulatory authority for registration and marketing authorization in the country where it seeks to manufacture and distribute the drug, and for exporting the drug if they wish to sell it abroad. The drug regulatory authority's role is to ensure that health, safety and quality standards have been observed in the development of the drug and the conducting of trials, as well as in its manufacturing and safekeeping procedures, with a view to protecting the health of the population.

Developers may also apply to the local patent office for patent protection for a new drug, with a view to obtaining a set of rights that can exclude others from, *inter alia*, producing the drug for a period of 20 years from the date of application – if successful – enabling it to exclude generic competition and charge a premium for the drug in the market where the patent was granted. Very often, however, patents are sought at an earlier stage, to ensure exclusive rights over the new chemical entity even before the patent applicant knows whether it will ever be useful in a drug.<sup>9</sup> It has been argued by the large R&D-based pharmaceutical industry that premiums from exclusive rights are necessary to recoup some of the costs for drug development and to ensure future R&D for new, innovative drugs.<sup>10</sup> Firms may also file applications for patents on minor improvements or variants of a drug that may extend, *de facto*, their exclusive rights (i.e. the issue of so-called “me-too” drugs and “evergreening”).<sup>11</sup> Additionally, firms may register to file a trade name for a new drug and/or for an accompanying trademark, with a view to distinguishing the product from similar products.

Pharmaceutical firms in LDCs are generally not involved in drug discovery; their interest lies more in being able to access new drugs that would help meet the health needs of their population, or in innovations that tailor existing drugs to local needs.

After a drug has been registered by the drug regulatory authority, the authorized company may begin to manufacture and distribute the drug. Generic equivalents of originator drugs must also be registered with the drug regulatory authority, but in most cases the requirement of conducting fresh clinical tests for a generic equivalent will be waived as long as the generic applicant can demonstrate bioequivalence, that is, that the generic product is essentially the same as the originator product in chemical composition and quality, and has the same effect on the human body. At present, many LDCs do not require evidence of bioequivalence for generic medicines and there are varying requirements for the same among other developing countries.

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<sup>9</sup> Pugatch (2006), p. 119.

<sup>10</sup> See, for example, IFPMA (2004).

<sup>11</sup> Boldrin and Levine (2008), chapter 9. See also WHO (2006), p. 150.

**Figure 1. Pharmaceutical manufacturing**



API – active pharmaceutical ingredient; OTC – over-the-counter drugs

Source: UNCTAD (2011)

Pharmaceuticals are manufactured in a factory setting, using very specialized equipment. The production process has three distinct phases (see figure 1). The first is primary production, where active pharmaceutical ingredients, intermediates and excipients are produced. Then, these raw materials are combined to produce pharmaceuticals in a process known as formulation (secondary production). Finally, tertiary production involves the packaging of finished products or repackaging of bulk finished products.

The actual manufacturing process requires close attention to ensure that quality, safety and hygiene standards are maintained and necessitates rigorous adherence to established operating procedures – good manufacturing practices – as the use of substandard medicines could potentially have dire health consequences for the user (i.e. quality control and quality assurance procedures). The inputs, for example, must be kept in very specific conditions, that is, stored at the correct temperature and humidity and in the correct containers. The procedure to formulate, while automated, requires the attention of skilled technicians who are familiar with the mixing of chemicals and of engineers who are familiar with precision instruments. Machines require constant cleaning and upkeep. Areas dedicated to formulation must be kept sterile and special clothing and gear is required when staff enter these areas.

The outputs of the process are pills, liquids, ointments, powders, injectables and the like, which are tested thoroughly to make sure there are no impurities and that dosage forms are consistent. These are then packaged and labelled with required information, such as the ingredients and the dosage to be taken. The output medicament may also need to be stored in a specific setting, such as in freezers. The process to manufacture biologics such as vaccines and monoclonal antibodies tends to be more complex and requires even more attention to detail than for mixing active pharmaceutical ingredients and excipients for pharmaceuticals.

The output medicines are then distributed. Distribution may be made to retail sources, that is, to pharmacies or other sellers such as supermarkets in the case of certain over-the-counter drugs, or they could be bought by hospitals, or by bulk procurement, perhaps by a government or by an international agency. Retail marketing efforts by pharmaceutical firms often focus on convincing doctors or hospitals that a certain medicament is an effective solution over competitor items for a certain medical condition and should be prescribed.

All of these processes may not necessarily be integrated within one single firm and/or its affiliates. As will be shown in later chapters, this is an important point to keep in mind when formulating a strategy to attract foreign direct investment to this sector.

### **C. Pharmaceutical production in developing countries**

Broadly speaking, there are two types of markets for pharmaceuticals: one for on-patent originator drugs, and the other, for generic off-patent drugs. Making the issue more complex, however, is the fact that what is on patent in one country may not be on patent in another.<sup>12</sup> Moreover, a number of R&D-based firms are concerned about the impending expiration of patents on many of their so-called blockbuster drugs, with few good prospects for replacing the income generated by these originator drugs in the face of generic competition.<sup>13</sup> Further, the generic market is segmented between a branded generic market, where generic medicine manufacturers attempt to charge a premium for their drugs based on the reliability of their brand name, and a non-branded generic market, which offers drugs far closer to production cost. The branded generic market is much bigger than the non-branded generic market. This backdrop is important when examining the present situation of pharmaceutical production in developing countries.

Up-to-date data on pharmaceutical production in developing countries is hard to obtain. The *World Medicines Situation*, published by WHO in 2004, analyses data from 1985 to 1999. The findings from the summary in chapter 1 of the 2004 report, which is the latest version of the document available, reflected the situation at the time:

- When measured in monetary terms, two thirds of the total value of medicines produced globally in 1999 (\$327.2 billion) is accounted for by firms with headquarters in just five countries – the United States, Japan, Germany, France and the United Kingdom;
- A small number of transnational companies dominate global production, trade and the sales of medicines. Ten of these companies account for almost half of all sales;
- The 10 best-selling drugs accounted for 12 per cent of the value of all medicines production;
- Large volume markets of lower-priced medicines exist in the highly competitive domestic markets of China and India.

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<sup>12</sup> At the end of 2010, the Indian Patent Office rejected a patent application for the HIV combination drug ritonavir/lopinavir, for example, while the same combination drug receives patent protection in the United States of America.

<sup>13</sup> See Viana (2011).

Also of interest in this report is the classification of all countries according to their medicines production capability. While 10 developed countries were classified as having a sophisticated industry capable of significant R&D of new chemical entities, already 17 countries were identified as having some innovative capability. Some 97 countries were identified as having a domestic medicines industry, which already included a number of LDCs. While the majority of these manufacturing countries produced finished medicines from imported ingredients, 13 countries, predominantly developing countries, were identified as having industries that are capable of producing both active ingredients and finished products.

What has changed in the decade that followed? While there has not recently been a comprehensive study of world medicines production similar to the 2004 WHO study, there appears to be three notable developments.

First, as mentioned above, many of the products that sold well during the prior decade are coming off patent, with few prospects for replacement products (see chapter 2). This creates significant opportunities for firms in countries that have some reverse-engineering capacity in pharmaceuticals and are involved in the manufacture of generics. However, a number of countries that had heretofore not been obliged to grant patents on pharmaceutical products and had used that opportunity to nurture a generic industry, such as India, now find themselves having to grant patents on both pharmaceutical products and processes as WTO Members.

Second, in many developing countries, the market share once held by transnational corporations has now been taken over by local firms. Before 1982, eight transnational corporations controlled up to 70 per cent of the local market in Bangladesh. According to UNCTAD research, local firms now control over 70 per cent of the local market.<sup>14</sup> Similarly in Indonesia, in 1991, multinational pharmaceutical firms controlled a similar 70 per cent of the local market. Here too, as of 2010, local firms control over 70 per cent of the market.<sup>15</sup> In these and other countries, the market consists primarily of local branded generics, which appears to be flourishing, and non-branded generics.

Finally, larger, more advanced pharmaceutical firms from developing countries are now beginning to formulate medicaments in other developing countries, including LDCs. The Indian giant Cipla, for example, has established a joint venture with a local company to produce antiretrovirals in Uganda, for which these parties recently agreed to a further investment of \$30 million to fund an expansion.<sup>16</sup> Chinese manufacturers have established a joint venture with a local company in Ethiopia to produce hard gelatin capsules. A joint venture owned by Cadila of India and the United States-based Holzman group, CSM Global Pharma, has recently announced a \$65 million joint venture in Rwanda to establish a factory to produce medicines, active pharmaceutical ingredients and in the future, biologics such as vaccines.<sup>17</sup> A Jordanian pharmaceutical firm has established a joint venture in Eritrea to produce for the local market in a post-conflict LDC. Some Brazilian manufacturers are also targeting the Lusophone African countries

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<sup>14</sup> UNCTAD et al, Bangladesh Case Study (2011, forthcoming). This research was conducted by UNCTAD in the context of a case study that forms part of a larger EU-funded project with WHO and ICTSD), designed to examine the state of local production of pharmaceuticals in developing countries and related technology transfer.

<sup>15</sup> UNCTAD et al, Indonesia Case Study (2011, forthcoming).

<sup>16</sup> See <http://www.in-pharmatechnologist.com/Industry-Drivers/Uganda-s-QCI-to-invest-80m-in-AIDS-and-anti-malarial-drug-capacity>. 3 February 2011.

<sup>17</sup> See <http://www.in-pharmatechnologist.com/Industry-Drivers/Cadila-JV-to-set-up-plant-in-Rwanda>. 7 March 2011.

such as Mozambique. These examples<sup>18</sup> point to the increasing importance of South–South investment for countries seeking to attract investors in the pharmaceutical sector.

That having been said, a number of things do not appear to have changed significantly since the 2004 *World Medicines Situation* report appeared. North America, Europe and Japan still account for well over 80 per cent of global sales in the pharmaceutical industry, and global sales are mainly made up of products from the R&D-based transnational corporations located in these countries.<sup>19</sup> A large number of countries still rely predominantly on imports of raw materials for pharmaceutical production, particularly active pharmaceutical ingredients. Among the developing countries, the larger ones such as Brazil, China and India still dominate the production landscape, owing to their ability to produce large-scale low-cost generic medicaments. The latter two also have the advantage of being major producers of active pharmaceutical ingredients, which most countries where the industry is involved in formulation continue to have to import. Last, but not least, a large number of the world’s poorest remain without access to needed medicines.

#### **D. Imperatives for the local production of pharmaceuticals in developing countries**

##### *1. Global imperatives*

The interest in the local production of pharmaceuticals in developing countries as a means to improve access to high-quality affordable medicaments is manifested in a number of important international and regional declarations.

Most notably, in May 2008, the World Health Assembly, through resolution 61.21, adopted the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI). Drawing upon the findings of the 2006 *Report of the Commission on Intellectual Property Rights, Innovation and Public Health*,<sup>20</sup> GSPA-PHI acknowledged the need to develop new products against diseases affecting developing countries and to increase access to existing health products and medical devices in developing countries. It also highlights the potential contribution of local production of pharmaceuticals, vaccines and diagnostics as part of the solution to increasing access to essential medicines in developing countries and places emphasis on the need to build and improve innovative capacity in developing countries (element 3) and on measures to facilitate the transfer of health-related technologies to developing countries (element 4).

In 2001, the WTO Ministerial Conference adopted the Doha Declaration on the Agreement on Trade-Related Aspects of Intellectual Property Rights and Public Health. The Doha Declaration stated that “the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health”. A compromise to implement paragraph 6 of the Doha Declaration was adopted by WTO Members on 30 August 2003, whereby a system of notifications was established to permit countries to manufacture and export under compulsory licence to countries with insufficient or no manufacturing capacity in the pharmaceutical sector. The system is incorporated as a draft amendment to the TRIPS Agreement (to appear as article 31bis), and formally takes effect upon

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<sup>18</sup> See UNCTAD et al, Ethiopia, Jordan and Uganda Case Studies (2011, forthcoming).

<sup>19</sup> WHO (2006), p. 28.

<sup>20</sup> WHO (2006).

acceptance by two thirds of WTO Members.<sup>21</sup> Some scholars encourage the use of this notification system at the regional level among groups of developing countries.<sup>22</sup>

At the regional level, the European Parliament has urged the EU and its Member States to:

"take additional measures ... to facilitate and increase the production of pharmaceutical products by the developing countries themselves ... [and] to provide concrete financial support for ... local production of pharmaceuticals in all developing countries, especially LDCs ...."<sup>23</sup>

Individual EU Members, such as Germany, have been very active in supporting local production of pharmaceuticals in developing countries with initiatives under their official development assistance umbrella (see table 1 for an exhaustive list of companies that have received German support and comply with good manufacturing practices or are close to it).

**Table 1**  
**Pharmaceutical companies in developing countries**  
**that are supported by German technical assistance and**  
**are compliant with good manufacturing practices, or close to compliance**

<b>Bangladesh</b>	Square Pharmaceutical Ltd., Bangladesh
<b>Cameroon</b>	Cinpharm S.A.
<b>Ethiopia</b>	Cadila Pharmaceutical Ltd.
	Sino-Ethiop Associate
<b>Kenya</b>	Cosmos Limited
	Universal Pharmacy
<b>United Republic of Tanzania</b>	Shelys Pharmaceuticals
	Tanzania Pharmaceutical Industries (TPI)

Source: German Agency for International Cooperation (2011)

These pronouncements are underpinned by a number of more general international imperatives on improved health in developing countries. Adopted in 2000 by the Member States of the United Nations, three of the eight Millennium Development Goals are explicitly devoted to issues of health. Moreover, Goal 8E recognizes the importance of partnership with pharmaceutical companies to increase access to affordable essential drugs in developing countries. The September 2005 meeting of the United Nations General Assembly reiterated the commitment of Heads of State and Government to reach all of Goals by 2015.<sup>24</sup>

<sup>21</sup> See Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, Decision of 30 August 2003, General Council, WT/L/540 of 2 September 2003.

<sup>22</sup> Reichman (2006).

<sup>23</sup> See resolution P6\_TA-PROV (2007) 0353, items 3 and 4, of 12 July 2007 (available from <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2007-0353+0+DOC+XML+V0//EN>).

<sup>24</sup> United Nations (2010).

With respect to international human rights treaties, while there has been no specific reference to local production of pharmaceuticals or access to medicines as such, article 12.1 of the International Covenant on Economic, Social and Cultural Rights codifies the “right of everyone to the enjoyment of the highest attainable standard of physical and mental health”. Article 24 of the Convention on the Rights of the Child recognizes the right of all children to the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health, and mandates that States Parties must strive to ensure that no child is deprived of the right of access to health care services. These provisions have been interpreted as incorporating access to medicines as part of the right to health.

## *2. Health policy imperatives*

Ensuring greater access to affordable, high quality medicines raises many challenges. The world relies to a large extent on the private sector and market dynamics to manufacture medicines that address public health needs. In this regard, a number of developing countries have encouraged the local production of pharmaceuticals as part of an industrial policy.<sup>25</sup> The potential benefits of building a thriving pharmaceutical industry capable of meeting domestic and foreign demand for medicaments are similar to dynamics in many other industries, and include, inter alia, profitability, the ability to create jobs, an inducement to transfer technology and the generation of foreign exchange. The rationale for encouraging local production goes beyond simply supporting a budding local industry, however. What distinguishes the pharmaceutical sector from other industries is the underlying health rationale for local production.

Very few countries in the world, including developed countries, are able to provide their entire supply of medicines for their health needs through local production alone. Thus, most countries must import medicines, but the degree to which countries are able to rely on imports to satisfy their health needs varies. Developed and middle-income countries are able, for instance, to combine both imports and local production to meet domestic health needs. However, LDCs are particularly vulnerable in this regard. As countries that, taken individually, generally do not constitute an attractive market for international private pharmaceutical firms, whether R&D-based or generic, because of limited market size and purchasing power, many private firms generally would not find the prospect of selling pharmaceuticals to an LDC a particularly attractive business proposition. Therefore, LDCs without manufacturing capacity will often be forced to rely on donations and philanthropic initiatives for their supply of quality medicaments.

In some cases, supply may not be able to keep pace with demand. For example, predictions of a severe flu season have often resulted in a spike in demand for certain antiviral drugs, such as Oseltamivir phosphate (commonly known as Tamiflu®), caused in part by the efforts of certain developed countries to stockpile medicines to meet their domestic demand.<sup>26</sup> In this regard, the declaration by WHO of a pandemic of the H1N1 virus during the 2009–10 flu season led not only to a sharp increase in the demand for flu

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<sup>25</sup> The August 2010 Growth and Transformation Plan announced by the Government of Ethiopia, for example, identifies the pharmaceutical sector as a priority sector for the first time.

<sup>26</sup> See, for instance, Roche to suspend Tamiflu shipments to US private sector, *Forbes*, AFX News Limited. 27 October 2005. <http://www.forbes.com/feeds/afx/2005/10/27/afx2305441.html>. Retrieved 17 January 2011. Japan to keep stockpiling Tamiflu, *Sydney Morning Herald*, Reuters. 28 March 2007. <http://www.smh.com.au/news/World/Japan-to-keep-stockpiling-Tamiflu/2007/03/28/1174761539222.html>. Retrieved 17 January 2011.

vaccines, but also for Tamiflu®. Compounding the problem is that wealthier countries will rely on their domestic pharmaceutical firms to meet domestic demand first and can afford to stockpile drugs, while poorer developing countries will not have the resources to do so.

It has been argued that it would make more sense for mass producers of medicines in countries such as Brazil, China and India to manufacture and supply the developing world with inexpensive medicines, rather than trying to develop pharmaceutical production capacity in other developing countries.<sup>27</sup> This paper recognizes that it may not always be possible for other developing countries to produce quality medicines at a cost cheaper than certain mass producers of generic medicaments in the larger developing countries, and that it may not make economic sense for every country to embark on a programme to build a local pharmaceutical industry. The main reasons behind the difficulty experienced by other developing countries in competing on the basis of price, despite potentially lower costs of labour, are first, that most countries will still need to import most raw materials for pharmaceuticals production, including active pharmaceutical ingredients, from China, India or western countries; and second, that it will be difficult to match the economies of scale offered by manufacturers in the two Asian giants. But this is not the end of the story.

Recent research by UNCTAD, WHO and ICTSD shows that firms in the larger developing countries will not always sell their medicaments to the poorer countries of the developing world, even though this may be the most desirable outcome from a purely economic standpoint. While they remain major suppliers of medicines to the developing world, many of the leading firms in China and India are increasingly partnering with developed-country R&D-based pharmaceutical firms and targeting more lucrative markets in the developed world.<sup>28</sup> A case in point is the large generic manufacturers of India. A recently concluded economic partnership agreement between India and Japan, for instance, includes a specific article (article 54) supporting the rapid approval and sale of generic medicaments in the market of the other country, which is probably the first time ever that a preferential trade and investment agreement includes a provision designed to promote the sale of generic medicines.<sup>29</sup> At the same time, Indian firms are becoming involved in local manufacturing initiatives in other developing countries, preferring joint ventures and licensing arrangements over exports with respect to certain drugs.<sup>30</sup> In the longer run, poorer countries may no longer be able to rely on China and India to be the “pharmacy for the developing countries”.

The underlying premise of this guide is therefore as follows: close to two billion persons lack access to essential medicines, attesting to the need to examine the option to produce in countries outside the big developing countries, which offer a feasible base for such production – even if it were cheaper to import at present. This is so because UNCTAD research to date has found that pharmaceutical firms in many developing countries other than Brazil, China and India have been able to successfully become sustainable in their own right, and to produce a range of medicines for their domestic market at a profit and in

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<sup>27</sup> See Kaplan and Laing (2005). In this World Bank study, the authors suggest that because few other developing countries will have the ability to compete in terms of cost with the mass production of pharmaceuticals in countries such as Brazil, China and India, firms in these countries should be left to supply the developing countries with inexpensive medicines.

<sup>28</sup> One example is the 2009 merger by Japan’s Daiichi Sankyo KK of India’s generic firm Ranbaxy.

<sup>29</sup> See the Comprehensive Economic Partnership Agreement between Japan and the Republic of India (2011).

<sup>30</sup> See UNCTAD et al Ethiopia and Uganda Case Studies (2011, forthcoming).



some cases, even export to other markets. Examples of such firms are cited throughout this guide, and include firms from LDCs such as Bangladesh and Ethiopia.<sup>31</sup>

Lastly, this guide recognizes that the local production of pharmaceutical products should not be seen as an end in itself. If undertaken, it should be cost effective and sustainable, taking into consideration other available options. While donations of medicines and other philanthropic initiatives will continue to be important for LDCs, in certain emergency situations, many developing countries are recognizing the importance of ensuring health security and see local pharmaceutical production as one means to achieve this objective. They cannot build productive capacity without the help of foreign firms and their technology, or without the conducive policies adopted by their governments, however. The following chapters address the requisites to develop, and strategies to attract, foreign direct investment into the pharmaceutical sector, particularly at the policy level.

Ultimately, increased access depends upon much more than stepping up local production. The health care system, an effective drug regulatory authority to ensure the quality of the medicines in terms of their safety and efficacy, distribution networks, the availability of insurance, prescription practices of medical professionals and government procurement practices are all relevant factors that affect access. As the emphasis of this guide is on the potential contribution of local production, it is beyond its scope of to discuss these other factors in any detail beyond their relevance to the immediate issue of investment and local production.

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<sup>31</sup> See UNCTAD et al, *Bangladesh and Ethiopia Case Studies* (2011, forthcoming), which cites the examples of Square and Beximco in Bangladesh and the Sino-Ethiop joint venture in Ethiopia.

## ***Chapter 2***

### ***Understanding the Dynamics of Investment in the Pharmaceutical Sector***

#### **A. Prerequisites for investment in the pharmaceutical sector**

As a largely market-driven activity, the pre-conditions for attracting investment will apply to the pharmaceutical sector as it would to any other industrial sector. These include having a relatively open economy, the establishment of rule of law (i.e. the ability to enforce a contract), the ability to repatriate profits, guarantees against arbitrary treatment and the like. This sector has a number of unique features that make it unlike many other sectors typically found in LDCs, however. The scientific complexity of the pharmaceutical production process and the necessary attention to hygiene and quality control for the purpose of meeting health and safety standards make it a sector where a number of prerequisites need to be met before any firm would even consider investing its capital and technology in a firm in another country to produce medicaments.

It is worth reviewing those prerequisites here, because as important as encouraging local production may be for the national public health interest, countries need to realistically assess the likelihood that they will be able, after a number of years, to produce medicines of satisfactory quality and cost for the domestic market. It is also important insofar as countries will want to identify those areas that need to be strengthened in order to have a reasonable chance at attracting foreign direct investment into the local pharmaceutical sector.

##### *1. Human resources*

Perhaps more than any other factor, it is important for a country that is trying to maintain and expand local pharmaceutical production capacity to have a critical mass of skilled human resources. These include pharmacists, but also include graduates from universities with chemistry and biochemistry degrees, as well as technicians who are experts in the use of precision scientific equipment and engineers that are familiar with the machinery used to manufacture medicines and quality control and quality assurance processes. Staff with this background is required regardless of whether a firm is involved in R&D or simply formulating. While heavily automated, the required safekeeping protocols for input chemicals and the tests involved for quality assurance and quality control call for a far more educated pool of human resources than would be required of, for example, a garment factory. Key indicators in this regard include whether the country has a pharmacy faculty in its university and the numbers of graduates in the sciences, particularly in pharmacy, pharmacology, chemistry and biochemistry. The quality of scientific education in the country therefore is very important and investors will be looking for whether there is a critical mass of human resources with the appropriate scientific background to hire as local staff. It is no coincidence that LDCs that have been

able to attract investors in the pharmaceutical sector all have a relatively strong pharmacy faculty at their leading national universities.<sup>32</sup>

Equally important as having a critical mass of human resources in certain sciences is having human resources with good business and managerial skills. The ability of a developing country pharmaceutical firm to sustainably generate revenue to cover costs depends on a wide range of managerial skills, including factory management, distribution, as well as sales and marketing. Therefore, investing firms will also be looking to see if a country has business management schools at its universities, as well as whether graduates of foreign business schools are returning to manage local companies.

## *2. Basic infrastructure – reliable power and clean water*

A pharmaceutical firm will not be able to obtain marketing authorization for their products from a national drug regulatory authority in the absence of satisfactory proof that both their factory and their outputs meet an acceptable quality standard. Periodic machine failures and impurities greatly affect the consistency and quality of the medicines produced. Many input chemicals and output pharmaceuticals need to be kept at specific temperatures and moisture levels, and otherwise free of contamination. As a result, potential investors will look closely at whether other factories in the country have a reliable source of electricity and access to clean water.

Both electricity and clean water can be problematic in the developing country context, and especially in LDCs. One way to address this issue is to set up special industrial zones that have access to independent sources of electricity if the local grid is unreliable, as well as to reliable water purification facilities. Alternatively, or in addition, companies may also set up their own water purification facilities and electricity generators at factory sites.

## *3. A functioning national drug regulatory authority*

As noted in chapter 1, each country has its own drug regulatory authority, which is usually an agency under or affiliated with the Ministry of Health. The reputation of the domestic pharmaceutical industry can either be helped or hindered by the capacity of that drug regulatory authority. The reason should be self evident: a poor drug regulatory authority makes it more likely that substandard medicines are made available on the market, while a well-functioning one ensures that the medicines produced locally –or imported – are in accordance with good manufacturing practices.

It is true that individual firms can attempt to meet external quality standards, such as the WHO good manufacturing practices, quality standards applied in developed country markets such as the European Union, Japan or the United States, or otherwise certified by major developed-country-based pharmaceutical manufacturers, notwithstanding the regulatory review of the local drug regulatory authority. Firms in Bangladesh, such as Beximco and Square, for example, have been certified as having met good manufacturing practices and are certified by some multinational pharmaceutical companies for a number of their products. Meeting these standards will likely also mean that local standards applied by the drug regulatory authority have been met or exceeded.

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<sup>32</sup> For example, in Bangladesh, a pharmacy school was established at the University of Dhaka in 1964. Uganda's Makerere University has a department of pharmacology in its medical school.

In this regard, a well-functioning drug regulatory authority may not necessarily have a great impact on a decision to invest in a particular firm. However, from the perspective of trying to encourage foreign direct investment into the local pharmaceutical industry more broadly, the collective reputation of the local industry depends on the existence of firms that have been subject to rigorous scrutiny and for which the domestic population can rest assured that medicines on the market meet an acceptable level of safety and quality.

Further, a well-functioning drug regulatory authority can also assist the local pharmaceutical firms by providing relevant information and assistance regarding issues of technical compliance required for regulatory approvals, conduct training on the preparation of pre-qualification dossiers and other issues that often represent significant hurdles for smaller firms. However, ensuring the operation of a well-functioning drug regulatory authority is not necessarily an easy task in the LDC context, as these agencies are often under-resourced and understaffed – and also reinforces the need for qualified human resources, as mentioned previously.

Lastly, a well-functioning drug regulatory authority also builds confidence among exporting countries, which is critical for accessing foreign markets whereby the manufacturers of the exporting country has to fulfil the regulatory requirements of not only its national drug regulatory authority but also the requirements set by the drug regulatory authority of the importing country. The drug regulatory authorities in the developed countries generally have much higher quality standards than those required by those in LDCs.

#### *4. Timely and cost-effective access to key inputs, especially active pharmaceutical ingredients*

With the exception of firms in China and India, pharmaceutical companies in developing countries generally depend upon the importation of the raw materials needed for pharmaceutical production.<sup>33</sup> This is particularly true in the case of the active pharmaceutical ingredients in medicines, which accounts for most of the input raw material cost incurred by firms in the drug production process. Government initiatives to enable the local production of antiretrovirals in Indonesia by a state-owned pharmaceutical firm through the issuance of government-use licences have been discontinued mainly because of the inability to procure active pharmaceutical ingredients at a reasonable cost, for example.

Most developing countries involved in the production of generic medicines source their active pharmaceutical ingredients from China and India. While this may mean that it will be difficult to manufacture medicaments at a lower cost than in these two countries, several other labour and infrastructure cost advantages may help low-cost manufacturing in other developing countries. Concerns have emerged over the rising cost of labour in China and India. However, efforts are being made to build local capacity to manufacture some active pharmaceutical ingredients in other developing countries, most notably in countries such as Argentina and Bangladesh.

Efforts to contain the cost of active pharmaceutical ingredients and to diversify sources of active pharmaceutical ingredients are addressed in chapter 3 below. It should be borne in

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<sup>33</sup> See UNCTAD et al, case studies (2011, forthcoming).

mind, nonetheless, that active pharmaceutical ingredients are a key input cost that investors in the pharmaceutical sector will certainly keep in mind.

## **B. Drivers and determinants for investment in the pharmaceutical sector**

The global pharmaceutical landscape has been changing rapidly. While pharmaceutical companies appear to be less affected by the global financial crisis which began in 2008, the larger R&D-based pharmaceutical transnational corporations have been put under significant pressure by the expiry of patents on a number of their leading drugs, eroding the profit margins made possible by the exclusion of generic competition during the patent term. Table 2 presents the expiration dates in the United States for a number of the so-called blockbuster drugs, as well as other major drugs, for which the R&D-based pharmaceutical transnational corporations in developed countries hold the patent.

**Table 2. The patent cliff: patent expiration dates of major products for R&D-based pharmaceutical transnational corporations**

Patent Owner	US Drug Name	Used in Treatment for	US Patent Expiry
Abbott	Kaletra®	HIV/AIDS	2016
	Norvir®	HIV/AIDS	2014
Astellas	Prograf®	transplant rejection	2008
	Protopic®	dermatitis	2014
	VESIcare®	overactive bladder	2015
AstraZeneca	Crestor®	cholesterol	2016
	Symbicort®	asthma	2012
	Seroquel®	schizophrenia	2012
Boehringer Ingelheim	Flomax®	prostatic hypertrophy	2009
Bristol-Myers Squibb	Efavirenz	HIV/AIDS	2012
Daiichi Sankyo	Cravit	infectious disease	2010
	Mevalotin	Cholesterol	2006
	Olmotec	high blood pressure	2016
Eisai	Aricept®	Alzheimer's	2010
	AcipHex®	gastroesophageal reflux	2013
Eli Lilly	Zyprexa®	schizophrenia	2011
GlaxoSmithKline	Epivir®	HIV/AIDS	2014
	Relenza®	influenza	2014
	Seretide/Advair®	asthma	2010
	Hycamtin®	cancer	2010
Johnson & Johnson	Cozaar®	hypertension	2010
Merck	Diovan®	hypertension	2012
	Singulair®	asthma	2012
Novartis	Zometa®	cancer	2013
Pfizer	Lipitor®	cholesterol	2011
	Viagra®	erectile dysfunction	2012
	Xalatan®	glaucoma	2011
Sanofi-Aventis/ Bristol-Myers Squibb	Plavix®	anticoagulant/heart disease	2012
Sanofi-Aventis	Taxotere®	breast cancer	2013
Takeda	Actos®	diabetes	2011
	Blopress®	high blood pressure	2012
	Leuprorelin	prostate cancer	2014
	Prevacid®	Ulcer	2009

*Notes:* Trademark registrations compiled by UNCTAD from the United States Patent and Trademark Office, Trademark Electronic Search System; patent expiry dates compiled by UNCTAD from various sources, including investor reports and Internet searches (2011), and from Ito (2010).

In response, producers of pharmaceuticals, both R&D based and generic, have been restructuring, investing, divesting and entering into alliances practically all at the same time. Policymakers interested in attracting foreign direct investment into the local pharmaceutical sector need to be aware of these changes, as it will help shape a policy response and strategy that will make the country more competitive in this field.

Earlier UNCTAD research suggested a framework for analysing the investment patterns in various sectors,<sup>34</sup> where profit-driven firms invest from an economic standpoint (a) to seek a market; (b) to obtain resources or strategic assets; or (c) to seek efficiencies, or (d) some combination of the above. Also equally important are the overall policy framework for investment and active business facilitation efforts. In order to better understand the current patterns of investment in developing country pharmaceutical firms, the following section examines specific examples of investment in developing countries using this model.

### *1. Market access*

The potential to sell to the large emerging economies such as Brazil, China and India are of great interest to transnational corporations. The existence of a large market is one of the main motives for foreign direct investment by the large R&D-based pharmaceutical firms from developed countries to establish factories to produce medicines in China. For example, Western transnational corporations such as GSK and Pfizer, as well as Japanese pharmaceutical firms such as Eisai and Takeda, have all established factories in China to produce their products and to sell them to the Chinese market. Likewise, Novartis has set up factories in India. Such decisions should come as no surprise, given the size of these markets and the phenomenal growth of their economies over the last decade.

What is perhaps less widely known, however, is that the large pharmaceutical transnational corporations have also been establishing and maintaining factories in smaller emerging markets, with the hope of profitably selling to that market in the longer term. A key example is the two Japanese pharmaceutical firms mentioned above. Eisai has factories in Taiwan (Province of China) as a manufacturing base for exports of its products to South-East Asia, and Indonesia, where it has maintained a factory in that country since the 1970s with a view to selling to the local market. In contrast, Takeda supplies the larger South-East Asian market from a manufacturing base in Indonesia.<sup>35</sup> According to Brian Tempest, the former chief executive officer (CEO) of India's Ranbaxy, pharmaceutical companies understand the importance of establishing presences in markets across developing Asia.<sup>36</sup>

Neither is the drive to access those emerging markets through local production limited to the efforts of R&D-based pharmaceutical transnational corporations in the developing countries. Generic pharmaceutical firms are also investing in local production for similar reasons. The decision of Cipla, a major generic pharmaceutical manufacturer in India, to invest in a factory to produce antiretrovirals in Uganda was based in part on the vision of its CEO that the new facility could serve as a manufacturing base for providing the East African Community countries<sup>37</sup> with a reliable supply of low cost, high-quality AIDS

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<sup>34</sup> UNCTAD (1998), p. 91.

<sup>35</sup> UNCTAD et al, Indonesia Case Study (2011, forthcoming).

<sup>36</sup> UNCTAD-ICTSD Policy Brief (2011, forthcoming).

<sup>37</sup> Burundi, Kenya, Rwanda, the United Republic of Tanzania and Uganda. All but Kenya are LDCs.

medicines.<sup>38</sup> Under the agreement to establish Quality Chemicals, Cipla shares equally in the profits of the firm, while holding a minority share of the joint venture.

Recent mergers and acquisitions in the pharmaceutical industry are also driven by the desire of pharmaceutical firms to access new markets. The 2008 acquisition by Japan's Daiichi Sankyo of India's largest generic manufacturer, Ranbaxy, appears to have been in part by a strategy to gain access to the worldwide distribution network that the latter has in the developing world (49 countries). United States-based Abbott's acquisition of India's Piramal and GSK's acquisition of a minority share of South Africa's Aspen Pharmaceuticals appears to be driven by similar concerns (Aspen is a leading African generics manufacturer). While greater access to various potential blockbuster drugs in the pipeline is thought to drive much of the mergers and acquisitions among the R&D-based transnational corporations and/or those transnational corporations and certain biotechnology companies, at least part of the desire by Merck of its 2009 acquisition of Schering-Plough appears to have been the former's desire to make use of the latter's distribution network in the emerging economies.<sup>39</sup>

By the same token, firms will divest if they see that markets are too small and can better be serviced from another location, most likely in the same region, more cost efficiently. For instance, the major R&D-based transnational corporations built factories in Colombia during the 1940s and 1950s. During the 1990s and 2000s, however, a large number of them divested – from 100 factories in 1995 down to only 10 in 2010 – choosing instead to service the local market from other countries in the region, conclude licensing arrangements with local firms or export directly from the home country to Colombia.<sup>40</sup>

## *2. The quest for strategic assets*

The expiration of patents on which many of the R&D-based pharmaceutical transnational corporations relied has led to a trend to acquire firms that are developing potential drugs, also known as pipeline drugs. Most notable amongst these deals are Roche's acquisition of Genentech and Sanofi Aventis' acquisition of Genzyme. The larger firms have shown particular interest in smaller firms working in biotechnology, including fields such as monoclonal antibodies, genetic engineering and vaccines. Most of this type of research takes place in developed countries, however, with few exceptions.<sup>41</sup>

The other means by which the largest pharmaceutical transnational corporations have sought to remain competitive is by acquiring or merging with generic pharmaceutical firms to expand their portfolio of products beyond the patent-protected blockbusters. The acquisition of Ranbaxy by Daiichi Sankyo and the acquisition of Piramal by Abbott cited in the section above can also be seen in this light. These deals provided both Daiichi Sankyo and Abbott with a new portfolio of generic medicines.<sup>42</sup> In this regard, the merger

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<sup>38</sup> UNCTAD et al, Uganda Case Study (2011, forthcoming).

<sup>39</sup> For an analysis of the Daiichi Sankyo-Ranbaxy and Merck-Schering-Plough mergers, see chapters 5 and 6, Ito (2010).

<sup>40</sup> UNCTAD et al, Colombia Case Study (2011, forthcoming).

<sup>41</sup> A notable exception may be vaccines research, where the genetic material is found to a greater extent in developing countries, as in the case of H5N1 avian flu.

<sup>42</sup> Daiichi Sankyo seems to have put this portfolio to good use by introducing a generic version of its competitor Eisai's drug Aricept in the United States immediately following the expiry of the underlying patent. The generic drug was produced by Ranbaxy. Aricept is used to treat Alzheimer's disease. See *Nihon Keizai Shimbun*, 29 December 2010, p. 11.

between Ciba and the generics firm of Sandoz to form Novartis in 1996 was an early precursor of these recent developments. The type of strategic assets sought by the larger transnational corporations is unlikely to be a major concern for LDCs, however.

This does not mean, though, that there are no strategic asset-seeking investments in this sector of relevance to LDCs. Some Chinese companies have sought avenues to produce pharmaceuticals in other developing countries for reasons of risk reduction. One example that stands out is the decision by Dandong Jinwan Group and China Associates Group to partner with an Ethiopian distributor to establish a factory for the manufacture of hard gelatin capsules, which is an excipient. An important motivation for this investment was to reduce the risk of spoilage involved in transporting the capsules from China to African manufacturers by producing them closer to home. The resulting joint venture, Sino-Ethiopian Associate (Africa) Private Limited Company, not only supplies empty capsules to Ethiopian manufacturers, but now supplies capsules to firms across Africa and the Middle East.

### *3. Seeking efficiency*

As is evident from the discussion above, the pharmaceutical industry has been undergoing a sea change. Most of the larger transnational corporations have announced consolidations in recent years.<sup>43</sup> One area in which the larger transnational corporations have sought to take advantage of efficiencies and lower costs in an effort to consolidate is by moving some of their R&D activities to China and India. Novartis, for example, has established a biomedical research centre in Shanghai. The company GSK also has an R&D facility in Shanghai, and has recently opened two R&D centres in India. While advances in technology have made it possible to operate R&D platforms across multiple jurisdictions, the ability of countries such as China and India to attract R&D facilities attests to the high calibre of available local human resources in the relevant sciences at competitive rates and the increasing preference of local professionals to be closer to home while in a dynamic economic setting. The expertise that Indians have developed in reverse engineering in particular has been of interest to R&D-based companies as they seek to expand into the generics market as a strategy to remain competitive. This skill is critical for developing new generic products from originator drugs; this an area where some developing countries that have nurtured the skill have a competitive advantage.

It should also be noted that firms need not rely exclusively on integrated R&D facilities. More and more firms are researching on open platforms and conducting joint R&D activities, both among firms and with government and university research institutions.

### *4. Key policy determinants*

The above sections indicate that there has been a clear trend towards diversification of the industry in terms of products, places of production and R&D, and target customers, in response to, inter alia, the pressures faced by the expiration of patents held by larger firms in developed countries. The landscape for pharmaceutical production has also been shaped by the policy environment, both at the international and national levels. This section examines the key policies that have demonstrably affected the pharmaceutical production and investment landscape.

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<sup>43</sup> Such consolidations started even before the financial crisis.



*Drug registration requirements.* Pharmaceuticals are a heavily regulated industry, and for good reason. Products are ingested, injected, applied topically and so forth; they therefore need to be proven efficacious, safe and quality controlled. Drug regulatory authorities ensure that firms under their jurisdiction comply with these standards. They are also responsible for gauging the demand for and helping to ensure the supply of essential medicines in the country. Countries differ widely on how pharmaceuticals are regulated, however, and the scope of regulation may greatly affect the incentives for local and foreign firms. Selected examples of the impact of certain drug regulations on local production and foreign direct investment are examined below.

Drug regulatory authorities have the responsibility to register those drugs that will be allowed to be marketed in their specific countries, and depending upon the domestic law, also for export. They are also responsible for verifying compliance with good manufacturing practices by manufacturers. Those drugs that are not registered and produced in a good manufacturing practices-compliant facility cannot be distributed. Registration must satisfy certain requirements, including having met applicable laboratory, clinical and bioequivalence tests for safety, consistency, quality and the like. Good manufacturing practices approval should meet technical requirements with respect to the handling of raw materials, manufacturing and packaging processes, treatment of water for use in the production process, air-quality and quality-control equipment and systems.

Changes in drug registration policies have often had a significant impact on the domestic landscape for pharmaceutical production in some developing countries. For example, the Bangladesh National Drug Policy of 1982 deregistered all medicines that had been classified as non-essential or useless, and introduced for the first time an essential medicines list. This action, however, ended up deregistering a significant part of the portfolio of products held by the R&D-based transnational corporations, relegating them to producing mainly injectable vitamins after 1982. Moreover, foreign companies that do not have their own production facility in Bangladesh are not allowed to market their products, even if they are manufactured in the country by contract manufacturing. As a result of this policy action, most of the R&D-based industry sold their factories to local investors, and local firms now control over 70 per cent of the local pharmaceutical market.<sup>44</sup>

Indonesia's Ministry of Health issued in late 2008 Decree No. 1010, requiring every company to manufacture every one of its pharmaceutical products in Indonesia, failing which, their registrations would eventually be withdrawn. Foreign firms that are importing drugs will be classified as pharmaceutical wholesalers – they lost their registration rights for their products after a grace period of two years following the issuance of the Decree. Imported pharmaceuticals can be registered by local pharmaceutical companies with written consent from a foreign company, which must include technology transfer to allow local manufacturing within five years.<sup>45</sup> Decree 1010 applies to all products earlier policies that required pharmaceutical firms to establish factories for local manufacture as a prerequisite for the right to distribute in Indonesia, subject to certain exceptions. The Indonesian policies have in part contributed to greater domestic investment in and the control of a predominant share of the pharmaceutical market by local firms. Given the size of Indonesia's market and its potential for growth, however, many Western and Japanese R&D-based pharmaceutical transnational

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<sup>44</sup> UNCTAD et al Bangladesh, Case Study (2011, forthcoming).

<sup>45</sup> UNCTAD et al, Indonesia Case Study (2011, forthcoming).

corporations have established factories in Indonesia and intend on staying in spite of the Decree.

*Drug pricing.* Pricing policies can have a major impact on the economic decisions of pharmaceutical firms, both in terms of trade and investment. Those prices are often determined by the drug regulatory authority, often in consultation with the industry.

An interesting example of this is in Jordan, where price controls target certain essential medicines. For these medicines, the public price of imported medicines is determined according to the corresponding price at which the product is offered in the home market, plus cost and profit margins for those importers and distributors. While a profit margin has been factored into this equation, the effect of this control, together with a strong regulatory framework, has been generally higher prices in Jordan for pharmaceuticals. Chinese and Indian manufacturers have in large part refrained from entering the Jordanian market, as they would have to meet strict Jordanian good manufacturing practices, while offering their products at close to Chinese and Indian prices, respectively, resulting in lower profit margins than their Jordanian counterparts.<sup>46</sup> One should therefore be conscious about the possible effect that price controls may have, both on investment and on the competitiveness of domestic firms.

*Intellectual property.* With the adoption of the TRIPS Agreement in 1994 as part of the set of treaties to which aspiring WTO Members needed to adhere, most of the world became obliged to make available the possibility of obtaining a patent for pharmaceuticals. Countries that had excluded patent protection for pharmaceuticals, which included both developing countries such as India, and developed countries in the past such as Switzerland, could no longer continue not to offer the possibility of product patent protection for new chemical entities.

The TRIPS Agreement did not, however, lead to a completely uniform system of patents – nor was it designed to do so. Instead, by implementing the Agreement through national legislation, countries were allowed flexibilities to tailor the patent system to their particular needs. Additionally, developing countries that had heretofore not offered the possibility enjoyed a transition period until 1 January 2005 and LDCs, until 1 January 2006 – which has now been extended until 1 January 2016, to provide for the possibility to obtain patents for pharmaceuticals under the TRIPS Agreement. Thus, because of these disparities, patent systems remain nationally based to a large extent, and what is patentable in one country is not necessarily patentable in another.<sup>47, 48</sup> Adding to the complexity is that R&D-based pharmaceutical firms have generally sought to seek patent protection for new chemical entities in jurisdictions where they have a potential market for good returns, but have generally not sought patent protection in other markets.

The landscape for the production of generic medicines in developing countries has been heavily influenced by this complexity. India, for instance, had not offered patent protection for pharmaceutical products since the 1970 Patent Act and until the implementation of the TRIPS Agreement. It successfully nurtured a pharmaceutical industry that was home to some of the world's largest manufacturers of generics,

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<sup>46</sup> UNCTAD et al, Jordan Case Study (2011, forthcoming).

<sup>47</sup> This concept is called the independence of patents and is codified in article 4bis of the Paris Convention for the Protection of Industrial Property.

<sup>48</sup> While the Patent Cooperation Treaty administered by the World Intellectual Property Organization makes it easier to file patents in multiple jurisdictions, it is not designed as a tool to offer a worldwide patent on inventions that meet patentability criteria.

including giants such as Cipla, Dr. Reddy's and Ranbaxy. In order to support the local generic industry, the Indians developed a capacity for reverse engineering. This enabled them to produce generic equivalents of even the more complex molecules produced by originator companies. They could then offer them for sale to markets where there was no patent protection for those molecules, either because protection was not available under the local patent law, the originator did not seek patent protection in that jurisdiction, or the originator filed an application for patent protection that eventually failed to obtain protection. The recent introduction of patent protection for pharmaceutical products in India is expected to change the landscape over the coming years, however. The local industry is currently in a state of flux, with the acquisition of major generic companies by R&D-based transnational corporations. Further, the development of both Argentina's and Brazil's generic industry is also attributable in part to the absence of pharmaceutical patents in the pre-TRIPS era.<sup>49</sup>

Meanwhile, certain LDCs are positioning themselves as possible manufacturing bases for generic medicines in light of the transition period they enjoy until 2016. Bangladesh, for instance, has indicated that it has no intention of introducing patent protection over pharmaceutical products until the expiration of the transition period, and is leading a campaign to obtain an extension of the transition period. It has built a relatively large domestic pharmaceutical industry that produces a wide range of generic medicaments, catering mostly to domestic demand, but also seeking to export to other countries where their products are off patent.<sup>50</sup> As mentioned above, the joint venture between Cipla and Quality Chemicals to produce antiretrovirals in Uganda is also driven by the transition period available to LDCs under the TRIPS Agreement.<sup>51</sup>

While the existence or absence of pharmaceutical patents is underlined here as an initial question in the decision to invest, the relative attractiveness of a country as a base to manufacture generic medicines may depend on a wider range of intellectual property considerations. A range of flexibilities under the TRIPS Agreement are of relevance to generic manufacturers, including appropriate safeguards protecting undisclosed data, which have a broad research exception to the patent law and the possibility of introducing precise and more elaborated patentability criteria, to name a few. It is beyond the scope of this guide to discuss all of them here, however, as other literature addresses these flexibilities at length.<sup>52</sup>

*Restrictions on investment.*<sup>53</sup> Some countries prohibit foreign investment or place a cap on foreign investment in certain sectors. Such restrictions on the pharmaceutical sector generally tend to be justified on the grounds of public health. This type of restriction, often called a "negative list" obviously has an impact on the overall composition of domestic and foreign firms within a country. Most countries now permit the full ownership of pharmaceutical manufacturing operations by foreign investors, with only a handful of exceptions.<sup>54</sup> For example, Indonesia limits foreign ownership of

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<sup>49</sup> UNCTAD et al, Argentina Case Study (2011, forthcoming).

<sup>50</sup> UNCTAD et al, Bangladesh Case Study (2011, forthcoming).

<sup>51</sup> UNCTAD et al, Uganda Case Study (2011, forthcoming).

<sup>52</sup> See, for example, UNCTAD (2011) and South Centre (2008).

<sup>53</sup> Aside from these sectoral restrictions, a number of other restrictions could exist that may affect a firm's ability to operate, including, for example, requirements that the CEO or directors of a firm must be a host country national and requirements that restrict the use of foreign labour.

<sup>54</sup> This is not necessarily the case for retail sales of pharmaceuticals; however, many countries still restrict the activities of foreign firms.

pharmaceutical companies to 75 per cent of all shares.<sup>55</sup> The United Kingdom's Industry Act prohibits the transfer to foreigners of 30 per cent or more of the shares of important British manufacturing businesses, which include the manufacture of pharmaceuticals. A number of countries still maintain restrictions on foreign ownership of companies engaged in the retail sale of pharmaceuticals.

### *5. Business facilitation and investment promotion determinants*

The ability to attract foreign direct investment can be helped or hindered by certain business facilitation efforts. A number of countries have identified pharmaceuticals as a key industrial sector or as a target sector for investment. This has led to important policy actions as well as investment promotion efforts, especially by LDCs that seek to leverage their competitive advantage in not having to offer patent protection for pharmaceuticals until 2016. Specific incentives will be examined in detail in chapter 3 below. It suffices for the purposes of this chapter to highlight a few countries that are making a conscious effort to build a local pharmaceutical sector through foreign direct investment.

*Ethiopia.* Among LDCs, Ethiopia has been considered as having potential to manufacture quality medicaments at a reasonable cost for both the domestic and export markets.<sup>56</sup> Its most promising pharmaceutical companies have received technical assistance, most notably from the Government of Germany and the United Nations Industrial Development Organization (UNIDO), and the wider industry has benefited from multilateral capacity-building efforts, including from UNCTAD.<sup>57</sup> As a culmination of various reform efforts in the pharmaceutical sector that have been taking place since 2007, the Ethiopian Government has now included the pharmaceutical manufacturing sector as a priority sector for industrial development and investment for the first time in its August 2010 Growth and Transformation Plan. This categorization will make it easier for local firms in the sector to receive priority treatment for access to credit, tax holidays, upgrades of infrastructure and availability of technical support and technology transfer.

*Uganda.* The Government actively supported efforts to broker a deal that established a joint venture between Indian firm Cipla and the local distributor Quality Chemicals (chapter 3, box 1, examines the set of incentives offered in detail).

*Zambia.* Steps are being taken to attract Indian pharmaceutical companies to move their generic operations to the country. As part of overall investment promotion efforts, UNCTAD, the Japanese Bank for International Cooperation (now part of the Japan International Cooperation Agency) and the Ministry of Commerce, Trade and Industry organized a joint investment forum in Lusaka in 2007 to showcase domestic pharmaceutical capabilities for Asian pharmaceutical companies.

### *6. Humanitarian and moral determinants*

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<sup>55</sup> Many of the R&D-based pharmaceutical firms with factories in Indonesia are wholly owned subsidiaries and were established prior to the restriction.

<sup>56</sup> See Von Rosenstiel (2007).

<sup>57</sup> In 2007, UNCTAD provided advisory services to Ethiopia on the use of TRIPS flexibilities for local pharmaceutical production and in 2008, UNCTAD assisted the authorities of the Oromiya region in better exploiting efforts to attract investment into pharmaceutical firms in the region.

Aside from strictly economic motives, humanitarian concerns can also potentially influence the decision to invest in the production of pharmaceuticals locally. As noted in chapter 1, there have been a number of international and regional decisions that reiterate support for the local production of pharmaceuticals in developing countries. The support provided by bilateral and multilateral technical assistance programmes – such as the German initiative – to the production of pharmaceuticals in certain developing countries, shows that local solutions can be found to address certain health crises, such as HIV and AIDS (see chapter 1, table 1).

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This section examined the prerequisites of pharmaceutical manufacturing and the motivations for investment in the sector, with particular reference to developing countries and LDCs. This understanding is important when weighing the set of options that can be used to maximize the chances of successfully increasing foreign direct investment into the sector, with a view to improving access to medicines in the country. Those options are examined in chapter 3 below.

## ***Chapter 3***

### ***A Concise Guide for Least Developed Countries Seeking to Attract Foreign Direct Investment in the Pharmaceutical Sector***

The final chapter presents possible elements for a coherent package to attract foreign direct investment into the pharmaceutical sector in developing countries, LDCs in particular. This chapter will begin by examining the importance of government support and the institutional framework for promoting foreign direct investment into the pharmaceutical sector. The following section discusses how development dimensions can strategically be integrated into investment promotion efforts, the choice of local firms to support and the investors to target. The prerequisites for local production are reviewed and the role of investment promotion agencies and incentives are examined.

#### **A. Why government support is important**

If investment decisions are primarily market driven, is there a rationale for governments and its agencies or ministries to become involved? Is it not sufficient for market forces to dictate where resources are allocated to produce medicines globally? The need for government support, at least where LDCs are concerned, is that investment in this sector will not come on its own. The discussion in chapter 2 about the prerequisites for pharmaceutical production is particularly important in the LDC context. Most LDCs lack resources and will lag behind other developing countries in the capacity to offer the appropriate infrastructure and human resources to ensure sustainable production of quality pharmaceuticals at low cost. The few LDCs that are currently producing such medicines are also only just able to do so. Therefore, regardless of how attractive LDCs may be to generic manufacturers that are eyeing the possibility to develop generic versions of medicines that are patented elsewhere as a result of the TRIPS Agreement exemption, investors will need assurances by government that the basic prerequisites for the manufacture of high-quality medicaments at a reasonable cost are possible in the country in question.

Governments are responsible for creating a policy environment that either encourages or discourages foreign direct investment into local production. Additionally, they can induce investment through incentives that lower the cost or risk for the investor, or both. As pointed out at the beginning of this publication, there is a need to correct the clear inadequacy of the current model of pharmaceutical production and distribution – despite gains in the past 10 years, close to 2 billion people around the world remain without access to essential medicines. From a public health perspective, to the extent that an LDC intends to pursue local production, government intervention will be needed to help ensure that efforts to attract foreign direct investment into the sector meet the real health needs of the country and/or the region.

Efforts to attract investment into a sector may be embodied in a promotion strategy centred on a number of key messages and well-coordinated actions. In this regard,

investment promotion agencies will often have an important role in a government's efforts to support foreign direct investment in the local production of pharmaceuticals, acting as a catalyst in promoting several industrial policy objectives.<sup>58</sup>

The following sections examine what key elements need to be contained in a possible strategy. However, no strategy is fool proof, and there is no guarantee that any promotion strategy that is employed will be successful. There is much that can be learned from current efforts to promote investment, whether domestic or foreign, into the local production of pharmaceuticals.

***Key point***

- Investment in the pharmaceutical sector will not come on its own, especially for LDCs; concerted efforts led by government will be necessary for countries that seek to attract foreign direct investment and technology transfer.

**B. Institutional framework for supporting local production**

While government support will be important for efforts to attract foreign direct investment and technology transfer into the domestic pharmaceutical sector, the public-sector institutional framework for supporting the local production of pharmaceuticals is likely to be spread out over a number of different agencies and ministries in a given country. This is true for both developed and developing countries.

With regard to health, key agencies will include the Ministry of Health and the drug regulatory authority. Both institutions are important actors in shaping medicines policy and in assessing the extent to which they believe local firms can improve the access situation in the country. The drug regulatory authority is also responsible, inter alia, for implementing policies concerning the marketing authorization of medicines in the country and is likely to provide important inputs into the formulation of national policy. Since many LDCs have a weak drug regulatory authority, bilateral and multilateral technical assistance needs to scale up activities to improve staff capacity and infrastructure.

Where economic issues are concerned, the ministries and agencies responsible for trade, industry and investment all have roles to play to the extent that the local pharmaceutical sector has been identified by the country as an important sector for the country's development. The investment promotion agency may be responsible for setting and administering incentives for the pharmaceutical industry; it may act as a processing window for necessary permits for investors. Customs and trade ministries set and administer policies with respect to export and import tariffs. Tax concessions are likely to be administered by the national revenue authority. Industrial incentives and support structures are set out by the industrial policy framework of a country, which includes policies relating to science, technology and innovation; education and other infrastructures. Finally, patent granting is undertaken by the intellectual property office

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<sup>58</sup> Investment promotion agencies are certainly not the only institutions that are involved or lead efforts to promote investment, as not all countries have such entities. The President's office, the Ministry of Commerce or the Ministry of Industry may lead such efforts. The issues raised in this chapter apply equally to any government institution leading efforts to promote the local production of pharmaceuticals through a coherent strategy.

and may influence the decision on the extent to which certain TRIPS Agreement flexibilities are made available.

Because the institutional framework is likely to be fragmented, any effort to attract foreign direct investment and technology transfer into building a local pharmaceutical sector will require close communication between these ministries and agencies, as well as internal coherence within each of these ministries and agencies. As each agency and ministry will see the problem through their own expertise and mandates, it is important that all actors understand the imperative of supporting local production in this sector and agree on the strategy employed to attract foreign direct investment and related technology transfer. It is therefore critically important for all key agencies and ministries to agree, for example, on which medicines they seek to produce locally and why – given the country’s public health needs – and to identify potential investors and local partners.

***Key point***

- Because the institutional framework for the regulation, manufacture and distribution of pharmaceuticals is fragmented, key ministries and agencies will need to agree on the rationale and strategy for promoting local production through improved coordination and policy coherence.

**C. Incorporating the development dimension**

When examining the details of how to attract foreign direct investment into the local pharmaceutical industry, it is easy to lose track of why this is an important public health imperative in the first place. Local production is not an end in itself. Developing countries seek greater access to high-quality, reasonably priced medicines. Developing countries wish to be assured that when faced with pandemic situations, the larger producer countries will not try to hoard medicines and vaccines solely for their own populations. Developing countries want medicines that address medical problems in their country. The existence of local firms that produce medicines is supposed to help tackle these issues.

The mere existence of a local pharmaceutical industry supported by foreign investors will not, in and of itself, guarantee that any particular pharmaceutical investment project will yield these desired development benefits. As stated many times in this guide, pharmaceutical production is essentially a private-sector activity, despite its major impact on public health, and it should not be assumed that generic companies, local or foreign, would act any differently in trying to maximize profits than their R&D-based transnational corporation counterparts in the developed countries. Moreover, pharmaceutical production is a complex process and it will take more than increasing the available stock of medicines to see the desired development gains materialize.

The premise of this publication is that the development dimension needs to be properly appreciated by all domestic stakeholders and incorporated into the investment deal negotiations from the outset. Moreover, within an LDC, the burden of incorporating the development dimensions into a deal will necessarily lie primarily with the multiple government agencies and ministries mentioned above, since the firms in question are first and foremost responsible toward their shareholders. From a negotiation standpoint, it therefore makes sense for those development dimensions to be addressed in the context of the discussions involving the basic policies they need in place to support local production



and the incentives to be granted to attract investors. Donor governments need to be aware of these dimensions when supporting projects as well.

The following are four important issues from a development and public health perspective, which are relevant in the context of a decision to try to leverage foreign direct investment into the local production of pharmaceuticals.

*1. Which medicines should be produced, and for whom?*

The WHO 2008 GSPA-PHI makes it clear that there is lack of access to essential medicines and vaccines in developing countries, as well as a lack of treatments, especially for neglected diseases affecting developing countries disproportionately. For this reason, efforts to encourage local production in developing countries should focus on those essential medicines that are in short supply, as well as medicines to treat other poverty-related, tropical and neglected diseases (i.e. those that affect developing countries and are in short supply). For instance, the Cipla-Quality Chemicals joint venture in Uganda cited above produces antiretrovirals in a country where the prevalence of HIV/AIDS is at 6.4 per cent as of 2007, and produces anti-malarials where the disease is the leading cause of death in the country. With respect to the former, only 35 per cent of the population living with HIV/AIDS currently have access to antiretroviral treatment in Uganda. Investment proposals to produce generic lifestyle drugs in LDCs for export, while potentially profitable, would have less of a development impact. At the same time, producers may need to produce certain products that allow them to generate adequate revenue, even where their public health relevance is limited insofar as such production may help them sustain the manufacturing of essential medicines.

Beyond this, this publication will make no attempt to suggest any particular medicaments that would be good candidates for local production, as this will necessarily differ from country to country. There is nonetheless a need to have a strong drug regulatory authority in order to ascertain the specific medicines for which local production would have a positive impact in terms of public health needs. The drug regulatory authority needs to have a good understanding of the supply of and demand for particular medicaments. In addition, local firms should have the necessary capacity to meet quality standards at a reasonable cost.

The example of the Sino-Ethiopian joint venture in Ethiopia presents another interesting possibility for LDCs and other developing countries. This joint venture produces hard gelatin capsules, which is an input for medicines. The possibility to produce parts of the value chain, rather than a finished pharmaceutical product, represents a possible model of production, given the desire of the Chinese partners to reduce the risk of spoilage by producing locally.

Further, the development impact of investment in local production of pharmaceuticals becomes greater if the local factory produces medicines for those who currently do not have access, rather than those who are able to pay or are otherwise covered under some type of medical insurance. As the population of LDCs is generally not covered under an insurance scheme and their purchasing power is very limited, government purchases become an important means to channel medicines to those who need it. Using the Uganda example, the output of the Cipla-Quality Chemicals joint venture is purchased by the government for distribution by public health facilities. The outputs generated by a government-use licence to manufacture certain antiretrovirals issued in favour of

Kimiafarma, a state-owned enterprise in Indonesia, were purchased by the Indonesian Government for distribution in its public health programme, which covers those living below the poverty line. Again, this may be counterintuitive from a free-market perspective, since the incentive would normally be to try to charge prices according to what the market will bear.

***Key points***

- A decision to support the local manufacture of pharmaceuticals should also tackle the question of which medicines should be produced locally.
- From a public health perspective, development gains are greatest if local production increases the supply of good quality and affordable essential medicines for which there is a shortage, as well as for other poverty-related, tropical and neglected diseases.
- The drug regulatory authority is an important source of information with respect to which drugs would be good candidates for local production from a public health perspective.
- Local firms may also need to produce drugs other than those identified in order to be sustainable in the long run.
- As regards those for whom the medicines should be produced, government purchases are important in the LDC context, as there are generally no insurance systems and individuals are frequently unable to purchase needed medicaments out of pocket.

*2. How to produce quality medicines at a reasonable cost?*

Medicines produced by a local factory will not result in public health gains unless they are safe and effective. Poorer developing countries usually do not have the innate capacity, however, to produce medicaments of satisfactory quality without outside assistance. Both the underlying contracts for the Sino-Ethiopian joint venture between two Chinese companies and an Ethiopian distributor, as well as the Cipla-Quality Chemicals joint venture in Uganda, include substantial assistance from the Chinese and Indian firms, respectively. That assistance is often provided in the form of a technology transfer package, which may include, but is not necessarily limited to, the dispatch of technicians from the foreign partner; on-site training; the provision of manuals containing standard operating and troubleshooting procedures, as well as testing and technical standards and study tours of local staff to the foreign investors' plants in the home country (see also the discussion below). In the example relating to Uganda, the Government even offered to pay for the cost of dispatching technicians from India to support the start-up of the joint venture.

As far as cost is concerned, it is not necessarily cheaper in absolute terms to manufacture medicaments locally than to import. As noted in chapter 1, this is not always a reason for governments to avoid promoting investment in the local production of pharmaceuticals. The availability of lower-priced medicaments from countries such as China and India has certainly not resolved the question of access to essential medicines for large segments of the population in LDCs. Furthermore, the high-growth economies of China and India, as well as the recent change in patent legislation that makes available patent protection for pharmaceutical products in the latter, are likely to result in higher prices for those medicaments in the longer run. Finally, these countries appear to be increasingly

interested in selling generic medicines to the lucrative markets in developed countries. It therefore may make sense to nurture local pharmaceutical production in LDCs as a long-term investment.

With respect to the absolute cost of production, efforts are under way to lower costs by establishing facilities locally to produce active pharmaceutical ingredients, such as Bangladesh's proposal to build an active pharmaceutical ingredient park. Duty-free imports of active pharmaceutical ingredients will also help to keep active pharmaceutical ingredient costs to a minimum (see discussion on tariffs below). For countries interested in the local production of pharmaceuticals to deal with the security of supply, diversifying sources of active pharmaceutical ingredients and developing such capacity locally would appear to be one of the best means of achieving this objective.

At the consumer level, governments can take a number of measures to reduce the out-of-pocket cost paid by the poor. The offer by government to purchase medicaments for the public health system would help reduce costs, as was the case in Uganda. Such efforts should also be compliant with applicable procurement rules, both nationally and internationally,<sup>59</sup> with which government must comply. Additionally, sometimes medicines are purchased and distributed free of charge to populations through donation-driven programmes. Public insurance schemes can also help to reduce the cost to the consumer.

### ***Key points***

- It is not always cheaper to manufacture medicines locally than to import them. However, that is not necessarily a reason to abandon the idea of producing medicines locally.
- Since exporter countries may become more interested in targeting more lucrative markets in the OECD countries, LDCs may not be able to rely on their current import sources.
- Building the domestic capacity to produce active pharmaceutical ingredients is one means to try to reduce the absolute cost of production and achieve security of supply.
- There are a number of means through which the out-of-pocket cost to the consumer can be held to a minimum, such as the availability of public insurance or government purchases, though this may not have an impact on the absolute cost of production.

### ***3. How can the investment deal best promote technology transfer?***

Any firm or individual considering a direct investment in pharmaceutical production in the poorer developing countries realizes that technology transfer needs to be part of the investment package, for it enables firms in LDCs to scale up from producing simple medicines to more complex medicines. The typical components of technology transfer in a pharmaceutical investment deal are mentioned above. What may differ from deal to deal, however, are the efforts made by investors to contain the spillover effects of technology transfer. The R&D-based pharmaceutical firms make significant efforts to ensure that the

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<sup>59</sup> The WTO plurilateral Agreement on Government Procurement is not binding for any developing countries or LDCs, except for Malaysia and Taiwan (Province of China).

technology being transferred remains with their subsidiaries and licensees, for example by including strict non-disclosure requirements for employees when they leave the company, or on the positive side, offering competitive salaries to technical staff as a disincentive to leave.<sup>60</sup>

It is worth discussing here the potentially different viewpoints of the investor and the host country government with respect to technology transfer. Pharmaceutical production is an inherently complex process, as shown in chapter 1. Even with regard to generic medicines, while the medicament itself may be off patent, some technologies that must be transferred to ensure the consistent production of high-quality medicines may be proprietary, embodied in patents, know-how and/or trade secrets. Investing firms, especially the R&D-based pharmaceutical transnational corporations and even the generic firms, therefore have an incentive to limit technology transfer to the licensee.

Developing countries seek to maximize technology transfer gains. Host governments welcome the widespread diffusion of technology beyond the target firm of an investment deal. If individual staff leave that target firm and go on to establish local firms on their own that produce high-quality medicines using the acquired know-how, then that is seen as a development benefit. Some countries have gone so far as to introduce significant technology transfer performance requirements in this sector.<sup>61</sup> In the absence of adequate protection of proprietary know-how, however, investors may be dissuaded from making the technology transfers necessary to establish a successful pharmaceutical production facility.

In many cases, technology transfer is also part of a set of policies that governs national science, technology and innovation systems. These systems actively encourage partnerships with local universities and research institutions. With regard to tropical diseases that affect developing countries, these institutions are very much important strategic assets that need to be promoted in conjunction with efforts to attract investments into local production. Further, such partnerships help to nurture the human resources upon which the direct investment will rely.<sup>62</sup>

Host country governments will need to carefully calibrate their policies on science, technology and innovation, technology transfer and employment confidentiality obligations so as to strike a balance between onerous protections that would stifle any hope of spillover effects and an absence of protection for undisclosed proprietary knowledge. Where to draw the line will differ from country to country, depending upon the level of development and other factors. Existing policies should be reviewed in this light and clearly explained to concerned investors. In this regard, it should be noted that article 8.2 of the TRIPS Agreement makes clear that governments are permitted the leeway to formulate appropriate measures that prohibit practices that adversely affect the international transfer of technology.

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<sup>60</sup> See, for example, the UNCTAD Indonesia Case Study (2011, forthcoming), which examines the firm PT Eisai Indonesia, a manufacturing subsidiary of Eisai Co., Ltd. of Japan.

<sup>61</sup> Indonesia, for example, requires under Ministry of Health Decree 1010 (2008) that in order to distribute drugs that are not manufactured in Indonesia, foreign companies must provide a local firm with technology transfer to enable that firm to manufacture that drug within five years.

<sup>62</sup> Gehl-Sampath (2011).

***Key points***

- Technology transfer needs to be part of any investment in the local production of pharmaceuticals, especially with respect to LDCs.
- There is often an inherent tension between the transferor of technology and the recipient country of technology transfer, with the former seeking to limit technology transfer to the target firm, and the latter seeking widespread diffusion of the technology into the economy.
- Policies affecting technology transfer need to strike a balance between onerous protections that would stifle any hope of spillover effects and an absence of protection for undisclosed proprietary knowledge.
- In-built partnerships with local universities and research institutes in investment deals could help nurture the human resource base upon which the long-term success of the investment relies and could potentially be a good strategic asset with respect to research on local diseases and finding possible cures.

*4. To what extent should local production be pursued as a component of industrial development and to what extent should the pharmaceutical industry be protected from foreign competition?*

The hope of host governments is that eventually their countries would have a critical mass of local pharmaceutical factories producing medicaments that increases the stock of available good-quality medicines at a reasonable cost. Developing country governments sometimes choose to frame this goal in terms of an industrial policy for the pharmaceutical sector. Ethiopia, for example, has recently included the pharmaceutical sector as a priority sector in its August 2010 Growth and Transformation Plan.

Pursuing local pharmaceutical production in developing countries as part of an industrial development policy can open up the sector to various opportunities, including access to credit, tax incentives, export concessions and otherwise more favourable treatment, compared with other sectors, making available a range of tools that support local firms in becoming profitable. However, pursuing local pharmaceutical production as an industrial policy is not necessarily equivalent to pursuing local pharmaceutical production to achieve public health goals, though the two may be complementary.

First, the goal of an industrial policy is usually to develop an industry for economic growth purposes. While this objective is certainly not incompatible with public health objectives, the motivations behind these two development objectives could lead to different outcomes. For instance, an industrial policy may favour pharmaceutical production for export, while a public health perspective would favour the growth of local pharmaceutical production of priority essential medicines for domestic consumption. An industrial policy may emphasize the creation of jobs, while a public health policy may seek the transfer of the latest machines for pharmaceutical formulation. The difference between these perspectives may be exacerbated by the fact that industrial policy is usually overseen or implemented by officials of a Ministry of Industry, while the Ministry of Health or the drug regulatory authority will probably have a role in shaping a country's public health goals and the role local production should play in meeting those goals. Coherence of policies becomes an important issue and should be borne in mind by policymakers who need to be clear for what reasons they are supporting the local production of pharmaceuticals.

A related question of coherence exists with respect to the extent to which the local pharmaceutical industry may benefit from rules and regulations that explicitly or de facto favour domestic manufacturers over foreign competition. As discussed in chapter 2, with relatively few exceptions worldwide, investment into pharmaceutical manufacturing remains open to foreign investors. This has not prevented, however, drug regulatory authorities in some countries from requiring, for instance, that a pharmaceutical firm should have a domestic factory in order to secure rights to distribute pharmaceutical products or establish, inter alia, pricing policies that deter foreign firms from selling certain medicaments locally. Central government procurement agencies may establish bidding regulations that allow local firms an advantage in tender offers for the bulk purchase of medicines.

Such measures should be considered carefully. At a legal level, measures need to be consistent with the country's international obligations, including any most-favoured-nation and national treatment obligations under various treaties, and whether any grounds, such as developing country status, LDC status or public health, can be cited to permit special and differential treatment for a particular practice. Most developing countries are currently not bound by WTO-related public procurements commitments.

Second, policymakers should consider whether such measures are indeed consistent with the objective of greater access to medicines. Efforts that deter foreign pharmaceutical manufacturers from offering certain important medicaments domestically may reduce the available range of treatments of certain conditions. It should also be noted that countries that have introduced rules to the advantage of domestic firms generally have relatively strong generic industries already. Smaller and poorer countries where the industry is not as yet developed may be at a stage where it is more appropriate to encourage foreign technology transfer and capacity-building.

***Key points***

- Pursuing local pharmaceutical production as part of an industrial policy is not necessarily equivalent to pursuing local pharmaceutical production as part of a health policy, though the two policies can be complementary.
- Coherence of policies is critically important if policymakers wish to leverage pharmaceutical production to meet public health needs, as the dynamics and proponents of the respective policies within a country are different.

**D. Determining which local firms to support**

Investment promotion agencies will need to be conscious of which firms are the strongest candidates to attract investment into the sector and what global opportunities exist in this context. While more advanced developing countries may have a number of firms that could potentially be of interest given the prerequisites for investment, the reality is that there may be few firms of this calibre in LDCs. They may be guided by certain activities of the drug regulatory authority, which may be of use to investors in identifying the best existing local manufacturers. Drug regulatory authorities often classify and rank the local companies according to their ability to maintain quality assurance and safety standards. This is not to say that the drug regulatory authorities should pick and choose “winners” and “losers”, but simply that they will, by the nature of their mandate, necessarily classify

local firms in terms of their ability to meet applicable standards. However, there is no such formal classification system that is followed by the drug regulatory authorities.

Interestingly, some investors in the generic pharmaceutical industry have actually opted to establish new green field factories with distributor companies in certain LDCs, rather than to partner with existing local manufacturers. In both the Sino-Ethiop joint venture to produce hard gelatin capsules and the Cipla-Quality Chemicals joint venture in Uganda to produce antiretrovirals, the local partners were, in fact, strong distributors in the country and/or region.<sup>63</sup> These examples show that if a viable market exists, then having a strong local distribution network is something that is potentially attractive for investors. Moreover, if the activity to be undertaken in the country is primarily formulation, hired staff for a green field factory could be trained to become a quality provider of pharmaceuticals, provided a critical mass of human resources is available in the country.

***Key points***

- A drug regulatory authority often has important information concerning the firms within its jurisdiction and their potential to be partners with foreign investors in the local production of pharmaceuticals.
- The field of potential partners need not be limited to existing producers; distributors often have a network to sell products, which can potentially be attractive to investors.

**E. Choosing which investors to target**

As noted in chapter 1, many developing countries got their initial start in the pharmaceutical sector by encouraging the large United States, European and Japanese R&D-based pharmaceutical transnational corporations to set up factories in their country and to train their staff in the use and maintenance of equipment in factories that were, more or less, carbon copies of their factories in the developed world as part of an integrated technology transfer package. Bangladesh, Colombia and Indonesia have followed this model. Even countries that have never had a significant presence of foreign transnational corporations in the sector, such as Jordan, started out by in-licensing technology from the large pharmaceutical transnational corporations based in developed countries.

The pharmaceutical sector has changed drastically, especially in the last decade. The generic pharmaceutical sector, especially with regard to branded generics, has expanded rapidly in both the developed and developing world. The growth is supported in part by the expiration of patents on blockbuster drugs that drove the growth of the R&D-based pharmaceuticals. In developing countries, local generic firms have overtaken markets that were previously dominated by the R&D-based pharmaceutical transnational corporations. Countries such as China and India not only have become major centres for the manufacture of generics and active pharmaceutical ingredients, but have also developed their own R&D capacity in the health sector. At the same time, transnational corporations are keen on expanding their reach to at least some, if not all, robust markets in the developing world. The policy environment too has changed. India must now offer intellectual property protection to pharmaceutical products that meet patentability criteria as a result of the TRIPS Agreement. Policymakers in developing countries are

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<sup>63</sup> UNCTAD et al, Ethiopia Case Study (2011, forthcoming) and Uganda Case Study (2011, forthcoming).

increasingly concerned about the supply security of drugs and vaccines in the light of recent pandemics, such as those relating to the H1N1 and H5N1 viruses.

These changes have led to a world map where the large R&D-based pharmaceutical transnational corporations are seeking strategies for adaptation. A number of these transnational corporations are now diversifying their portfolios away from exclusive reliance on patent-protected blockbusters. In this context, some firms have sought partnerships with or have acquired some of the leading generic firms in developing countries. Leading firms in developing countries and LDCs also offer established marketing and distribution channels that global transnational corporations could find attractive in selling their products in these countries. As noted above, it is no coincidence that the joint venture projects in Ethiopia and Uganda cited throughout this study involved the selection of a distributor firm to establish a green field factory. Meanwhile, capital-rich generic firms in the developing countries are increasingly investing abroad to meet demand in other countries.

With a few exceptions, such as in traditional medicines, the reality of most developing countries is that their competitive advantage is not in developing new, innovative medicines. Their strength lies predominantly in generics, which accounts for the overwhelming proportion of pharmaceutical firms in the non-developed countries. Thus, while the more advanced developing countries with established, stronger branded generic firms may be able to attract the interest of the R&D-based transnational corporations, other developing countries where the local firms are not as yet established may choose to focus on attracting foreign direct investment and technology transfer from other developing countries which have stronger and larger generic manufacturers. Important examples cited in this guide are of firms from China, India and Jordan investing in local production of pharmaceuticals in LDCs. In this case, the main axis of investment is South–South. While it may theoretically be possible for LDCs to attract Northern-based generic firms, these firms are more likely to form partnerships with generic manufacturers in the larger markets of China and India.

It is important to underline that many LDCs will lack a favourable investment climate for pharmaceutical production. For LDCs that have some, but as yet weak, pharmaceutical capacity that might have the potential for upgrading in the long term, one consideration is whether local firms could at least serve as factories where tertiary production, that is, packaging, for generics takes place.

A sometimes overlooked investor in the case of pharmaceuticals is the public sector, that is, the government, especially in the early phase of pharmaceutical industrial development. A government can sometimes help finance local pharmaceutical production initiatives, either in the form of loans or by taking an equity share in the local firm. GPO-Mèrieux Biological Products is a joint venture company that was established between Thailand's Government Pharmaceutical Organization and Sanofi Pasteur Ltd., which produces measles and Japanese encephalitis vaccines, among others. With regard to the Cipla-Quality Chemicals joint venture to produce antiretrovirals in Uganda, the Government agreed to provide financing to the local firm, effectively taking an equity share in the joint venture. As with private sector investors, governments will need to be persuaded on a case-by-case basis that investing in a particular pharmaceutical production initiative makes sense from both economic and public policy perspectives.



**Key points**

- Most LDCs will need to focus their efforts on attracting generic manufacturers rather than the big R&D-based pharmaceutical companies in developed countries.
- Recent investment activity in this sector with respect to LDCs has been on a South–South nexus, featuring generic firms from Brazil, China and India.
- The government can also be a potential investor, and may be influential in steering the product offering of the local firm towards certain medicaments that meet public health needs.

**F. Getting the basics right**

Before examining the components of an effective promotion strategy to attract foreign direct investment into local pharmaceutical production in LDCs, efforts should focus on certain measures that justify investing in pharmaceutical production in the country; further, it should be clear that the country concerned is serious about ensuring the fundamentals of pharmaceutical production. These measures, which are not necessarily investment promotion measures as such, are discussed below.

*1. The least developed countries can legally produce medicines that may be patented elsewhere*

A unique advantage of LDCs, as compared with other developing countries, is that they are exempt from complying with the TRIPS Agreement until 30 June 2013, and until 1 January 2016, from introducing pharmaceutical product patents, which is otherwise required under the Agreement. There are ongoing discussions at WTO about whether this exemption should be extended, a move that is gaining support from both donor governments and the R&D-based pharmaceutical industry.<sup>64</sup> Some LDCs, such as Bangladesh, Ethiopia, the United Republic of Tanzania and Uganda, have used this argument as a major selling point for attracting investment into their local pharmaceutical industry. The best way to demonstrate this advantage is to ensure that domestic patent law excludes the possibility of patent protection for pharmaceutical products.

One should not take this argument too far, however. First, as noted above, the exemption is only temporary, and LDCs will be expected to offer patent protection once the waiver expires. Second, many LDCs have adopted patent legislation that already makes available pharmaceutical product patents notwithstanding the waiver. Third, many countries have signed preferential trade and investment agreements that include intellectual property provisions that may curtail their ability to take advantage of the temporary exemption. Finally, most originator companies do not file patents for their pharmaceutical products in LDCs and smaller developing country markets, leaving the door wide open for the manufacture of generic equivalents in these countries in any event.

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<sup>64</sup> See New (2011).

***Key points***

- The ability to legally produce generic equivalents of medicines that are on patent elsewhere is a competitive advantage unique to LDCs.
- The legal regime should ensure that LDCs that are interested in supporting local production can make use of this competitive advantage.
- This advantage by itself is unlikely to convince foreign firms to invest in local production, however.

*2. A commitment to the prerequisites for pharmaceutical production*

It should be emphasized, as mentioned above, that the waiver given to LDCs to delay the implementation of the TRIPS Agreement obligation making available patents on pharmaceutical products will not by itself be a sufficient argument to convince potential generic investors, domestic or foreign, that it makes sense to invest in the domestic production of pharmaceuticals. This waiver is only a temporary reprieve until 1 January 2016, after which LDCs, too, must make available the possibility of granting patents for pharmaceutical products unless the waiver is extended further by agreement of the TRIPS Council.

Investors therefore need to be satisfied that the prerequisites for pharmaceutical production highlighted in chapter 2 have been met, or that government is taking measures to ensure that the country concerned is well on its way to meeting these prerequisites. It is worthwhile reviewing those prerequisites here.

First, it will be important to upgrade human resources, particularly in the pharmaceutical and managerial fields, and to ensure that companies have access to stable power, clean water and other related infrastructure. While there may be technological or other solutions to address the latter such as in-built generators and water purification facilities, LDCs should be aware that it may take years to build human resources if they do not already have them. One way to show that a country is well on its way to having a critical mass of human resources is if it has in place a science, technology and innovation policy with an emphasis on developing expertise in the relevant scientific fields. Another means, which is certainly not exclusive of the science, technology and innovation policy, is to seek development assistance projects that are designed to upgrade the skills of the local population in the relevant fields.<sup>65</sup>

The reputation of a drug regulatory authority is built up over the years, if not decades. This calls for consistent upgrading, not only in laboratory facilities and the technical competence of the drug regulatory authority, but also building up organizational competence and a clear, cogent institutional mandate. No amount of public relations will be able to cure a drug regulatory authority that permits substandard medicines to be made available to the public at large. It is also widely known that LDCs generally have under-resourced drug regulatory authorities, which makes it much more difficult to show that the local industry is subject to strict standards of regulatory review.

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<sup>65</sup> Such technical cooperation projects could be used also to show how article 66.2 of the TRIPS Agreement, which requires developed countries to provide incentives to encourage technology transfer to LDCs, can be operationalized.

It is therefore important to show that the drug regulatory authority is receiving technical support, and/or that individual firms are meeting quality standards above and beyond those applied by the drug regulatory authority. With respect to technical support, one example of good practice is a regional bioequivalence centre for Kenya, Ethiopia and the United Republic of Tanzania, which was recently established at Addis Ababa University with the assistance of German bilateral official development assistance. Pharmaceutical firms in these countries can share the use of this facility in order to undertake bioequivalence testing. In addition, WHO provides assistance to drug regulatory authorities in developing countries designed to build capacity in discharging its mandates. With respect to the latter point, chapter 2 highlighted certain firms in Bangladesh that have sought and obtained European certification for their pharmaceutical products. The Cipla-Quality Chemicals joint venture in Uganda also recently obtained WHO pre-qualification for its products.<sup>66</sup> Highlighting such efforts will give some assurance to potential investors.

Building human resources or upgrading a drug regulatory authority may require both time and resources. It is not suggested here that LDCs should rely on the private investor to support such initiatives, although there may be interest on the part of the investor in certain partnerships with local universities and research institutions, depending upon the situation. Such activities, when they occur, are often part of official development assistance or technical assistance packages designed to build science and technology capacities, or through support programmes for drug regulatory authorities. When prioritizing areas for assistance, LDCs may wish to take this into account.

#### ***Key points***

- LDCs interested in supporting local pharmaceutical production should show investors that certain basic requirements to support an industry are in place.
- Countries need to build their human resource base in relevant fields such as pharmacy, chemistry and management; countries also need to be able to deliver the appropriate infrastructure.
- A well-functioning drug regulatory authority is essential for countries that are considering supporting local production.
- LDCs may wish to negotiate to channel donor assistance towards these activities.

### *3. A home-grown market for locally produced medicines*

No investor would make an investment in the absence of a market. A country needs to show that there is a market for locally produced medicines, assuming that the local companies can produce at high quality and at reasonable cost. The argument goes back to the point made at the beginning of this publication, which is that for most of the world, people rely on the private sector to produce their supply of medicines. This means that the medicines must be sold at a profit in order for the firm to operate sustainably. The problem for many of the LDCs is that they are often less attractive a market than the economies of the Brazil and certain Asian countries such as China, India, Indonesia, Korea, Malaysia and Thailand, where, amid impressive growth rates, the number of people living in absolute poverty is declining and both the middle and upper classes are growing in size; those segments tend to be better able to afford prices commanded by the

<sup>66</sup> See [http://apps.who.int/prequal/info\\_press/pq\\_news\\_12March2010\\_UGA\\_Manufacturer.pdf](http://apps.who.int/prequal/info_press/pq_news_12March2010_UGA_Manufacturer.pdf) (accessed on 9 February 2011).

branded generic and originator pharmaceutical companies. Smaller countries imply small local markets, and thereby, low economies of scale.

One way to deal with this issue is to show investors that a guaranteed local market exists. This can be done through government purchase commitments, for example. In developing countries in particular, the government is a major purchaser of pharmaceuticals. In Indonesia, for example, the Government bought the entire output of antiretrovirals produced by the state-owned firm Kimiafarma under a government-use licence. In Uganda, the Government guaranteed the purchase of output for antiretrovirals manufactured by the Cipla-Quality Chemicals joint venture. As procurement is an area that is sometimes covered under preferential trade and investment agreements, efforts should, however, be made to ensure that any preferences given to local manufacturers of medicines in procurement are otherwise compatible with national law and the country's international obligations (i.e. bilateral and multilateral treaties), and that those preferences can be lifted once the local industry has matured.

The existence of a public health insurance scheme may also help to ensure an investor that there will be a purchaser of the medicines being produced. Such insurance is often introduced as part of a policy of universal health care coverage. Public insurance may be combined with a government purchase commitment (i.e. medicines purchased under the public health insurance are those that are procured by the government, as in the case of Thailand) or they may be independent of one another.

Another means to show the existence of a target market is to treat the target market as not only the country of production, but of the wider region. This may call for measures that allow for greater regional cooperation in this sector, so that firms can more easily target the regional markets. Such measures may include, for example, the harmonization of technical standards (i.e. for approval of medicines or intellectual property protection) for the production of pharmaceuticals at a regional level. The Cipla-Quality Chemicals joint venture in Uganda is designed, for example, to eventually supply the entire East Africa region with high quality antiretrovirals. The Sino-Ethiopian joint venture in Addis Ababa to produce hard gelatin capsules sells their output to manufacturers across Africa and to certain Middle East countries. Eminent academics such as Reichman argue, for instance, that the system of notifications of compulsory licences established under the 31 August Decision, and incorporated into the pending amendment to the TRIPS Agreement, article 31bis, supports regional production bases for trade blocks comprised primarily of LDCs.<sup>67</sup> However, this approach requires a great deal of political will, since it will require the countries of the region to standardize their approaches to drug regulation, intellectual property, procurement and other practices.

### ***Key points***

- LDCs are inherently not a market of choice for pharmaceutical investors, whether generic or otherwise. Efforts should be made to show that a market where local ventures could potentially be profitable exists.
- One way this can be done is through advance purchase commitments by the government, with preference to local manufacturers within reasonable limits.
- Another means to show the existence of a market is to pursue a regional market, through, for example, the standardization of drug regulations and related intellectual property standards.

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<sup>67</sup> See Reichman (2008).

## **G. Strategic use of investment promotion agencies and investment incentives**

Beyond having in place the basic requirements for local pharmaceutical production (or at least showing that a country is well on its way to meeting these requirements), LDCs need to effectively communicate to potential investors that the above prerequisites are being met. This task will typically fall within the mandate of the investment promotion agency, which must therefore be sufficiently informed about these policies.

Countries can employ a set of investment incentives to help make the case for a specific investment. The investment promotion agency is often a window investors can use to take advantage of available incentives and is sometimes responsible for the administration of incentives. In this regard, countries that seriously consider attracting foreign direct investment into local pharmaceutical production may wish to consider setting up a sectoral desk within the investment promotion agency for this purpose, or at least to designate a focal point within the agency to follow relevant international and domestic developments closely.

Because any investment in the pharmaceutical sector entails both high cost and significant risk, the most effective incentives tend to be those that reduce either or both. The most important incentives are described below.<sup>68</sup> The guide then examines the case of the Cipla-Quality Chemicals joint venture in Uganda to show how such incentives were employed to close this deal.

### *Duty free or reduced tariffs on import of raw materials and capital goods*

Aside from China and India which manufacture their own active pharmaceutical ingredients, most other developing countries must import active pharmaceutical ingredients. Firms in these other developing countries therefore often obtain their final or intermediate active pharmaceutical ingredients from China and/or India.<sup>69</sup> The ability to import active pharmaceutical ingredients duty free therefore helps to keep costs down, and thereby helps the firm operate profitably, enabling it to become a 'going concern'. The same could potentially be said about imports of capital goods, such as the precision machinery used in formulation.

### *Free or inexpensive land*

The physical requirements for a pharmaceutical factory include immovable assets such as land and a building complex, complete with appropriate storage facilities. As a strategic industry, countries have often been prepared to offer free land or reduced rent for pharmaceutical sector investments. These also help to reduce costs. Factories are a more difficult issue as pharmaceutical factory facilities must meet very stringent specifications, including those for storage and hygiene. An offer to provide an existing unused factory may not necessarily be an attractive incentive for investors in the pharmaceutical industry.

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<sup>68</sup> The lists of possible incentives are not intended to be exhaustive. It should be considered as the key incentives in addition to standard incentives such as the availability of investment insurance, as well as various investor protections such as the freedom to repatriate capital or assurances against expropriation.

<sup>69</sup> The exception to this would be in the case of wholly owned subsidiaries of the R&D-based pharmaceutical transnational corporations, which generally require their subsidiaries to buy active pharmaceutical ingredients from the same source as their other factories.

*Tax holidays*

A typical incentive offered not only for this sector but also in many others where investment is being targeted is a tax holiday. Tax holidays exempt or reduce a firm from paying corporate income tax for specified time period. For developing country bureaucracies, tax holidays are relatively simple to administer compared with other tax incentives.

*Visa streamlining and waivers*

In the early stages of a technology transfer project it is often necessary for skilled staff from the investor to be on site to coach and teach local staff. Visa waivers, or at the very least streamlined procedures for skilled staff involved in the technology transfer, will help to reduce the transaction costs of foreign direct investment in a pharmaceutical production facility. If visas are needed, it may also help to ensure that those visas are issued for an appropriate duration allowing the foreign staff to complete the technology transfer project.

*Joint shareholding*

Investment in a pharmaceutical production facility in a developing country is often seen as a high-risk investment. In some cases, government is prepared to share the risk of the investment by becoming a joint shareholder in a proposed investment to establish a local pharmaceutical factory. Such an action is designed to provide assurances that the government is fully committed to the project and will not be allowed to fail easily after the investment has been made. In other cases, international organizations, such as the International Finance Corporation of the World Bank Group, have often co-financed investments in pharmaceutical firms in developing countries, sending a similar message to possible private-sector investors.

*Purchasing commitments*

As noted earlier, governments tend to be a major purchaser of pharmaceuticals, especially in poorer countries where the population may have trouble paying out of pocket for their medical needs. In such cases, governments have sometimes given preference to local firms by allowing greater price tolerance in procurement, or in other cases have even committed to purchase the output of an invested local firm. While certainly reducing the risk of the investment, countries should take care to ensure that such actions are consistent with their national procurement laws and international treaty obligations.

*Special economic or industrial zones*

Making high quality medicaments requires the appropriate infrastructure. While reducing the cost of that infrastructure is one issue, providing an appropriate location with guaranteed access to uninterrupted power and clean water is an issue of business risk. Some countries have offered prime areas in their special economic zones or industrial zones to pharmaceutical investors, as these zones often have their own infrastructure facilities attached to them that better guarantee consistent power and water quality.

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The following box shows how certain incentives have been employed in an LDC environment. It examines an actual investment deal in the pharmaceutical sector, the joint venture between the Indian generic manufacturer Cipla and a local distributor in Uganda named Quality Chemicals. This example has been mentioned numerous times in this guide; however, it is worth examining the specific steps taken by the Ugandan Government to secure the investment under which the joint venture has been producing antiretrovirals and anti-malarials in a WHO pre-qualified factory since 2009.

**Box 1:  
Incentives and the Cipla-quality chemicals joint venture in Uganda**

Under the joint venture, which was established in 2007, Cipla has a foreign equity share of 38.55 per cent and Quality Chemicals has a local equity of 61.45 per cent. The two firms agreed to distribute future benefits among themselves equally, however. The venture resulted in a new factory, since Quality Chemicals was not an existing manufacturer, but was instead a local distributor.

The Ugandan Government offered the following incentives:

- (a) Financing 23 per cent of the capital investment as part of Quality Chemicals' investment in the joint venture company;
- (b) Providing a cost-free set-up of the entire infrastructure, including land at Luzira, which is near the capital, and the factory and warehouses;
- (c) Guaranteeing access to roads, power supply and clean water;
- (d) Paying salaries for Cipla's pharmaceutical experts to train local staff;
- (e) Agreeing to procure with Cipla antiretrovirals worth \$30 million per year for seven years from the new plant;
- (f) Granting a 10-year tax holiday on corporate income tax.

In addition, tariff rates on the import of active pharmaceutical ingredients for pharmaceutical production across the East African Community are set at 0 per cent, allowing for the duty-free import of active pharmaceutical ingredients from Cipla for the production of the antiretrovirals and anti-malarials.

The efforts of government investment promotion agencies were critical to secure this deal, as Quality Chemicals alone would never have been able to offer the type of assurances and financial assistance needed for Cipla to agree to manufacture antiretrovirals and anti-malarials in Uganda. The combination of these incentives make the joint venture virtually cost and risk free for Cipla.<sup>70</sup>

The Quality Chemicals plant is now certified for good manufacturing practices by WHO. The parties have recently agreed on an expansion of this investment (see footnote 14).

Source: UNCTAD (2010).

It has been argued, however, that the excessive use of incentives could result in competition between countries to attract similar investments, resulting in a "race to the

<sup>70</sup> UNCTAD (2010) and UNCTAD et al, Uganda Case Study (2011, forthcoming).

bottom” in terms of standards and a “race to the top” in terms of incentives, with little or no development gains.<sup>71</sup> Countries therefore need to be selective in the deployment of appropriate incentives, given the specific nature of the investor and the development gains envisaged. It should also be pointed out that incentives entail an economic cost, such as tax revenue forgone.

Policymakers reading this guide should also note that each deal is unique and the set of incentives that will work best for attracting investment can only be determined in a specific negotiation context. The above set of incentives used in this deal should be taken strictly as an example of how a country mixed and matched certain incentives to make a project more attractive to a potential investor.

***Key points***

- LDCs will need to communicate, perhaps with the help of their investment promotion agencies, to potential investors that the prerequisites for pharmaceutical production are being met.
- A range of investment incentives may be employed to support the case for specific investments in the local production of pharmaceuticals.
- The decision concerning which incentives should be utilized differs from case to case, and should be weighed carefully, taking into consideration the full cost of the incentives and the benefits of the investment, both in terms of health and economic gains.

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<sup>71</sup> UNCTAD (2002), p. 244.



## ***Conclusion***

This guide attempts to capture some of the experiences of developing countries in the local production of pharmaceuticals, and to present it in a way that is clear and understandable for policymakers, who may have little or no background in this area.

The manufacture and distribution of pharmaceuticals is a complex process and is increasingly global in scope. The landscape of pharmaceutical production has changed greatly in the past 10 to 15 years and increasingly, developing countries are becoming part of the value chain. While philanthropic efforts and the larger developing countries such as Brazil, China and India certainly enjoy a competitive advantage in terms of producing mass medicines at low cost and have contributed to greater access to medicines worldwide, the number of individuals who still lack access point to the need to consider additional measures.

UNCTAD research and technical assistance over the past five years have shown that the local manufacture of pharmaceuticals is one means by which countries are currently attempting to address the remaining gap in access. Firms in a number of developing countries beyond Brazil, China and India are becoming major suppliers of pharmaceuticals, with some countries also developing their capacity to conduct R&D, and others, to produce their own active pharmaceutical ingredients.

Especially in the LDCs, however, these firms need support – and that support can come only through sustained efforts, including foreign direct investment and technology transfer. To the extent that pharmaceutical production is largely a private-sector activity in most countries, only governments, through appropriate policies and investment negotiations, can encourage investment in a manner that meets important public health objectives in a financially sustainable fashion. In these negotiations, investment promotion agencies are important players and will need to be informed about sectoral developments, both domestic and international.

The policies that affect efforts to attract investment, to build capacity in the local pharmaceutical industry and to promote public health objectives need to be understood and applied in a coherent manner. Investment and industrial policies are inherently geared toward economic objectives, while drug regulations are directed toward protecting and improving public health. The deployment of tools to attract investment or develop the local pharmaceutical industry without the consideration of health objectives may end up defeating goals of greater access to good quality, reasonably priced medicines for the country. Institutional coordination is therefore critically important.

Moreover, the choice of policies to deploy in any specific case must be underpinned by the availability of good human resources and infrastructure, a functioning drug regulatory authority and other important prerequisites. Without those prerequisites, LDCs have little chance of attracting the desired investment and related technology transfer.

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