

Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines

An Overview of Key Concepts, Issues and Opportunities
for Future Research

Warren Kaplan and Richard Laing

January 2005



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Health, Nutrition and Population (HNP) Discussion Paper

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Health, Nutrition and Population (HNP) Discussion Paper

LOCAL PRODUCTION: INDUSTRIAL POLICY AND ACCESS TO MEDICINES An Overview of Key Concepts, Issues, and Opportunities for Future Research

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Abstract: Local production of pharmaceuticals in developing countries may be seen as helping to stimulate industrial policy and/or as stimulating pharmaceutical “access” to needed medicines. However, if a developing country with manufacturing facilities is able to finish off bulk active ingredients sourced from developed or other countries at high costs, such manufacture may have no impact whatever on patient access to needed medicines. There has been some critical thinking in the past regarding whether or not small developing countries should make their own pharmaceuticals, but no recent comprehensive summary of the issues and policy options. This paper summarizes the issues surrounding “local production” from a policy and public health viewpoint. It provides four brief country-level case studies, and reviews the evidence supporting the industrial policy assumptions underlying the goal of local production. In brief, in many parts of the world, producing medicines domestically makes little economic sense. If many countries begin local production, the result may be less access to medicines, since economies of scale may be lost if there are production facilities in many countries. The document concludes by providing a research agenda specifically designed to test assumptions about local production of pharmaceuticals.

Keywords: pharmaceutical, local production, health policy, industrial policy

Disclaimer: The findings, interpretations and conclusions expressed in the paper are entirely those of the authors, and do not represent the views of the World Bank, its Executive Directors, or the countries they represent. This paper was written when both authors were affiliated with the Boston University School of Public Health.

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FOREWORD

Several inputs are indispensable in ensuring that health services function properly. This includes pharmaceuticals, equipment, other consumables, capital, human resources, and knowledge. This publication – *Local Production, Industrial Policy, and Access to Medicines: An Overview of Key Concepts, Issues, and Opportunities for Future Research* – by Warren A. Kaplan and Richard Laing, reviews the strengths and weaknesses of local production of pharmaceuticals in developing countries. It is part of a series of publications on the role of pharmaceuticals as critical inputs to health services in low- and middle-income countries.

Drugs are often the most important cost driver of health care expenditure on hospitals and ambulatory care. Patients that have access to adequate and effective drugs at the time of need are more likely to be happy with the treatment they receive. When such drugs are not available or ineffective after use, patients will go elsewhere, even if they have to pay high prices to private providers, to get the care they think they need.

The availability of affordable and effective drugs is, therefore, one of the most visible indicators of the quality of health services. Satisfaction with the drugs received is a key determinant of utilization of health services and return visits in the public sector. And out-of-pocket spending on drugs is a major contributor to the impoverishing effects of illness.

Despite significant progress in increasing access to essential medicines in low- and middle-income countries during the past decades, many of the health services used by the poor still lack adequate supplies of basic medicines. Drug shortages and quality problems continue to undermine the performance of health systems throughout the developing world.

Many factors influence whether poor people can obtain affordable drugs of good quality. This includes issues related to pricing and procurement of existing drugs, new product development, patenting/intellectual property rights, manufacturing or import of drugs, macroeconomic constraints, and foreign exchange fluctuations. Without addressing these issues, many countries will fail to reach their poverty reduction and Millennium Development Goal targets.

This paper summarizes issues relating to local production of pharmaceuticals from a policy and public health point of view. The authors conclude that in many parts of the world, producing medicines domestically makes little sense economically. In fact, local production may even limit access to medicines if economies of scale are lost in the process.

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INTRODUCTION

THE TENSION BETWEEN INDUSTRIAL POLICY AND HEALTH POLICY

Regardless of whether one is talking about medicines, guns or butter, there are many reasons why a manufacturer would want to make something rather than buy it: the desired quality is not available; the need to maintain design and process secrecy; the fact that suppliers are unreliable; the desire to control one's own production scheduling (it being easier to adjust to shifting supply/demand); the desire to develop a local employment base; the need to increase technology transfer; the wish to become 'self sufficient' in medicines; the need to reduce reliance on imports and manage foreign exchange flow; and the desire to produce medicines for export.

All these are primarily industrial policy reasons for local production. Particularly for medicines, some of these reasons may be incompatible with health policy reasons to produce medicines locally: to improve the supply of needed medicines; to improve the quality of needed medicines; to lower prices of needed medicines; and possibly to make traditional medicines.

Local Production of Pharmaceuticals: One Aspect of this Tension

National governments are faced with multiple responsibilities with regard to procurement, quality control and dissemination of pharmaceuticals destined for humans. In resource-constrained developing countries, the consequences of government policies to improve access to medicines and to promote access to needed medicines through promotion of generic versions of branded products, may be in conflict with policies to promote a domestic pharmaceutical industry as part of a larger industrial policy.

There are important practical and policy distinctions among: a) promoting access to medicines (which we define as the process of (re)distributing to needy patients those medicines available somewhere in the world); b) creating the necessary research and development to discover or develop innovative medicines in the first place; and c) developing an industrial base to make medicines locally. These three goals may, or may not, be aligned with each other. Indeed, the responsibility to stimulate R&D and promote local industry is most often discussed in terms of industrial, rather than health, policy.

In developing countries there is a great disparity between the demand for medicines to treat endemic diseases and the lack of purchasing power of (or for) patients most at risk. The idea that local production of medicines should be encouraged in developing countries to provide increased access is attractive since we might expect that many of the costs involved will be lower than in developed countries. It is clear, however, that investments in local medicine production will be efficient only if pharmaceuticals can be produced more cheaply locally than they can be imported on the open market. This sets up the inherent tension between a health policy directed to the access problem of making available low cost and quality-assured medicines and an industrial (primarily private sector) policy of optimizing profits and growth by promoting a local industry whose products may be more expensive than those on the international market.

Certain national drug policies, notably those of Bangladesh, have included recommendations on promotion of local pharmaceutical production as a means to achieve national self-sufficiency¹

(ICDRA 1999). But the decision as to whether pharmaceuticals should be imported solely or partially or should be supplied through local production is complex and simultaneously involves health policy, industrial policy, and development. It is part of the debate about how best to provide needed medicines to those least likely to afford them. This particular debate has sometimes suffered from a lack of clear objectives in national drug policy.²

This Tension is Exacerbated by Global Trade Rules

The WTO negotiations in 2001 culminated in the Doha Declaration on public health, the central tenet being its paragraph 4, declaring that the Trade Related aspects of Intellectual Property Rights (TRIPS) agreement “... can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all.” The TRIPS accord permits compulsory licensing of pharmaceutical, and other, patents for a variety of public interest objectives, including the protection of public health. Both importing and exporting countries clearly have the flexibility under TRIPS to issue a compulsory license for manufacture that would allow export of much needed patented medicines into countries that have no pharmaceutical manufacturing sector of their own. Nonetheless, countries without a manufacturing capacity of their own still face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. .

Moreover, as of 2005, product patent protection for pharmaceuticals is going to be required for the major generic medicine producing countries like India and China. If generic producers in these countries now will be required to take out patents on new pharmaceuticals, are these countries still going to put their industrial and health effort into making generics for the domestic and/or international market? Indeed, are smaller countries going to be forced to create their own local pharmaceutical industries for domestic supply? Thus, although the legal viability of compulsory licensing under TRIPS seems clear, the problems of countries that do not have the capacity to produce their own medicines remains. In Africa, South Africa, Kenya, Nigeria, Zimbabwe and around the world, many other countries have industrial capacity that might be available to produce some drugs for export or for domestic consumption in the face of what some would argue will be diminishing supply of generic medicines from the major producers. If the economic cost of creating local production capacity is excessive or the quality of the products is doubtful, this “local production solution” will be no solution at all.

Objectives of the Discussion Paper

What are the barriers to creating a local pharmaceutical capacity that can supply a domestic market and, at the same time, be sufficiently competitive on the international market? Any "solution" to the issues raised in WTO negotiations will need to address the legitimate concerns of these low and middle income countries, since generic industries in these countries may well be key to any solution that actually works. The critical question we ask is: Assuming that a national health policy goal of a low- to middle income country is to improve access to needed medicines, what is the evidence that local production of these medicines is feasible in the face of current realities of global trade, the international economics of the pharmaceutical industry, and an assumed real need of national governments to balance industrial policy and health policy?

The following section gives some definitions to create a framework for discussion and provides a brief background to this discussion by reviewing various trends in the political economy of the

pharmaceutical industry over the last several decades. The third section attempts to frame the specific issues of local production by summarizing the objectives and assumptions about local production from several viewpoints. The fourth section presents a summary of available information on local production in some developing countries. If local production to improve access to essential medicines is possible, is there a size or financial threshold below which a country cannot be internationally competitive? The fifth section presents gaps in the current knowledge base and proposes a realistic research agenda for further study of local pharmaceutical production in developing and transitional countries. Our conclusions are presented in the last section.

FRAMING THE ISSUES: (1) CONCEPTS AND DEFINITIONS

DECONSTRUCTING “LOCAL PRODUCTION”

What Do We Mean by “Production”?

The typology devised by UNIDO³ is a useful starting point. It views production based on differences in the source of the final product along the following continuum:

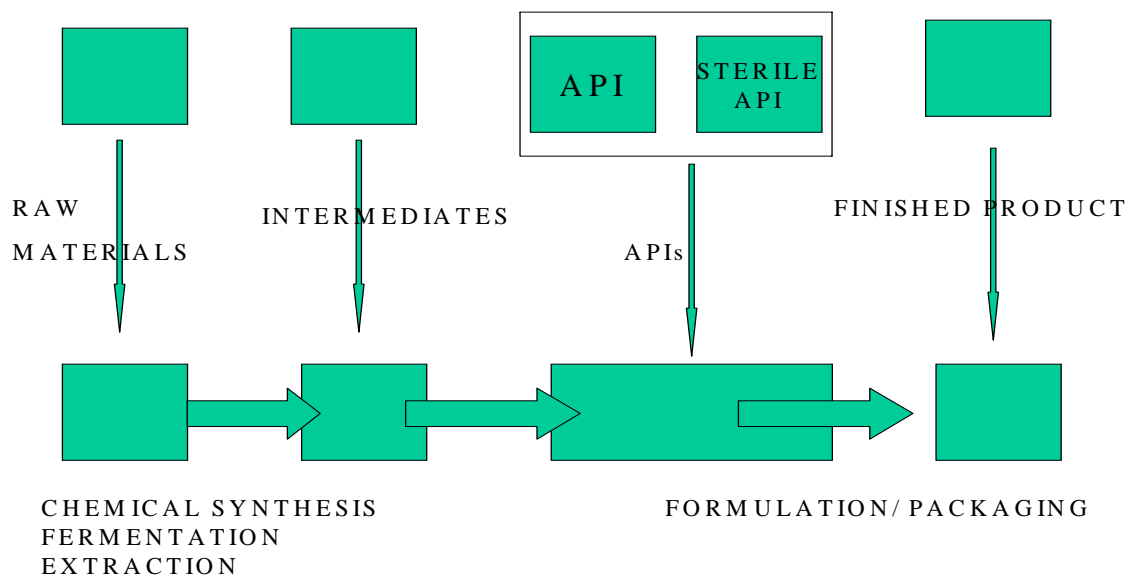
1. No manufacturing facilities and dependency on imported, finished medicines.
2. Packaging of already formulated medicines and small-scale local production of sterile or non-sterile formulations such as IV fluids.
3. Formulation of drugs in final dosage form and some production from imported intermediates.
4. Production from imported intermediates and manufacture of some intermediates from local materials.
5. Production of active substances and processing to produce the required pharmaceutical dosage forms.

The synthesis of medicinal chemicals may be done in a very small facility producing only one chemical or in a large integrated facility producing many chemicals by various processes. Most pharmaceutical manufacturing plants are relatively small. Organic chemicals are used as raw materials and as solvents. Nearly all products are made using batch operations. In addition, several different products or intermediates are likely to be made in the same equipment at different times during the year. Equipment dedicated to the manufacture of a single product is rare, unless the product is made in large volume. Production activities of the pharmaceutical industry can be divided into the following categories:

1. Chemical Synthesis - the manufacture of pharmaceutical products by chemical synthesis.
2. Fermentation - the production and separation of medicinal chemicals such as antibiotics and vitamins from microorganisms.
3. Extraction - the manufacture of botanical and biological products by the extraction of organic chemicals from vegetative materials or animal tissues.
4. Formulation and Packaging - the formulation of bulk pharmaceuticals into various dosage forms such as tablets, capsules, injectable solutions, ointments, etc., that can be taken by the patient.

Further, the various chemicals used in making pharmaceuticals may be categorized as follows: basic building blocks, intermediates and custom-made active ingredients, including active pharmaceutical ingredients (APIs) (See Figure 1).

Figure 1: Schematic block diagram of a pharmaceutical manufacturing process



- At any one time, within any one country and possibly within any one facility, some or all of the manufacturing processes illustrated in the flow diagram of Figure 1 are going on.
- Much of pharmaceutical production is “outsourced” to third parties, including supply of each one of the building blocks shown in the upper level of Figure 1.

We can define the following terms:

Intermediate: a material produced during steps of the processing of an API that must undergo further molecular change or purification before it becomes an API.

Active pharmaceutical ingredient (API): biologically active compound(s) in a drug formulation that imparts the desired therapeutic effect. Active pharmaceutical ingredients are usually first obtained in the crude state (if there is no biological activity they might be considered “intermediates”) and subsequent production operations convert the crude material to the final API that meets the pharmacopoeial and/or similar requirements. A sterile API is an API that has been subjected to additional processing steps to remove micro-organisms.

Examples of Pharmaceutical Products by Bulk Manufacturing Process

Chemical Synthesis	Natural Product Extraction	Fermentation
Antibiotics	Anticancer agents	Antibiotics
Antihistamines	Enzymes and Digestive Aids	Anticancer agents
Cardiovascular Agents	CNS Depressants	Vitamins
Central Nervous System (CNS) stimulants	Hematological Agents	Steroids
CNS Depressants	Insulin	
Hormones	Vaccines	
Vitamins		

The pharmaceutical industry includes a broad range of companies of very different size and technological capacity. The typology proposed by Balance et al.⁴ singles out three types of drug producers: **Integrated corporations**, which are multinationals engaged in all stages of the process of production, able to generate NMEs (new molecular entities) and distribute medical chemicals through subsidiaries and licensees. They are highly concentrated in a handful of developed countries. **Innovative companies** typically produce patent-expired drugs, although they may be capable of discovering and developing NMEs. **Reproductive firms** lack any in-house research capacity. They typically buy active ingredients either through international tenders or from the original innovator. They sell the medicines either under brand names or under international nonproprietary names (INN) as generics. Some developing countries have a pharmaceutical industry of the innovative type, which can produce active ingredients, but in the majority of developing countries the industry does only the final, technologically simple stages of drug production, and relies on importing active ingredients from other countries.

Multinational pharmaceutical companies usually have a wide range of products in their development and commercial portfolios. Most of these companies realize it does not make good business sense to retain the manufacture of all steps in the synthesis. Some companies prefer to outsource early stages of the synthesis while retaining the final steps in-house. Others outsource the manufacture of the API itself. The pharmaceutical company usually owns the intellectual property but is looking to develop its supply base in the shortest possible time and to minimize capital expenditure. Compliance with a technology transfer package is required.

Generic product companies may expect the API supplier to take full responsibility for process development, validation and registration. They require an API that is suitable for formulation, is of satisfactory quality and is provided at a competitive price. Strategic partnerships are often agreed in advance of patent expiry.

In the past, MNCs were identified with integrated corporations and generic companies were identified with domestic producers, i.e. companies that sold their product in the country of residence. This situation is, however, changing and some Indian and Chinese generics producers are becoming multinational in order to take advantage of economies of scale.

Larger Developing Countries are Becoming Important API Suppliers

Historically, innovators have relied on a small number of suppliers with which they work confidentially. Manufacturers of generic oral solids, on average, have between 40 and 50% of

their cost of goods sold tied up in raw material costs so that in a highly contested market where the ability to offer a low price is critical, generic manufacturers can get a competitive advantage by finding reliable bulk manufacturers who can deliver at a low cost. Innovators have begun to look beyond their current small number of API suppliers to realize benefits from partnerships with Indian and Chinese API manufacturers. India seems to be an attractive alternative for sourcing active ingredients. India has low development costs, complex synthesis capabilities, growing experience with good manufacturing practice (GMP) compliance, and a large local market in which to gain experience. India is also known for having a large number of strong chemists, many with Ph.D.s from the U.S. and Europe, providing rapid, and creative, process development. China is also rapidly evolving into a viable source for key intermediates and actives. China's entrance into the WTO is expected to expose domestic manufacturers to significantly more competition.

What Do We Mean by “Local”?

To illustrate this point, six different categories of companies have been described from an operational point of view.⁵

1. Uni-national pharmaceutical companies with sales activities that only occur within the country.
2. Multinational pharmaceutical companies with a single corporate headquarters that is located within the country.
3. Multinational pharmaceutical companies with corporate headquarters located in another country, but with relatively large research and development and sales activities within the country.
4. Multinational pharmaceutical companies with corporate headquarters in another country, and with a relatively large manufacturing plant or technical development laboratory and sales activity within the country; however, no major research and development group exists within the country.
5. Multinational pharmaceutical companies with corporate headquarters in another country, and only relatively small operations for technical development, research, or manufacturing, in addition to sales activity, within the country.
6. Multinational pharmaceutical companies with only sales activities within the country. Sales activities could be extremely large or small.⁵

From a strict ownership perspective, however, only companies in category 1 would qualify as part of the nation's **domestic** industry although from an economic perspective, companies in categories 1 through 4 should be included as part of the nation's domestic industry as they may contribute in a significant manner to that country's tax base and employment.

“LOCAL” PRODUCTION IN THE CONTEXT OF THE GLOBAL PHARMACEUTICAL MARKETPLACE

In 1986, the World Bank produced a document summarizing the role of pharmaceuticals in the developing world.⁶ At this time, there seemed to be great interest in creating or strengthening the drug manufacturing and formulation capacity of developing countries as an industrial policy. Nonetheless, the report concluded that, given economies of scale and technological needs required for making medicines, local production did not make economic sense for most countries. The exceptions were countries with large local markets and capacity to produce active pharmaceutical ingredients (APIs). These countries included China, India, Thailand, Egypt, Brazil, Mexico, and Argentina. In that same year, Foster wrote a paper questioning the basic assumptions used to justify additional investment in pharmaceutical production.⁷ Foster concluded that the choice of pharmaceutical production to lead industrial development was based on little or no evidence.

There was a more comprehensive review of the global pharmaceutical industry in the latter half of the 1980s.⁴ The pharmaceutical industry in developing countries accounted for about 20% of world production. It is far less today. Most firms were small and only a few developing countries made APIs (essentially the same countries identified in the 1986 World Bank report with the addition of Yugoslavia and Turkey). The impact of foreign (i.e., developed country) subsidiaries was significant. Foreign-owned companies accounted for about two thirds of all pharmaceuticals produced in the developing world. The pharmaceutical industry in most, but not all, developing countries depended on production by multinational affiliates and, to a lesser extent, licensed production of generic products.⁴ In both cases, domestic supply was met without heavy local investment in product development. Very few developing countries were able to launch any systematic pharmaceutical export. Indeed, roughly two thirds of all pharmaceutical exports were preparations or finished products. If a developing country was to be a net exporter of medicines, it required a processing industry capable of converting medicinal intermediates into finished products.

The overall situation is not much different today. On the broadest level, we can summarize the situation with respect to pharmaceutical production as follows:

- Ireland Global pharmaceutical market growth is accelerating, with the vast majority of the market dominated by the developed countries of Europe, Japan and the United States.
- Developing countries, particularly in Africa, are not contributing to this growth in market.
- Many Asian countries will increase their share of the global pharmaceutical market over the next few years.
- A key criterion in determining where a multinational will locate its pharmaceutical production facility is whether at that location the total cost of producing a given level of output can be minimized. Any firm uses labor, materials, and energy to produce “output” and hires or otherwise acquires labor, material and energy in competitive factor markets. Economies of scale are also key criteria generally in location decisions. It is also important to recognize that countries such as and Singapore have successfully attracted investment in pharmaceutical manufacture by offering low tax rates or ‘tax holidays’.

DYNAMIC AND FRAGMENTED INFORMATION AT THE REGIONAL/LOCAL LEVEL

At regional or individual country level, the situation is quite dynamic. It is probably important to note the following key points:

- Information on “local production” as well as the number and capacity of API suppliers is very fragmented and possibly proprietary. In particular, API suppliers to generic manufacturers in the U.S. and Europe require their activities to be confidential and secret, lest their preparations for filing dossiers for generic market approval become known to the branded manufacturers. A variety of factors places one on the continuum shown in Figure 1 and where a country/facility wants to go is a complex question informed by politics, economic, human resources, legal/regulatory, IP, health, and disease burden- now and in the future (see the third section).
- No one country, whatever its size and stage of economic development, is entirely self sufficient in pharmaceuticals. Although some developing countries such as India, China and Brazil are NET exporters of medicines, they still require imports of finished product, intermediates or APIs to provide this export base. Thus an industrial policy rationale for local production as providing “self sufficiency” in medicines is naïve and quite illusory.
- Many small, developing countries have domestic pharmaceutical industries but their presence begs the question of whether such production is viable in the longer term in the face of price and/or quality - based competition from ex-country producers. The policy implications of this are summarized in the third part.
- Going forward, there may be bottlenecks in the supply of APIs for various medicines. Despite the efforts of chemicals companies, many APIs of interest to generic companies still are not readily available. The API of certain conjugated estrogens (e.g., Wyeth’s Premarin ®), which comes from the urine of pregnant horses, is a good example. It is used to treat menopausal symptoms- obviously a chronic condition not limited to industrialized countries. Until last year, the API was not available to generic companies. Given the challenges of developing alternative ways to prepare the API, big rewards await any other company that could make the product available to other generic drug-makers. Will there be similar bottlenecks for the APIs needed to make antiretrovirals, anti-hypertensives, non-insulin diabetes medicines?

FRAMING THE ISSUES (2)

INDUSTRIAL AND HEALTH POLICY ASSUMPTIONS ABOUT LOCAL PRODUCTION

It is perhaps not surprising that against this backdrop of changing pharmaceutical and industrial policies and ambiguous definitions, there have been few attempts to look critically at the assumptions that have been made in deciding on investments in local production generally, and in pharmaceutical production specifically. The first attempt was probably by Foster⁷ who attempted to frame the issues by reviewing some basic and widely-held assumptions about local production. We review a few assumptions and some issues raised by this document:

“Local Production Will Save Foreign Exchange”

Raw materials, active ingredients, packaging, as well as the actual machinery used in the manufacturing process may be made in country or they all might be imported. All these need to be paid for in foreign exchange. Indeed, technology, quality control equipment, technical expertise, advertising and distribution networks must often be purchased in foreign exchange.

“Local Production Creates Jobs”

Modern pharmaceutical production (the kind we have defined as “local production” in this review) requires sophisticated and highly skilled workers. Are these in short supply in most developing countries? Is the pharmaceutical industry really an efficient employment creator? This industry is capital and technology dependent and may not create entry-level employment.

“Local Production Facilitates Technology Transfer”

A key stated objective of the TRIPS agreement is “the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations”.⁸ Although the agreement is silent as to how this will be achieved, it implies the establishment of local manufacturing of the patented product, since this is a principal vehicle for technology transfer. The success of technology transfer depends upon the commitment of the technology owner and on the type of technology transferred. Local production may stimulate such transfer but quite often “local production” for a developing country means secondary manufacture and finishing of bulk active sourced from global suppliers.^{9,10} In this situation, does any significant technology transfer occur? Technology transfer may or may not meet the immediate healthcare needs of developing countries, given the structural complexities of the pharmaceutical industry.

“Local Production Will Stimulate Exports to Neighboring Countries”

Large companies enjoy economies of scale so they can make drugs relatively cheaply but locally produced products made by smaller companies often cannot compete either in quality or price with versions made in large developing countries. Indeed, even in the face of a cheaper local product, there may be strong consumer preference for the more expensive version. World Bank guidelines provide for a 10-15% domestic preference margin for local manufacturers on government tenders.¹¹ Such local production preferences may actually distort the market since local companies may take the path of least resistance and will not try to be competitive- and thus end up supplying only the local market.

“Raw Materials Are Readily Available and Are Cheaper Than Finished Products”

Production of active ingredients and chemical intermediates is highly concentrated in only a few suppliers. Local manufacturers clearly have much less bargaining power than the large multinationals that are the major customers of the raw material producers. It is often the case that the volume of raw materials requested by local industry is too small to justify shipment.

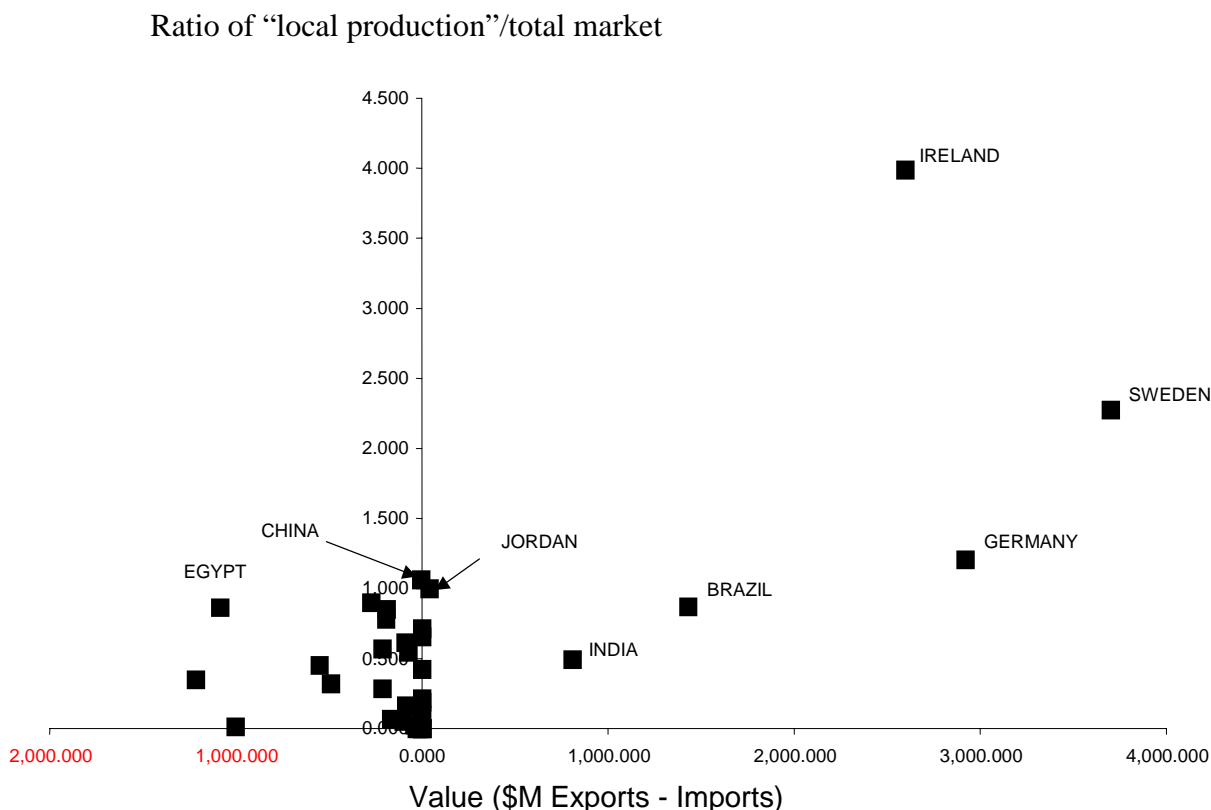
“Achieving Self-sufficiency in Drug Supply”

Even a country that provides the final formulations or packaging may need to buy intermediates. Figure 2 below illustrates some issues regarding the presumed key policy goal of self-sufficiency. The fourth part of the paper explains how data were obtained.

- The ratio of “local production”/total market (Y axis) indicates the extent to which a country is “self-sufficient”. The dataset for “local production” does not distinguish between production by domestic firms and production by subsidiaries of multinationals. The import and export values are for finished product, not APIs.
- “Self sufficiency” is rare: China, Jordan, the Philippines, Pakistan, Egypt, Brazil and certain EU/OECD countries supply more than 85% of their total market through “local production”. Nonetheless, except for China, Jordan and Brazil, most if not all developing countries require significant imports of pharmaceuticals even if they can supply their market through domestic production. So what do people really mean when they mention “self sufficiency” as a rationale for local production?
- The ability to be a net exporter of pharmaceuticals for non-OECD countries is even more rare. Of this dataset, only India and Brazil export significantly more pharmaceuticals (by value) than they import.
- We would expect these relationships would be different if we had information on the **volume** of active ingredients or final formulation imported and exported.

Should donor and other international entities put effort into promoting local production and “self sufficiency” in small developing countries? (i.e., countries at the intersection of the axes in Figure 2). Should effort be put into promoting local production in larger developing countries with innovative capacity such as Brazil, India, China, and a few others? Should effort be put into promoting trade, health and intellectual property policies to ensure effective, safe, inexpensive medicines and let “the market” choose who is the most efficient producer of assured quality, low-cost medicines? Unless we have an evidence base upon which to create policy, such questions will continue to be of academic interest only.

Figure 2: Pharmaceutical Balance of Trade: Supplying the Domestic Market



Recent Efforts at Revisiting the Local Production Assumptions

In the intervening years, there has been little further review of these assumptions. The World Health Organization¹² looked at the arguments for public sector pharmaceutical production (saving foreign exchange, exporting drugs to earn foreign exchange, achieving self-sufficiency) and found limited evidence to support direct public sector involvement in pharmaceutical production, in part because the above assumptions had not been met. See also Foster (2001).¹³ A review of pharmaceutical production policy¹⁰ concluded that local manufacturing can be successful, giving as examples Bangladesh and Kenya, the latter country having a “... profitable product line for local manufacturing despite substantial international competition,”¹⁰ although no data were provided to substantiate these statements. Moreover, the authors did not discuss whether Kenyan local production had improved access to quality, low cost drugs.

The World Health Organization¹⁴ also discussed similar assumptions as described by Foster.⁷ Key additional points were:

1. Generally, the pharmaceutical industry has not made much contribution to local industrialization efforts in developing countries. In particular, for generic products, technology is often available from a variety of sources but sources may be constrained for patented products that require license agreements and transfer pricing of raw materials.

2. Exports to neighboring countries via regional export markets tend to be the exception not the rule, although simple drugs are being made in many countries.

Notwithstanding this, self-reliance in drug production as a means of increasing access to medicines still seems to be priority strategy in a number of Eastern Mediterranean countries. The national capacity for pharmaceutical production has increased in most countries, and Egypt, Islamic Republic of Iran, Jordan, Morocco, Pakistan, Syrian Arab Republic and Tunisia produce between 60% and 95% of their national requirements of essential drugs.¹⁵ However, no evidence has been published that access has improved, quality has been assured, or prices have dropped.

IS LOCAL PRODUCTION FEASIBLE FOR SMALL DEVELOPING COUNTRIES? IF SO, WHICH ONES?

CASE STUDIES AND ECONOMIC AND TRADE DATA

Case Studies

There is a rich literature, much of it emanating from the World Bank, that deals with barriers to business and industrial concerns in developing countries. Most of the barriers are well known, particularly for sub-Saharan Africa: a shortage of skilled labor; a weak financial sector (banking/non-banking); diminished flows of foreign direct investment; the fact that smaller firms face more problems than larger firms with financing, taxes and regulation, inflation, corruption and street crime;¹⁶ a “scaling” problem whereby small country size restrains economies of scale (per unit costs of production) as well as governmental functions being more expensive per capita when the population is small; and weak legal and regulatory systems and enforcement.^{17 18 19 20} There are other potential barriers of particular relevance from the viewpoint of a medicine producer in a developing country: the sustainability of medicine production and, important from the manufacturers viewpoint, predictability of demand for the medicine. There is little available information on the present and future capacity to produce APIs for medicines to treat the infectious diseases HIV, TB, malaria, as well as non-communicable diseases such as type 2 diabetes.

Over the last few years, the number and kind of true, domestic “local producers” has generated renewed interest, in large part because of the need to make antiretroviral medicines to treat HIV/AIDS. Some of these recent efforts include:

- Cosmos Ltd. (Kenya) licensed by GlaxoSmithKline to make generic antiretrovirals (September 2004)
- An economic modeling paper on “local production” with a useful table listing domestic producers in sub-Saharan Africa²¹

To frame our discussion, we provide brief “case studies” of four countries: South Africa (the largest economy in Sub Saharan Africa and a presumed candidate for viable local pharmaceutical production as noted above), India (a major producer of generic medicines that will be faced

shortly with implementing stronger IP protection), Cuba and Jordan (small countries with viable pharmaceutical industries).

South Africa

A recent review of the South African pharmaceutical industry⁹ compared South Africa's domestic and multinational drug manufacturing with several other countries by looking at certain operational functions. These functions provide useful "benchmarking" to look at the differences among multinational pharmaceutical manufacturers in their home country, domestic subsidiaries of MNCs, and South African local producers. These functions, and their importance among types of pharmaceutical producers are summarized below:

- **Strategic Management** - Local producers had short planning horizons and little if any regular strategic planning process. They often lacked mission statements and tended to focus on prioritization rather than standards and targets. Domestic MNC subsidiaries and MNCs frequently evaluated their business strategy, usually with a 5-year outlook.
- **Outsourcing** - Local producers were invariably scaling down to achieve better economies of scale since they couldn't compete against imports from India. Domestic MNC subsidiaries were focusing on a few areas of expertise but were concerned about the high costs of compliance with manufacturing and regulatory standards. They believed it would be more efficient to limit South African activities to packaging and labeling. None of the MNCs interviewed were downsizing.
- **Drug Registration Process** - For local producers of new chemical entities, the process takes between 24-36 months. The first generic takes about 24-36 months and existing products or new indications for existing products take about 12-18 months.
- **Distribution** - Private local producers complained about too many points of sale; theft; mark ups along the value chain to pharmacy without anyone considering the actual costs and value added. Public local producers were concerned about thefts; poor information regarding drug requirements of local hospitals; poor payment by medical departments; and lack of exporting infrastructure (storage, corruption, long distances, inconsistent drug regulatory requirements).
- **Locally sourced raw materials** - Locally owned South African producers broke down local sourcing into several categories in which thirty nine percent (39%) of active ingredients, 97% of packing materials and 49% of excipients were locally sourced. South African-based MNC subsidiaries locally sourced just 1.5% of active ingredients, 36% of packing materials and 20% of excipients. Indian-based MNC outsourced from India fully 93% of active ingredients, and all packing materials and excipients.

Factors Affecting Local Production in South Africa

Feedstock and Raw Materials

Purchasing of active raw materials was inhibited by low order quantities, wide fluctuations in cost per unit and inefficient purchase of bulk materials, in which active ingredients are bought for convenience rather than suitable quality at the lowest possible cost. Companies could not

really import active ingredients competitively. The review suggested that local manufacturers should put more emphasis on evaluating other approved sources of raw materials and that manufacturers should evaluate cooperative sourcing of active materials in order to negotiate better prices.

Global trends in Manufacturing

The review identified a global trend by multinationals towards producing pharmaceuticals at a few “centers of expertise”, characterized by large, low-cost units in logistically well-placed areas attractive to service major markets. Many South African subsidiaries of multinationals are closing precisely because the country does not offer an attractive package for these “centers of expertise.” The review also noted that regulatory authorities in different countries tend to enforce manufacturing standards at different levels leading to the possibility that for similar standards, the cost of compliance can be significantly different between countries.

Production Issues

The review identified several production factors that hindered the local pharmaceutical industry from being competitive: plants are relatively old with high maintenance costs and poor efficiency; there is little emphasis on achieving large production runs and machine utilization rates are low; planned maintenance is given low priority and there is little availability of spare parts.

Labor Issues

The review identified several labor issues, including: high labor turnover and absenteeism; little provision of transport and recreation facilities to improve labor team spirit.

In short, the report summarizes the pharmaceutical industry in South Africa as being small and not very wealthy. It lacks an ability to achieve economies of scale in production. Production runs are short for the local market and higher costs per unit of production can only be counteracted by higher output. Much of the equipment has not been replaced or maintained. Over 30 companies have closed over the past 5 years. A key strategic question is whether South Africa can recognize the importance of the generic sector and shift to generic drug manufacture as the primary way of restructuring the pharmaceutical industry. There are areas within the South African manufacturing sector where existing or new producers could be introduced with a reasonable chance of success. The review identified 100 chemicals made in South Africa and ranked them according to a “market attractiveness” scale. Around 3/4th of them are on the WHO Essential Medicines List.

Regardless of whether South Africa, or any other developing or transitional country, can produce pharmaceuticals locally, the sustainability of the local sector depends in large part upon the relative competitiveness of the local manufacturing industry as well as the impact of external factors (overall state health policy, investment incentives and so on). Several factors undermine the sustainability of South African local production of pharmaceuticals. These factors are not unique to South Africa.

India

With a GDP of about \$500 billion (2001 current U.S. dollars), India has nearly half the GDP of China, which is still extraordinary. India's rich natural resources and manpower have not been fully exploited. The Indian economy is still predominantly agricultural. Agriculture has acquired a remarkable resilience in the last decade. About one-third of the national income is derived from agriculture and allied activities, employing about two-third of the workforce. India's pharmaceutical market was valued at more than \$3 billion in 1998. At its annual growth rate of 15% (almost double the world's 6% annual growth rate), this market is now about \$10 billion. Average per capita expenditure on pharmaceuticals in India is only \$3 as compared to \$412 in Japan, \$222 in Germany and \$430 in the U.S.²² This is due in part to the prevalence of alternative healing methods in India, such as ayurvedic medicine and homeopathy, but also because prices for drugs have been kept artificially low by the Indian government. India's pharmaceutical industry is one of the most highly regulated industries in the country. Price controls have a strong effect on profitability in the industry.²¹ Before 2005, India had no product patent protection but this posed only a short-term threat to foreign investment in India's drug market.

The sheer size and growth of India's domestic pharmaceutical industry is making it increasingly difficult for the government to regulate prices for every single firm. The market structure of the Indian pharmaceutical industry is skewed with a small number of large firms and many smaller pharmaceutical companies. The large private sector includes domestic manufacturers, foreign controlled companies (with more than 25% equity held by a foreign company) and smaller private firms. The Indian foreign controlled companies import most of their bulk drug requirements and produce formulations, their focus being the domestic market.²³ Pharmaceutical policy in India is perceived as industrial policy, not health policy.²⁴ Since 1970, domestic firms have increased in number and since 1999, about 8-10 of these have developed sufficient in house R&D capacity to be able to develop new drug molecules as well as produce bulk drugs. Indeed, some of these large Indian companies have become multinationals themselves.²³ However, the vast majority of private manufacturers are small-scale and have problematic quality assurance systems and procedures.

The success of the Indian pharmaceutical sector has come mainly from the larger Indian corporations. Smaller firms have limited capability for brand building or for developing distribution networks and will tend to contract with larger firms or collaborate with universities or research labs to remain viable. In terms of health policy, there is considerable variability in the quality and pricing of drugs throughout India and these differences are due primarily to differences in quality of training and infrastructure. About 1 in 10 of all private pharmacies reported quality violations, with most of the "out of quality" drugs being manufactured by smaller firms. Each Indian state is responsible for quality assurance activities and there is wide variation in implementation.²³

With the advent of TRIPs compliance in 2005, Indian pharmaceutical companies will now have to patent pharmaceutical products. This will likely provide access to international technology, R&D and global marketing but may also result in rising drug prices and intra-country competition from the many indigenous drug companies. Indian pharmaceutical companies will have to develop their own "know-how" and R&D centers to cope with what will be fierce global competition within and outside the Indian market. To achieve a globally competitive export

strategy, it may be that Indian pharmaceutical companies will enter into a period of domestic consolidation and collaboration with Western companies.

Cuba

Prior to the Cuban revolution, Cuba was like most Third World countries and imported medicines from abroad, principally from the United States,²⁵ so that at the time of the Cuban revolution in 1959, there was no domestic pharmaceutical industry. The imposition of the US embargo in 1962 effectively eliminated the U.S. drug supply source. After the revolution, the situation was transformed with expansions, remodeling and investment in new plants that have increased the capacity of local Cuban production to satisfy national consumption. However, when Washington officially suspended the sale of medicines to Cuba in 1994, over 20,000 North American products for medical use were registered by the medical authorities on the island.²⁴ The US embargo did not prevent drug imports from western Europe and the then-Communist bloc countries.

As early as 1972, the Cuban government established Medicuba, a state enterprise, for the purpose of importing and exporting pharmaceutical products and medical equipment. In the pharmaceutical area, the importation of finished medicine was gradually reduced to the current level of 18%, while Medicuba concentrated on arranging the importation of base chemicals for manufacture of products in Cuba. Early Cuban exports were “traditional” medicines on the World Health Organization’s essential medicines list. Cuba’s pharmaceutical trade was not insignificant, and by 1987 Cuba imported \$34.6 million worth of chemicals, largely from market economies, and exported approximately \$70 million of pharmaceutical products, principally to the West and particularly to Latin America.²⁴

Cuba’s pharmaceutical production capacity is backed by strong government support. In 1993, it was estimated that 1150 biologic and diagnostic products, as well as 30 nonprescription drugs and 132 generic products, were manufactured in Cuba.²⁶ The growth of the local pharmaceutical industry, which by the mid-1990s was bringing Cuba some 100 million dollars a year in export earnings, has not only covered domestic demand for medicines, but has also led to the development of products that compete on the international market. Cuba is the only country in the world, for example, that has come up with an effective vaccine against meningitis B.²⁵ The vaccine is administered free of charge to all children in Cuba, and sold to countries like Argentina, Brazil, Colombia and Mexico. With low, stable prices, China provides around 40 percent of the raw materials used by Cuba’s pharmaceutical industry, although the distances involved mean transportation of the products often takes a month and a half or even longer. At present, nearly 80 percent of finished pharmaceutical products used in Cuba are locally made.²⁵

In some cases, however, costs are driven up by the problems posed by the 40-year-old United States economic and trade embargo. For fear of reprisals from Washington, many merchant marine ships avoid docking in Cuban ports, a fact that frequently forces Cuba to resort to the more costly air shipment of raw materials and medicines.²⁴ The industry’s potential has been affected by the country’s lack of convertible currency to buy necessary raw materials for the production of medicaments. Given all of these difficulties, Cuba has found that it is cheaper to produce generic products than import the drugs. Cuba also has initiated several “South-South” collaborations. For example, in January 2002, India and Cuba announced efforts to strengthen bilateral trade and investment, including the construction of a plant to produce hepatitis B

vaccine in Chandigarh, established as a joint enterprise between CIGB and Panacea Biotec.²⁷ Probably because of its unique political history, Cuba is an atypical example of a small country that is a local producer of assured-quality pharmaceuticals.

Jordan

With just 5.5 million people and a GDP of slightly greater than \$8.3 billion (2001 U.S. current dollars), Jordan's economy is hampered by its size and inadequate supplies of water and other natural resources such as oil. Four companies dominate local production: Hikma Pharmaceuticals (a wholly owned subsidiary by Hikma Investments), Arab Pharmaceutical Manufacturers (APM), Dar Al Dawa (DAD) and the Jordan Pharmaceutical Manufacturing Medical Equipment (JPM). These companies were all established prior to 1980 and by 2000 their combined sales amounted to 83 percent of total Jordanian pharmaceutical companies' sales in 2000.²⁸

The pharmaceutical sector is fairly competitive, with over 15 pharmaceutical manufacturers seeking entry into new export markets and striving to capture a greater share of the small domestic market. Prior to 1990 there were only 6 pharmaceutical manufacturers in Jordan.²⁹ The increase in the number of manufacturers that took place in the last ten years is due to a number of factors, most importantly, that new entrants were hoping to tap into the same export markets as their predecessors. However, they did not anticipate accession to the World Trade Organization (WTO), and hence are facing stringent intellectual property and patent laws. Since Jordan joined the World Trade Organization in 2000, the makeup of Jordanian pharmaceutical production has changed. Approximately 97 percent of Jordanian pharmaceuticals are branded generics (at the end of the patent period, the drug can be produced by any manufacturer) and 3 percent are produced under licensing agreements.

One of the largest Jordanian companies, Al Hikma Pharmaceuticals, was originally financed by the World Bank. It sells about half its production in the low-margin, high-volume bulk tender market dominated by national health ministries. The other half goes to the high-margin retail market, supplying pharmacies with prescription drugs and over-the-counter medicines.²⁸

The World Bank, interested in the impact of the Al Hikma Pharmaceutical Company on development, found the company's contribution difficult to measure because the company "generated few backward or forward linkages".²⁸ Most of the "back" linkages included various inputs and raw materials used to make the pharmaceuticals but these were either imported or manufactured at the site. The "forward" linkages were limited to retail sales. Although the company contributes to the public revenue, most of the imports are exempt from duties. The tax structure for manufacturers is such that the company pays slightly more than \$1 million in taxes.²⁸ The IFC thinks there are "unquantifiable" impacts such as the generation of new jobs, generation of foreign exchange earnings and improving Jordan's "image as a place where entrepreneurs can succeed".²⁸ The company generates an annual payroll for its 530 employees of about \$2.6 million. Recently, however, Al Hikma has enlarged its strategic vision which includes the Jordanian companies plus the wholly owned Hikma Pharmaceuticals in Portugal and Westward Pharmaceuticals in the United States, and two joint ventures, Hikma Ibn Bitar in Tunisia and Jazeera Pharmaceuticals in Saudi Arabia.³⁰ We could not find any information as to whether prices of locally produced medicines were any lower than those of comparable medicines.

Economic/Trade Data

Methods

In this section, we review available information on local production of pharmaceuticals and attempt to correlate local production with various easily measurable economic and healthcare variables. The purpose of this exercise is to find a series of indices that might be used to predict the circumstances under which local pharmaceutical production of a country can compete in the international marketplace.

Some Comments on the Data Quality

For this paper, the major sources of information on local production, total market size, total imports and total exports of pharmaceuticals in various countries, particularly developing countries, were the “Country Guides” of the United States Commercial Service (<http://www.usatrade.gov>).ⁱ The dataset is poor and we were able to obtain information only on an *ad hoc* mixture of OECD and non-OECD countries. Data for local production and total market size (rounded off to the nearest dollar) are available from the authors. These “Country Guides” are brief documents that provide overviews for doing business in more than 120 countries with information on market conditions, best export prospects, financing, finding distributors, and legal and cultural issues. We note, however, that not all countries with pharmaceutical sectors are in the dataset although any country with a pharmaceutical sector of sufficient size to warrant interest by United States exporters is included. In these documents, the typical sources of trade information for developing countries are ministries of trade or commerce, customs data, union and trade associations (U.S. Department of Commerce, personal communication: October 2002).

- We assume, unless we note otherwise, that the data presented here include purely domestic as well as multinational subsidiary production. Unambiguous data on purely domestic local production appear either to be lacking or are very difficult to find.

Other data are similarly ambiguous. Data on “total exports” do not distinguish between export of domestically-derived products and re-export of products previously imported.

- We assume that re-exportation of products previously imported represents an insignificant fraction of “total exports”.
- We assume that, unless stipulated otherwise, data for “total market size” means total retail sales market in dollars and that the prices used were not manufacturers’ prices.

Generally the best quality data are likely to be found in the reports of market research companies and these were unavailable to us. We also obtained information from literature reviews and other Internet sources.

ⁱ Around the end of October 2002, the Department of Commerce changed its website, making it in our opinion much less transparent and more difficult to retrieve information on local production and trade statistics on pharmaceuticals. Such data are now available to US companies and researchers only. The website is now located at http://www.export.gov/comm_svc.

Data Analysis

We performed some simple statistical analyses of the strength of the association between local production and several independent variables (total population, total healthcare expenditure, Gross Domestic Product, human resources) for various countries. Since the values of these variables range over many orders of magnitude (local production: millions to billions of dollars), we transformed all the data into LOG (base 10) form and calculated the strength of association (Pearson correlation coefficient) on the log-transformed data. We obtained information from the World Bank on: 1) Gross Domestic Product (not GDP/capita) GDP is defined as the total output of goods and services for final use occurring within the domestic territory of a given country); 2) Total population; 3) Total Healthcare expenditure. We obtained a “competitiveness index” benchmark designed by UNIDO³¹ as an index of competitive industrial performance, educational statistics for 1999, including the population between ages 10-24 from the Population Reference Bureau,³² and gross enrollmentⁱⁱ (%) in secondary and tertiary schoolⁱⁱⁱ from the World Bank.

The UNIDO index is constructed from four basic indicators: manufacturing value added per capita (MVA); manufacturing exports per capita; share of medium and high-tech activities in MVA; share of medium and high tech activities in manufactured exports. Given the uncertainties in the definition of “local production” and the poor quality of the data, we suggest that the results reflect only rough order of magnitude trends. Since we are concentrating on local production in middle- and low-income countries, data for the United States have been omitted to avoid significantly distorting the picture.

These data sources represent aggregated national data and all of the limitations of such data apply. GDP data do not reflect the pattern of income distribution. Gross enrollment percentages in secondary or tertiary school do not reflect the quality of schooling. Notwithstanding the nature of the data, we believe the associations we have demonstrated remain useful in analyzing factors related to local production issues. For those unfamiliar with log (base 10) scales, LOG 9 is 1 billion (10^9). LOG 10 is 10 billion (10^{10}) and LOG 11 is 100 billion (10^{11}).

Results

Local Production and Various Indicators

The raw data are available from the authors with comments as to their source.

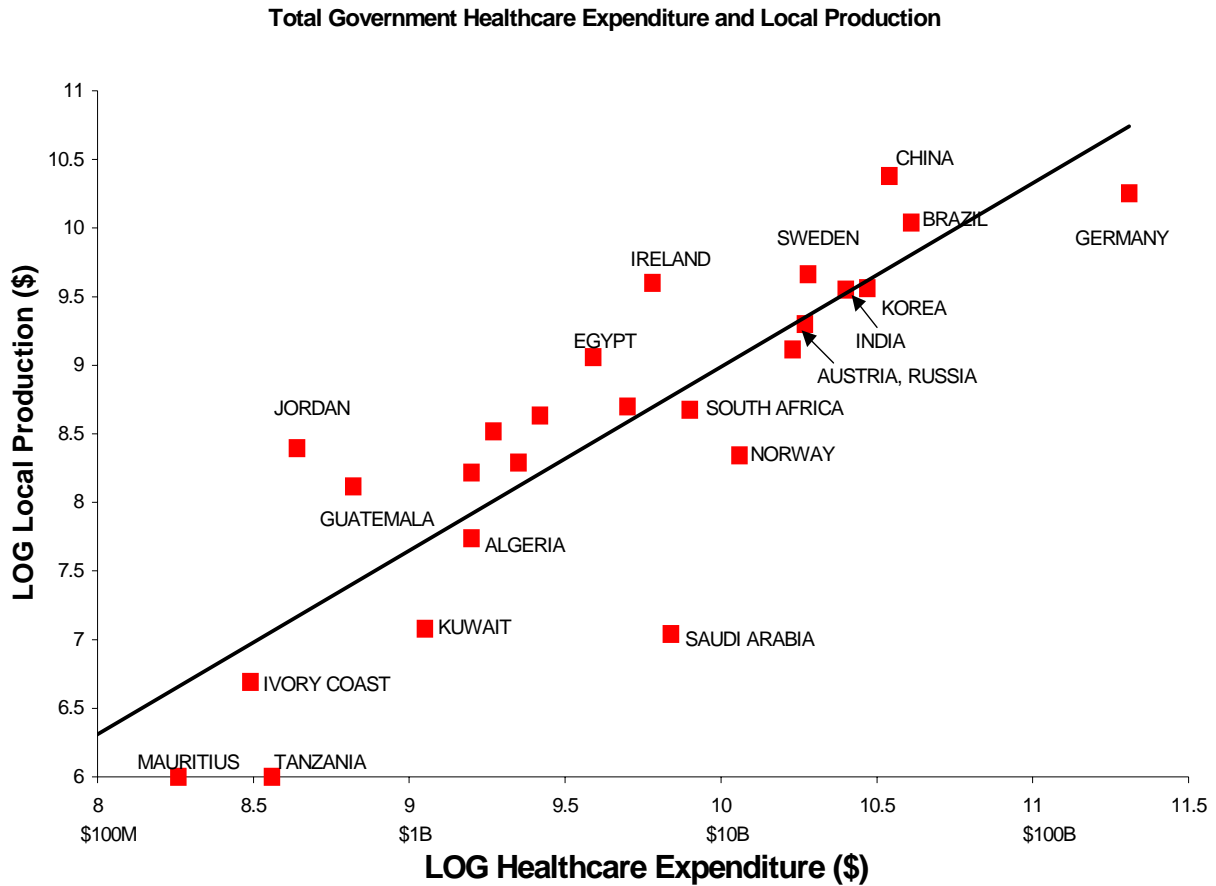
Local Production and Total Healthcare Expenditure

ⁱⁱ Gross enrollment is the number of students enrolled in a level of education, whether or not they belong in the relevant age group for that level, as a percentage of the population in the relevant age group for that level. The gross enrollment ratio provides an indication of the capacity of each level of the education system, but a high ratio does not necessarily indicate a successful education system as the ratio includes overage and underage enrollments.

ⁱⁱⁱ Secondary provides general or specialized instruction at middle, secondary, or high schools, teacher training schools, and vocational or technical schools. This level of education is based on at least four years of instruction at the primary level. Tertiary requires, as a minimum condition of admission, the successful completion of education at the secondary level or evidence of attainment of an equivalent level of knowledge and is provided at universities, teachers colleges, and higher-level professional schools.

The association is quite strong between local production and total governmental healthcare expenditure (Pearson coefficient = 0.82; 95% CI = 0.63 to 0.92; $p < 0.0001$; Figure 3). Data are for the year 2000. For reference, the LOG values have been converted to actual U.S. dollars on the X axis). The association is strong because total governmental healthcare expenditure is itself expected to be closely associated with total gross domestic product (but not GDP *per capita*).

Figure 3: Total Governmental Expenditure on Healthcare and Local Production



Local Production and Gross Domestic Product

We not unexpectedly therefore also find a strong positive association between the value of local production and GDP (Pearson coefficient = 0.85; 95% CI 0.68-0.93; $p < 0.0001$) (Figure not shown). Data are for the year 2000. A least squares regression (slope = 1.34; $p < 0.0001$) suggests a relationship between GDP and local production such that an order of magnitude rise in total GDP (not GDP/capita) is equivalent to about an order of magnitude rise in the value of local production. Those countries in the upper tier of local production (>five billion dollars: Sweden, Ireland, Korea, Russian Federation, India, Brazil, Germany, China) all have a GDP between one hundred billion and one trillion dollars. In terms of GDP, South Africa falls below the lower end of this range and its local production (about \$500 million) is an order of magnitude less than the countries in the upper tier.

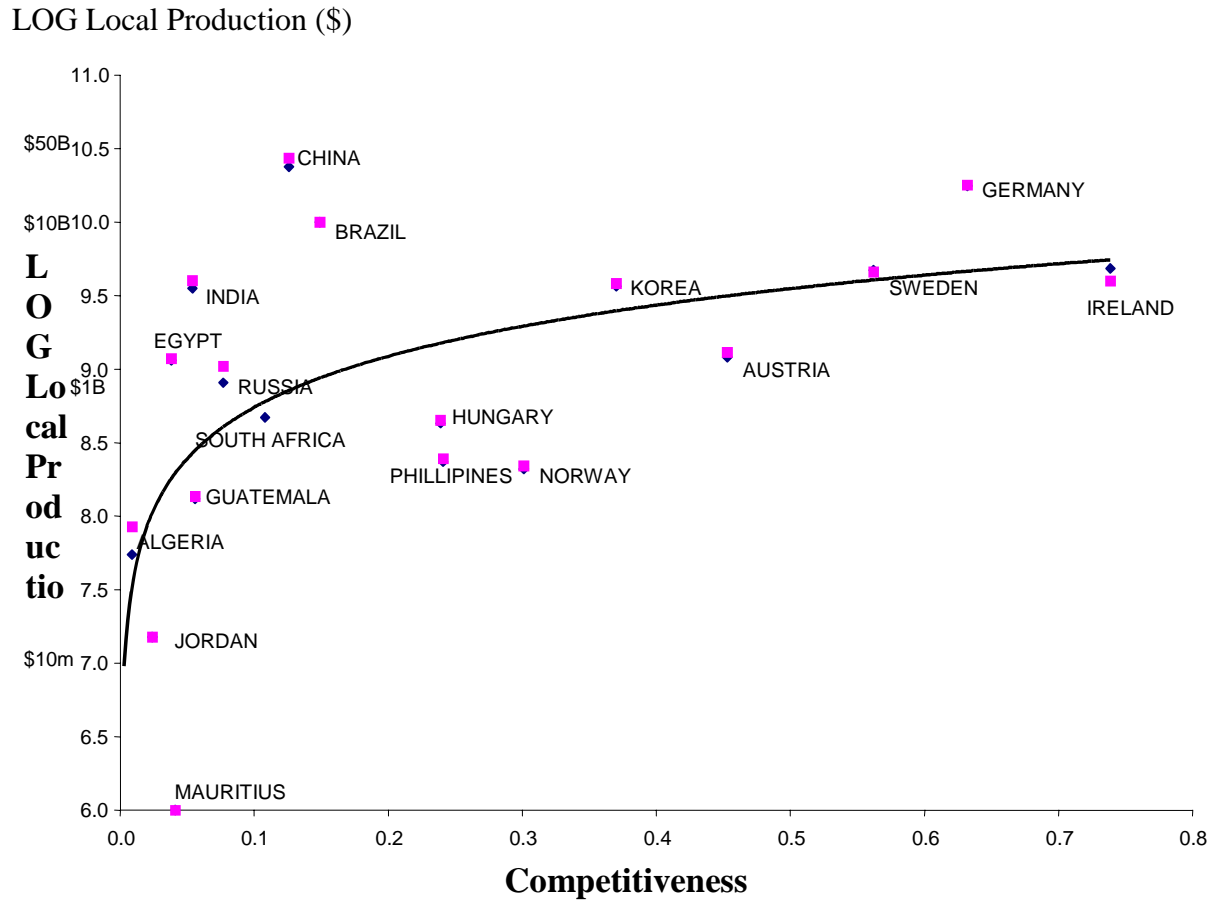
Local Production and Industrial Competitiveness

One might intuitively expect a positive relationship between the magnitude of local production and the level of industrial competitiveness (as a general proxy for industrial capacity). The situation is obviously far more complex. Figure 4 is a semi-log plot and shows the association between the UNIDO index of competitiveness³⁰ and local production recorded for some countries on two consecutive years (1998 and 1999). As a result, most countries are represented by two closely aligned data points. The curve was fit by eye. A small change in “competitiveness index” yields a large gain in pharmaceutical production capacity for low- and middle-income countries (marked by an index less than about 0.15). The UNIDO index takes into account the population size since it includes manufacturing value added per capita (MVA) and manufacturing exports per capita. Thus, countries with large populations such as India and China will likely have low indices, as shown.

Nonetheless, two countries with similar UNIDO indices can have quite different pharmaceutical production capacities. Saudi Arabia and India have about the same “competitiveness index” but India’s local production is more than two orders of magnitude greater even though the Saudi GDP/capita is about 15 times that of India.³³ In this cluster, within a narrow range of industrial capacity, there are enormous differences in the ability to have local production supply the market although generally, as a country moves “upwards” on the competitiveness index scale, local production of pharmaceuticals increases. This increase is not monotonic and there appears to be an upper limit to local production in this dataset at about five to ten billion dollars (US) that is relatively independent of “competitiveness.”

The striking result is that the value of local production for the developing countries Egypt, Brazil, India and China (all on the lower end of the ‘competitiveness’ scale) are on a par, or exceed, those of certain European countries. All these countries are presently competitive beyond their national borders in either the branded or generic pharmaceutical industries. South Africa is absent from this upper tier of local producers.

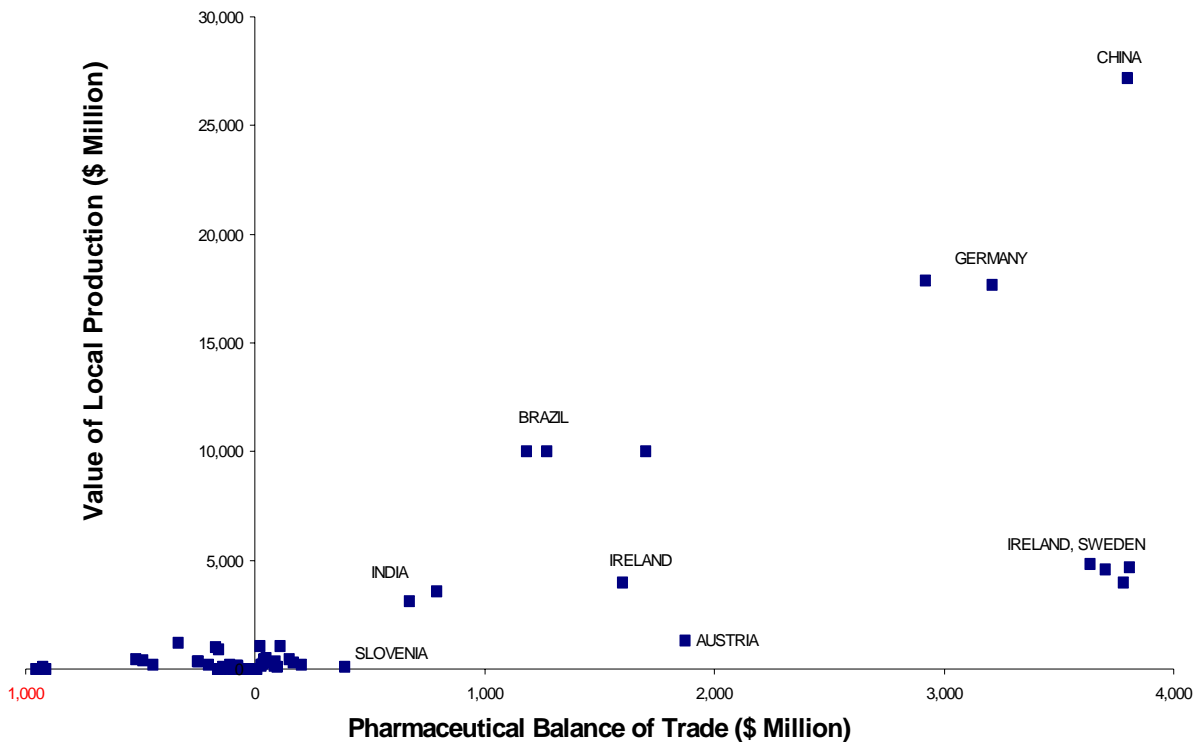
Figure 4: Value of Local Production and Industrial Competitiveness



Local Production and Pharmaceutical Balance of Trade

The relationship between local production and export/import balance of pharmaceuticals may be indicative of whether a relatively robust local economy (proxied by a trade balance favoring pharmaceutical exports) is coincident with robust “local production”. Using the most complete dataset, we calculated the pharmaceutical trade balance for various countries (1998-2000, where available for all three years) and plotted this as a function of local production (1998-2000 where available). Results are shown in Figure 5 where X-axis values to the right of zero are a “positive” balance in millions (pharmaceutical exports > pharmaceutical imports). The scales are not logarithmic. Several points are noteworthy. First, the majority of countries either import more pharmaceuticals than they export (a “negative” balance) or have a positive trade balance not exceeding \$400 million (median = \$100 million). Second, none of the net **importing** countries has local production exceeding \$1 billion. The data are insufficient to infer quantitative relationships.

Figure 5: Local Production (Y) and Pharmaceutical Trade Balance (X)



Local Production and Human Resources: Size of Population

There is a positive, but weak relationship (Pearson coefficient = 0.55; 95% CI = 0.20 to 0.78; p= 0.0045) between the value of total local production and total population (data not shown) when compared to an economic index such as GDP or total healthcare expenditure. Countries with populations between 3 and 30 million people (LOG population = 6.5 – 7.5), exhibit at least a two to three order of magnitude range in local production (e.g., Tanzania and South Africa). Similarly, countries whose local production is between \$1 and \$10 billion exhibit a three order of magnitude difference in population (e.g., Ireland and India).

Local Production and Human Resources: School Enrollment

We used available data on country populations between the ages of 10 and 24 (from reference 32) as a proxy for potential secondary and tertiary school populations and then calculated the actual populations between the ages of 10-24 enrolled in secondary and tertiary education based on percentage of these populations attending.³⁴ We compared the numbers of students enrolled in secondary education to the value of local production in Figure 6 (Pearson coefficient = 0.66; p< 0.005) and those enrolled in tertiary education in Figure 7 (Pearson coefficient = 0.73; p< 0.005). Lines are fit by eye, for reference only. We labeled only certain of the countries to define the boundaries. As expected, the number of students enrolled in secondary education is always greater than those enrolled in tertiary education. The trend is towards increasing value of local production as the number of secondary and tertiary enrollments increase. Clearly, the data say nothing about the quality of education and we cannot infer any causality between numbers of students and magnitude of local production although it is certainly true that the available “pool” of skilled workers is important to support a viable pharmaceutical industry.

Figure 6: Local Production and Secondary School Enrollment

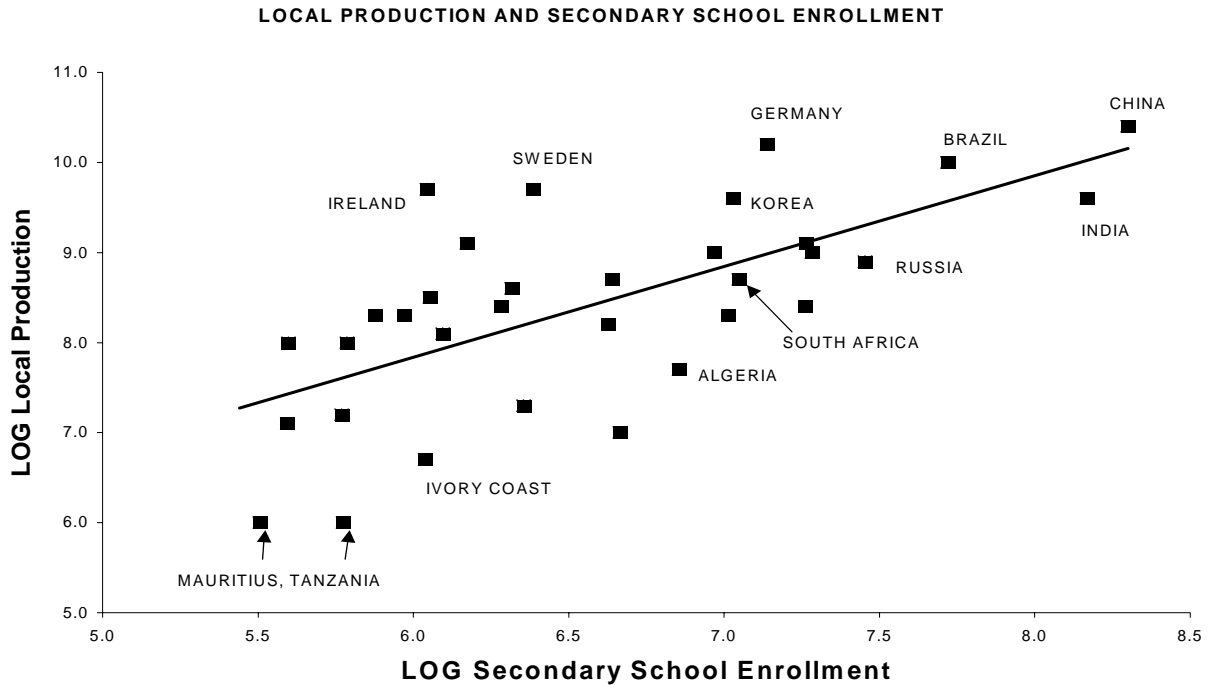
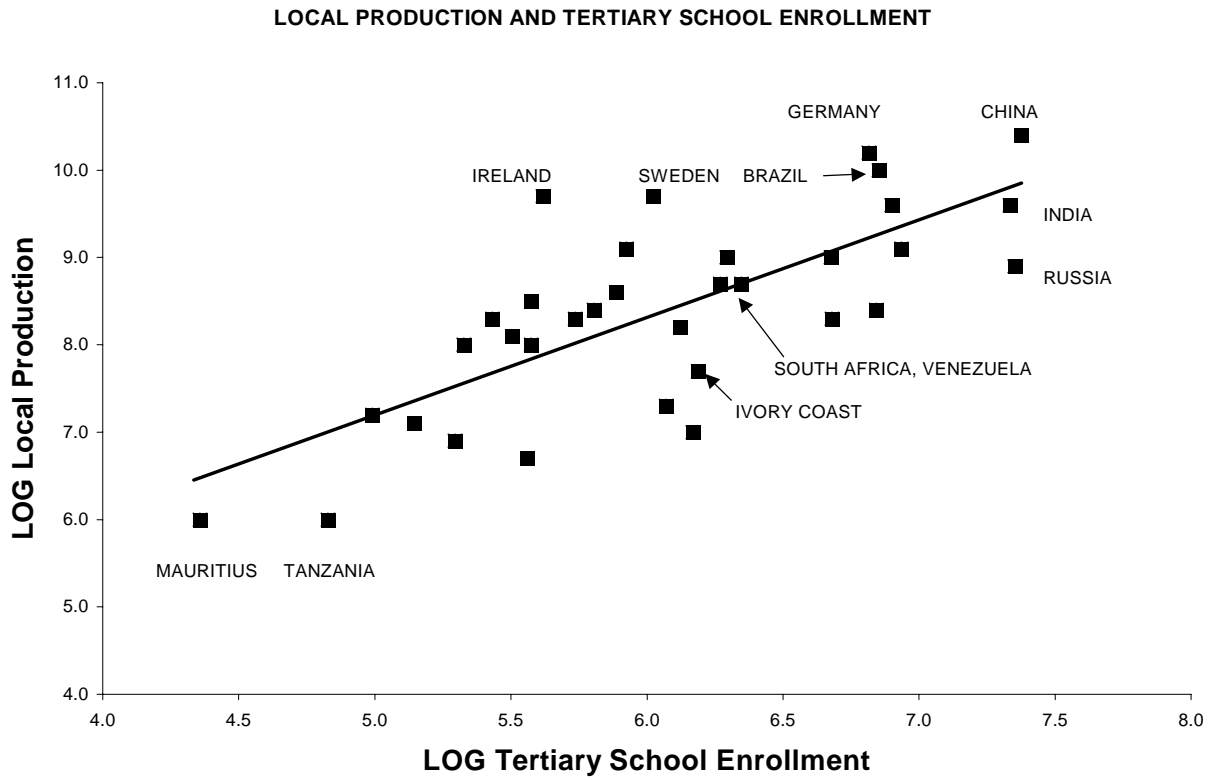


Figure 7: Local Production and Tertiary School Enrollment



Discussion

In only a few developing and transitional economy countries (China, Brazil, Korea, India, Egypt, Poland) is the industrial capacity sufficient to have local production approach or exceed \$1 billion, on a par with several European countries (Sweden, Germany, Ireland, Austria). The larger developing and transitional economy countries may be able to concentrate on producing, assured quality, low cost generics as a matter of health policy. The position of South Africa suggests that it is not yet capable of being a global player with the ability to produce large amounts of locally-made pharmaceuticals on a par with China, India, Egypt, and Brazil. The data in Figure 4 suggest a “threshold” level of industrial competitiveness/activity in these countries, above which the quantity of local pharmaceutical production does not vary significantly; the inference being that at this level, multiple order effects besides industrial “competitiveness” may be important. For example, a competitive pharmaceutical industry requires (and creates) backward and forward “linkages” which may be important--i.e., a link between the pharmaceutical industry and polymer/plastic/container manufacturers (“backward”) and shipping/trucking industries (“forward”).

Figure 3 suggests that a larger national market for pharmaceuticals (as indexed by the proxy values of healthcare expenditure) would be associated with larger local production by value- this being particularly true if “local production” includes subsidiaries of multinationals as well as true domestic production. We predict, but cannot know for certain, that had we the information to estimate true “home grown” local production, the association between such production and either GDP or total healthcare expenditure would be much weaker. .

Figure 5 suggests that only those countries with a “positive” pharmaceutical trade balance (exports exceed imports) are likely to have sustainable local production above the billion dollar mark. Although more comprehensive data are needed, it may well be that a positive pharmaceutical trade balance is a good index that a given country has at least the potential to reach this \$1 billion level.

We would, *a priori*, expect to find some association between local pharmaceutical production and total population. The actual association is somewhat misleading, however, since a pharmaceutical production capacity is not labor intensive but is technology-driven. Arguably, a positive association between the value of local production and total population is due to a simple “concentration” effect; i.e., the greater the sheer number of people, the greater will be the labor pool available to create and sustain the technology needed to support a pharmaceutical industry and the market to consume locally produced pharmaceuticals.

We think that it is not total population, but the quality of human resources, e.g., the number of skilled workers, which, in turn, is based upon the ability of the educational and vocational system to supply industry with these workers. That this is so is suggested by the data of Figures 6 and 7. It is plausible to assume that tertiary education (Figure 7) supplies the talent pool for bench scientists and engineers, while secondary education (Figure 6) is the basis for supplying technical and maintenance expertise. Information on true domestic production would be extremely valuable in further analysis of this “human resource” dimension. We note that India and China are not wealthy countries as measured by their per capita GDP, but their 1 billion-plus populations feed a large secondary and tertiary school population. Their high level technical and university systems have created formidable pharmaceutical industries. The Philippines, Ukraine,

Egypt, Russia and Poland (Figure 7) likely will produce a sufficiently strong educational pool in the future from which to draw their pharmaceutical scientific and technical expertise.

The present data are obviously insufficient to explain the factors responsible for the magnitude of a given country's local pharmaceutical industry but do suggest the obvious intuitive concept that there is a "critical mass" of industrial and socioeconomic development and human and technical resources that must be reached before any "indigenous" pharmaceutical industry can survive. To become globally competitive as a producer of pharmaceuticals requires a combination of factors that only a few developing countries can approach. These factors might include:

- GDP greater than about \$100 billion
- Population greater than about 100 million
- Sufficient numbers of the population enrolled in secondary and tertiary education
- Competitiveness index (UNIDO) greater than about 0.15
- A net positive pharmaceutical balance of trade

DISCUSSION: POLICY OPTIONS

POLICY OPTIONS: GLOBAL

There are several simple policy approaches that can be discussed.

Let the "Rich" Middle-Income Countries Supply Pharmaceuticals

Brazilian, Chinese, and Indian manufacturers have proven their ability to take a product from API to finished dose form at a level of quality suitable for use in regulated markets. In the future, if this ability is combined with low manufacturing costs (possibly in China and elsewhere), there is the potential to create an extremely competitive force in the generic market of the future. Further, if this API manufacturer were to vertically integrate with a dose form manufacturer, it might be able to supply generic products at very competitive prices. Brazil and India already have several vertically integrated manufacturers producing high quality finished generic products.

In the case of India, with the advent of TRIPs compliance in 2005, Indian pharmaceutical companies will now have to patent pharmaceutical **products**. This will likely provide access to international technology, R&D and global marketing but may also result in rising drug prices and intra-country competition from the many indigenous drug companies. Indian pharmaceutical companies will have to develop their own "know-how" and innovative R&D centers to cope with what will be fierce global competition within and outside the Indian market for branded medicines. To achieve a globally competitive export strategy, Indian pharmaceutical companies will likely enter in a period of domestic consolidation and collaboration with Western companies. Companies like Ranbaxy Laboratories and Dr. Reddy's Laboratories are pushing to expand their exports and are increasing their spending on R&D with hopes of becoming more important players worldwide.

In sum, this interest in overseas markets is based on the fact that traditional business models for Indian drug makers will not work much longer. For years, they have thrived by reverse-engineering drugs developed in other countries. But starting in 2005, the intellectual property of Indian and foreign pharmaceutical makers will need to be protected.

Support a True “Indigenous” Production with Various Types of Technology Transfer

Regional cooperatives

PHARMESA

In 1996 a manufacturing initiative began that involved the 23-nation Common Market of East & South African (COMESA). The International Trade Centre (ITC), under the sponsorship of the UN, developed a project to promote intra-COMESA trade of pharmaceuticals. COMESA countries buy only 10 percent of their pharmaceuticals from each other in spite of having high quality pharmaceutical manufacturing companies in several countries. Five companies were asked to form a “syndicate,” operating under the acronym PHARMESA. Their goal was to work collectively in developing ways to serve a broader market within Africa. The PHARMESA initiative did not survive.

ECOWAS

In late 2002, a new association, Economic Community of West African States (ECOWAS) Pharmaceutical Manufacturers Association, was formed. Its purpose is to increase people’s access to drugs, boost formal export market and increase capacity utilization of pharmaceutical companies in the West African sub-region.³⁵ The new association is expected to enable pharmaceutical companies in the region to cooperate and share technical details. It will also attempt to rationalize regional production according to local needs.

North-South technology transfer

North-South transfers, a major bargained-for exchange during the TRIPS negotiations, have not reached significant levels. Nonetheless, in early June 2003, Eli Lilly announced a partnership with WHO, CDC, the Gates Foundation and several universities to transfer \$70 million in technology to help companies in China, India, South Africa, and Russia to produce and sell their own supplies of two off-patent drugs to combat TB.³⁶ Lilly will transfer rights to generic companies to produce two drugs useful for treating multiple drug resistant TB. In exchange, the generics agree to limit the price of generics to 20% over cost.

South-South technology transfer

Zimbabwe and Ghana are apparently finalizing deals under which Thailand would provide the technical expertise needed to set up factories to produce ARVs in Africa. Thailand's state-run Government Pharmaceutical Organization announced in October 2001 it would start manufacturing locally produced HIV drugs by year's end that would cut the cost of treatment in half. There was no word on when factories would be set up or when the drugs might be available. In October 2002, Thai and Zambian ministries of Public Health began discussing a joint venture to make didanosine (ddI). The plant would be built in Zambia. The plant is also intended to enable another 13 countries in the Southern African development zone to enjoy access to more affordable generic drugs. The plant would cost US\$1 million (about 42 million baht) and would take a year to build.³⁷

Recently, Ethiopia announced that it was going to produce generic ARVs locally).³⁸ According to the UN press release, the scheme “... could save the impoverished country millions of dollars” because by “... producing its own drugs Ethiopia could afford to treat more patients.” This Ethiopian initiative is in conjunction with the South African NGO “Initiative for Pharmaceutical Technology Transfer (IPTT)” designed to “... establish a publicly controlled, transparent, sustainable system under which affordable, quality medicines are produced in required quantities, for Africa, by African countries themselves.”³⁹ A privately owned plant in Ethiopia, Bethlehem Pharmaceuticals, was selected by IPTT in October 2003. According to the press release, the plant can make 400 million tablets annually and has “created job opportunities for 105 people.”⁴⁰

The Brazilian government has been planning for some time to act as a “catalyst” of sorts by stimulating the transfer of technology to produce generic HIV/AIDS products to countries in Portuguese-speaking Africa, principally Angola and Mozambique.

Create a “Level Playing Field” by Enabling Trade, Regulatory and IP Rules to Allow Access to Assured Quality, Effective Medicines for Everyone and Let “the Market” Determine the Best “Local” Producers.

As but one example, the EU in May 2003 adopted a regulation that enables exporters of pharmaceuticals and essential medicines to deliver their products to developing nations at strongly reduced prices while ensuring that the goods will not be diverted back to the EU.⁴¹ Exporters are invited to put their products on a tiered-price list run by the European Commission. The new regulations agreed on by the Council would allow pharmaceutical producers to significantly increase the export of medicines for TB, anti-retroviral HIV treatments and drugs to combat malaria at lower, 'tiered' prices, while keeping the drugs at the same price in the EU.

POLICY OPTIONS: THINK GLOBALLY, ACT LOCALLY

Individual countries need to ask themselves difficult questions about where they want to be along the continuum set out in Figure 1. Where a country (or even an individual manufacturer) is located along the continuum in Figure 1 and where it wants to go, are complex questions informed by political and economic considerations, marketing strategies, human resource requirements, legal, regulatory and intellectual property constraints, as well as health-related considerations such as the country’s burden of disease, treatment guidelines and Essential Medicines List. The devil is truly in the details.

For instance, why should a developing country/industry specialize in a market with few players—such as injectable drugs or even sustained release formulations, which are some of the most difficult to manufacture? Once a branded sustained release/injectable goes generic, price erosion may not be as severe as there may be fewer competitors. Is this a really a viable reason to manufacture locally in most developing countries?

- Each country’s market, economic and health situation is unique and must be analyzed in context. This, of course, makes reliance on a monolithic, global “policy framework”

difficult, if not impossible. Whatever “framework” exists must be sufficiently flexible to allow for changing circumstances and development strategies over time.

For instance, India in particular has a skewed market structure with a small number of large firms and many thousands of smaller pharmaceutical companies. Should we assume that these smaller firms, many of which produce medicines of variable quality, will be dominated and be competitively replaced by the larger Indian manufacturers and will eventually play no part in supply of assured quality medicines for the global market? Should these smaller companies be encouraged to improve their quality mechanisms?

- What should be the proper mix of public v. private pharmaceutical production?

The WHO believes that state-owned production is “ill advised”.¹² Profit margins on bulk generic drugs are low, so public production must be as efficient as private manufacturing if losses are to be avoided. Brazil has shown that public production can be efficient. Cuba’s political history may make it a unique case. In 1993, it was estimated that 1150 biologic and diagnostic products, as well as 30 nonprescription drugs and 132 generic products, were manufactured in Cuba. The growth of the local pharmaceutical industry, which by the mid-1990s was bringing Cuba some 100 million dollars a year in export earnings, has not only covered domestic demand for medicines, but has also led to the development of products that compete on the international market. Cuba is the leading producer of an effective vaccine against meningitis B.^{24, 25}

The issue is worth analyzing. Is the ability to attract foreign investment compromised by a state-run pharmaceutical industry? Lessons learned from Cuba might suggest otherwise but lessons from Indonesia are also worth considering. For the last several years, the Indonesian government has been marking several state-run pharmaceutical companies for privatization, including Indofarma, which is the primary supplier of cheap generic drugs to the general public and government healthcare centers. These privatization schemes have been put off, in large part because of the poor management of Indofarma, which went from a reported \$10 million profit in the first half of 2002 to a net loss of \$2.3 million by the end of 2002.^{iv}

What are the risks in creating what may indeed become a permanently subsidized industry based on the public budget? As in most large bureaucracies, such as in some drug regulatory authorities, how does one avoid “regulatory capture” of the state-run operations by the pharmaceutical industry?

- What should be the role, if any, of non-profit institutions in local production?

Traditionally, the non-profit sector has been involved in small-scale production of sterile and non-sterile ointments, creams and solutions (hospitals, local NGO’s and non-profit mission organizations). The rationale for this kind of production is as a ‘backstop’ in case commercial products are in short supply. Is there another role for NGOs in production? We note the emergence of putatively non-profit pharmaceutical entities (One World Health, San Francisco and the Drugs for Neglected Diseases Initiative, Geneva). One World Health has decided to

^{iv} See, for example, Guerin, B., 2003, Indofarma debacle bitter pill for Jakarta, Asia Times, at <http://www.atimes.com/atimes/Southeast-Asia/EE15Ae01.shtml>, accessed 28 April 2004.

revive the off-patent drug paromomycin for treatment of leishmaniasis. Clinical trials might take several years at which point the organization will seek regulatory approval, probably in India.

- How does a country/industry best link industrial policy to health policy? Clearly local industry cannot compete if they produce an ineffective, or poor quality drug.

The responsibility to stimulate R&D and promote local industry is most often discussed in terms of industrial, rather than health, policy. This seems to be also the approach by the International Finance Corporation (IFC). Most of the pharmaceutical industry projects supported by the IFC focus on exports rather than seeking to satisfy internal health needs or address affordability problems.^v As noted previously, there is a tension between a health policy directed to the access problem of making available low cost and quality-assured medicines and an industrial (primarily private sector) policy of optimizing profits and growth by promoting a local industry whose products may be more expensive than those on the international market. Furthermore, the problem of substandard and counterfeit medicines is widespread in many countries.

- How can a country/industry increase their quality standards and encourage human resource development to staff the quality control/assurance process?
- How can other arrows in the policy “arsenal” such as regional procurement, equity pricing and compulsory licensing be integrated into a coherent and internally consistent policy framework?
- Is it really feasible to produce medicines locally that will be competitive on the open market? Has Sub-Saharan Africa in particular concluded that local production is a viable long-term industrial policy objective or is it just politically expedient to do this?
- Should a developing country first request “seed” money from an organization like the World Bank or should it in essence “create” the market by first coming to the World Bank with a coherent and well-thought out business plan that takes into account the present and projected health, legal and economic considerations? Why should the World Bank require anything less than full due diligence by a borrower seeking funding to support pharmaceutical production?

^v As of 2003, the IFC is funding pharmaceutical production projects in India (Orchid Chemicals); Uzbekistan (Core Pharmaceuticals) Ghana (Pharmacare); Jordan (Al Hikma Pharmaceuticals); Macedonia (Alkaloid); Croatia (Pliva); Bosnia/Herzegovina (SEF Bosnalijek); West Bank and Gaza (SEF Pharmacare, LTD); Algeria (Aldaph, SPA); Egypt (Sakem Holdings).

SETTING A RESEARCH AGENDA

TESTING THE LOCAL PRODUCTION ASSUMPTIONS AGAINST THE EVIDENCE

Generating Good Data on Local Production

Accurate information is needed on the distribution, type and output of different types of pharmaceutical producers in developing countries. There is little such information at present. “Local production” can include a range of possible products from raw materials to intermediates to finished dosage forms. Similarly, accurate information is needed on “local” production in low- and middle-income countries by subsidiaries of MNCs in which there is local production but not local ownership. To obtain such information, we need accurate accounting that is shared and standardized. This information could come from manufacturers’ associations and other trade groups, customs officials, and independent watchdog or accounting groups.

Testing the Long-term Effect of TRIPS on the Pharmaceutical Industry and on Pharmaceutical Access, Quality and Use

This research question goes well beyond a study of “local production” but it is perhaps the key question surrounding TRIPS and its implementation in developing countries. The World Health Organization has created a series of indicators for monitoring relevant aspects of pharmaceutical financing, pricing, investment, registration, prescription regulation, intellectual property protections and consumption.⁴² The indicators are designed to shed light on the following questions: How is patenting affecting drug pricing? How are patents and enhanced intellectual property protections affecting the rate of introduction of generic drugs? Are TRIPS and expanded intellectual property protections spurring development of drugs for neglected diseases? Are TRIPS and expanded intellectual property protections contributing to an increase or decrease in transfer of technology and direct foreign investment in developing countries?

Testing the Assumptions About Local Production

Case studies are needed that look at the sociopolitical context for local production of pharmaceuticals and document situations where such production was successful, and where it was not. What are the significant factors that are critical in determining the viability (at the local, national and international levels) of locally produced pharmaceuticals? The South African study is a first step in answering these questions, albeit for a single country. Country studies on local production need to be completed for middle-income countries with industrial capacity, such as South Africa, Thailand, Mexico and Egypt. Countries such as Cuba, Kenya, and Jordan are worth considering with regard to local production of pharmaceuticals and the factors that influence the quality of the end product. The available information that we have on South Africa is informative for beginning to answer several questions:

- *Does local production save foreign exchange?* This probably varies with the country. In South Africa, many ingredients and packaging are imported and even the nearly 40% of raw materials that are sourced by locally owned companies include purchases from importing agents.⁹ By contrast, respondents in India (questioned as part of the South

Africa study, to provide comparator information) indicated that nearly 93% of their active materials were locally sourced.⁹

- *Does local production create jobs?* There is little evidence of this for South Africa. Major labor shortages in the South African pharmaceutical sector are found in very high-level jobs most in demand, i.e., qualified management and technical level specialists such as chemists and pharmacists (particularly those with regulatory experience), laboratory analysts, and clinical research specialists.⁹ Earlier reports suggested that organized labor in South Africa is opposed to reward and incentive schemes that are linked to productivity since they purportedly undermine solidarity and divide workers.⁴³ The human resource factor is critical in this regard. To develop and sustain a pharmaceutical industry requires Ph.D.-level skills for many jobs, plus sufficient technical staff to run the process development and process stream functions, equipment maintenance and drug regulatory capabilities. It would appear that the populations of very few developing countries have the needed skills for these endeavors.
- *Does local production facilitate technology transfer?* There is no evidence for this in South Africa. In South Africa, there is little focus on initial R&D capacity. Costs are considerable and the market is limited so that there appears little interest in the type of technology transfer that local production might create.⁴⁴ Labor turnover is high and with the large number of plant closures, this creates a pool of skilled workers lost to the industry. Since the global trend in pharmaceutical investment is towards capital-intensive operations, South Africa needs to upgrade its manufacturing technology, although this will result in “relatively few jobs” (p.134).⁹
- *Does local production stimulate exports to neighboring countries?* Possibly but the South African study noted that South African pharmaceutical producers need to identify export markets with potential for them, and should use South Africa’s position in SADC “as a mechanism to develop SADC/Africa-based exports ...” (p. 114).⁹ This is likely to occur at the expense of the other SADC countries that are attempting to export pharmaceuticals as well.
- *Does local production lead to lower prices and/or improved access to pharmaceuticals?* The success of India and Brazil in this demonstrates that large countries with a well-developed “indigenous” pharmaceutical industry are capable of producing cheap, assured quality drugs. Nobody should be surprised at this. Can other, smaller countries repeat the success of India and Brazil? That nobody has an answer to this question should also not be surprising.

Testing any or all of these assumptions against an evidence base is challenging and will involve the participation of experts in economics, industrial policy, drug development and pharmaceutical policy. Sufficient data need to be available on foreign exchange, exports, imports, job demand and other economic and societal indicators. A common design that may be used for evaluating changes in policy compares study outcomes during a specified period prior to the change with study outcomes during a specified period after the change. Often, this “pre-post” design uses the same population as its own control, before and after the “intervention”. Other control groups may be difficult to find. One solution might be to use a control group that is

outside the geographic boundaries of the population that is subject to the intervention. Often, but not always, some policies are implemented suddenly and, provided that trends can be modeled with reasonable precision, time series are useful for observing whether an intervention causes abrupt, visible and measurable interruptions in underlying trends, i.e., an “interrupted time series” model.

In practical terms, information on foreign exchange, exports, imports, job demand and other economic and societal indicators needs to be evaluated before and after creating local manufacturing capacity; and before and after changes in industrial and/or pharmaceutical policy with regard to local production of pharmaceuticals.

Creating a Predictive Index of Local Production Based on Easily Measurable Markers

It would appear that some low- and middle-income countries have populations large enough to support the efficient manufacture of a range of pharmaceutical products. Based on our brief survey, does the viability of local pharmaceutical production depend on certain national characteristics such as GDP, population size, competitiveness, and/or health expenditure as we have suggested? The South African study⁹ suggested that its domestic pharmaceutical industry is barely viable nationally or internationally- this in arguably the richest country in Africa, one with a GDP and a per capita healthcare expenditure about equal to that of Venezuela. Certainly, smaller countries with fewer resources and a weak industrial base are unlikely to be viable in the global pharmaceutical market. The key research question is how “big” is it necessary to become in order for local production of pharmaceuticals to compete on the global market; how large a GDP, how much industrial base, how big a population? Further research is needed through in-depth country studies to determine the minimum requirements for a viable, competitive, national industry. It is an interesting question as to how such countries as Cuba or Jordan manage to maintain a viable pharmaceutical industry although they do not fulfill many of the criteria that we have identified.

CONCLUSIONS

Producing pharmaceuticals is a complex process that requires a reliable, high quality supply of raw materials, technical expertise and a stable supply of electricity, gas and other utilities, plus sufficient human resource capacity with Ph.D-level scientists and expertise in pharmaceutical process and regulation. Pharmaceutical plants are capital intensive and take many years to develop and tend to be located in countries with good infrastructure, reliable utilities and access to technical expertise.⁴⁵ Indeed, there already appears to be enough capacity to produce all needed active ingredients as well as to finish bulk formulations sourced from global suppliers.⁴⁴ Thus, it has been argued that increases in production can be accomplished within the present capacity of the global industry. Certainly, the vast majority of the manufacturing cost is in the primary manufacture of active ingredients and the opportunity for smaller local manufacturers to save costs is limited. The distinctions brought out earlier between local production as industrial policy and as a stimulator of pharmaceutical “access” are relevant. The fact that a developing country with manufacturing facilities is able to finish off bulk active ingredients sourced from developed or other countries at high costs may have no impact whatever on patient access to needed medicines.

In November 2001, when the trade ministers arrived in Doha, Qatar, to initiate a new round of global trade talks, developing countries asked for a declaration confirming their right—as part of TRIPS—to allow compulsory licensing of pharmaceutical patents in the interests of public health. The developing world thought that the Doha Declaration institutionalized their right to affordable medicines for all conditions that undermine public health. Indeed, the Doha Declaration cleared the way for this to occur. However, allowing developed countries to define conditions under which developing countries obtain access to pharmaceuticals compromises the national sovereignty of developing countries.⁴⁶ The question as to which countries are capable of sufficient local production to meet their own pharmaceutical needs and the needs of others is of central importance to this debate.

Based on the qualitatively and quantitatively limited data sets available to us, our preliminary conclusions are:

- **In many parts of the world, there is no reason to produce medicines domestically since it makes little economic sense.**
- **In the local pharmaceutical manufacturing sector, local production is often not reliable and, even if reliable, it does not necessarily mean that medicine prices are reduced for the end user.**
- **If many countries adopt local production, the result may be less access to medicines, since production facilities in many countries may mean forgoing economies of scale.**
- **It may be possible for small country markets to be coordinated or otherwise joined together to create economies of scale.**
- **Regarding state-controlled local production, the WHO considers state-owned production to be “ill advised”.¹² Profit margins on bulk generic drugs are low, so public production must be as efficient as private manufacturing if losses are to be avoided.**
- **For many countries, technical expertise, raw materials, quality standards, and production and laboratory equipment need to be imported, with the result that foreign exchange savings may be small or non-existent.**
- **Few developing countries have the capacity to produce active ingredients for pharmaceutical manufacture.**
- **We need much better and comprehensive data on types of local production, particularly purely domestic production.**
- **Industrial investment to promote local manufacture of pharmaceuticals in most, but not all developing countries could be better used to improve health infrastructure or stimulate the existing market, but developing countries need to decide this for themselves and not have such decisions imposed upon them by developed countries.**

- **A research agenda should be created that is specifically designed to test assumptions about local production of pharmaceuticals. This agenda must be based on evidence and not rely just on post-hoc case studies. It should provide for creation of accurate ‘baseline’ information on variables needed to test the “local production” assumptions and sufficiently robust experimental designs (pre/post, time series with controls) to garner and weigh the evidence.**

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