



Pharmaceuticals: Local Manufacturing

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Introduction

Pharmaceuticals are essential in every health care system. The objective of pharmaceutical policy is to make sure that there is a reliable supply of good quality medicines at affordable prices. Local manufacturing is sometimes offered as a potential solution to the “access” problem. Supporters of this concept suggest that local production in a developing country should result in a cheaper final product. Skeptics argue that small manufacturing units don’t achieve economies of scale, and that higher unit costs outweigh potential advantages such as lower transportation costs.[1]

Another factor in this discussion is the TRIPS agreement. TRIPS requires all countries (except the least developed) to introduce patents for pharmaceuticals in 2005. There are mechanisms in place, for example compulsory licensing, to balance the interests of patent owners with public interests in countries affected by a health crisis such as HIV/AIDS. So, for example, a country may declare that a health crisis makes it imperative for them to have access to a particular drug, and there is an established process through which the country can issue a license (whether or not the patent holder agrees) to a company to manufacture or import the drug. But it is not yet clear whether these mechanisms work well for countries that rely on imported pharmaceuticals only. Thus, the question of local manufacturing comes up, as a way to bypass the complexities of licensing agreements that cover more than one country.

This paper reflects on aspects of health policy and industrial policy relevant to local manufacturing, which need to be balanced according to development priorities. It advocates for a sound assessment of costs and benefits as the basis for rational decision making on pharmaceutical manufacturing.

The world market for pharmaceuticals

Global pharmaceutical sales were over 500 billion USD in 2004. Of this market, 88% is in the developed world (North America, Europe and Japan). Asia and Latin America together contribute about 11%, Africa’s share is less than 1%.[6]

These numbers would look different if units (tablets) were counted instead of sales value. Middle income countries with large populations would take up a much larger share, based on large volume / low cost markets for drugs in these countries (unfortunately, reliable data are not available because these numbers are not very relevant for industry decision makers). The large home market allows manufacturers in India and China to produce at low unit cost and exploit economies of scale. Given that drugs can be moved easily around the globe, if there were no or few barriers to importing, registration, marketing and distribution, presumably, it would be hard to beat Indian and Chinese manufacturers on price (although there may be lower price manufacturers who do not meet quality standards). Any market analysis that is done to establish the business case for pharmaceutical local manufacturing should recognize these facts and assess the sustainability of the business under changing policy conditions (opening of markets) in the future.

Overview of pharmaceutical companies in low- and middle-income countries

There are several types of pharmaceutical companies with different business models that operate manufacturing facilities in developing countries:

Subsidiaries of large multinational companies (i.e. Pfizer, BMS, GSK, Novartis) manufacturing proprietary, branded products for local and regional markets.

Generics manufacturers operating globally (i.e. Cipla, Ranbaxy, Sandoz, Teva) ranging from USD 0.5 to 5 billion in annual sales, working increasingly with a globally integrated manufacturing strategy. Key parameters influencing investment decisions are access to main markets, costs, infrastructure and skilled labor. Their core business is focused on developed markets in the US, Europe and large middle income markets such as India and China. Some of them have manufacturing operations in smaller developing countries or joint ventures with local manufacturers. They offer a large portfolio of generic drugs at competitive prices and are capable of meeting global standards for quality – a prerequisite for their presence in the developed markets. A few of these companies have made significant investments in R&D and may turn into viable competitors on the high-value market for innovative drugs in the future.

Generics companies with predominantly national operations: Their main market is the country of residence, although sometimes they export significantly into other (usually nearby) countries. For example, the Jordanian pharmaceutical manufacturers fall into this category: 18 companies with total sales of about 200 million USD in 2003, of which 73% are exported.[5] In some countries, these manufacturers adhere to Good Manufacturing Practice (GMP). In others they do not meet this standard. Their product range is typically based on off-patent drugs.

Small-scale local manufacturers: These companies are small in size and output and usually make a limited number of products. Most are not able to meet GMP standards. They tend to serve local or regional markets including the informal sector. Some specialize in traditional medicines. Others are owned and run by local NGOs or large hospital pharmacies in an attempt to cut costs by importing active substances in bulk and formulating the final product in-house.

Some companies cut across these categories: for example a regional manufacturer producing a branded drug under a license from a multinational at a GMP approved facility, at the same time making generics at manufacturing sites that are not accredited under current GMP standards.

Generics versus Branded Generics

The term “generic drugs” is used in this paper for all drugs that in principle can be obtained from multiple sources, as opposed to drugs that are sold only by the originator company or its exclusive licensees. Under this definition, the term “generic” does not specify whether the drug is sold under its INN name (active substance name) or under a brand name. Generic drugs are not always lower priced – some local “branded generics” are sold at prices equal to or higher than the originator product, depending on market conditions, access barriers and price transparency.

Stages of pharmaceutical manufacturing

Three major steps are required to make a finished pharmaceutical product.

Chemical synthesis

Extraction or fermentation is used to make the active drug substance or active pharmaceutical ingredient (API). This step is usually the most technically difficult and value-adding step.

Formulation

For example, a pill is made by blending the API with filling materials, granulating, compressing and coating. This step appears to be technically less demanding,

but has to be done according to precise specifications because it determines the ability of the product to dissolve in the stomach and generate adequate levels of the drug substance in the blood.

Packaging

The final drug is blister-packed or bottled, placed in cartons and labeled, so that the product can be transported and stored safely and the relevant information is available with the product. This is the least complicated and least value-adding step in the entire process.

Local manufacturing in developing countries is usually limited to formulation and packaging. There are exceptions in larger middle-income countries like India and China, which have the scientific and industrial base to master the more complex challenge of making active drug substances. In fact, India has become a leading provider of API raw material for the manufacturing of generic drugs all over the world.[2]

Quality and cost considerations

Pharmaceuticals need to be manufactured in a way that ensures effectiveness and safety and avoids any health risks that can result from impurities, variations in the amount of active substance or the dissolution pattern of a pill. Errors and mix-ups in formulation or packaging and other possible mistakes can be deadly and need to be avoided by all means. All major pharmaceutical manufacturers have implemented a comprehensive set of safeguards and procedures that are summarized under the term GMP (Good Manufacturing Practice) or cGMP (“c” standing for current, highlighting that the rules/practices change with scientific progress and need regular updating). GMP covers layout and functionality of buildings, qualification and training of personnel, cleanliness and sanitation, monitoring, supervision and many other aspects (for a detailed example see <http://www.gmp1st.com/dreg.htm#210.1>).

Adherence to GMP can add significantly to investment and operating costs of a manufacturing operation. There might be a tendency to “cut corners” when a manufacturer is under financial pressure and the supervisory agency is not equipped to enforce strict adherence to GMP.

Pharmaceutical manufacturing should only be encouraged in countries that have an effective control agency to enforce GMP. If this capacity is lacking, the costs of building and upgrading a drug regulatory agency that can oversee the industry effectively need to be considered in the overall calculation.

Factors influencing the competitiveness of pharmaceutical companies

Other costs that affect the competitiveness of a local manufacturing business are the labor costs for qualified personnel (locally available or expatriates?), cost of capital, construction costs, taxes and tariffs, costs for environmental safeguards, insurance, licensing, utilities and costs of externally procured goods and services. Starting a new manufacturing operation with inexperienced staff can lead to significant initial costs due to errors, for example if batches do not meet specifications and need to be destroyed.

On the positive side, a strong position in a large domestic market offers the possibility of manufacturing large lots, which reduces unit costs significantly.[3] Alternatively, a company can try to compete in export markets in order to increase its size and improve financial viability (see box on the Jordanian drug industry on page 4). A strong regulatory agency in the home market facilitates export business, as it provides a credible proof of quality.

Another important factor is market strength: an established company, with a number of brands that are well known and trusted by consumers, will be able to introduce a new product more successfully and with lower costs than a newly established manufacturer.

In short, the ideal environment for a profitable pharmaceutical manufacturing business is in a country with a solid regulatory agency, a good business and industrial infrastructure, easy access to capital, ample supply of cheap but qualified labor, low costs for construction, equipment and utilities, and a large domestic market that allows substantial economies of scale in production. Looking at all these factors, it is no surprise that India has become a major player in pharmaceutical manufacturing.[3, 4]

Governance framework

Unfortunately, manufacturing and trade in pharmaceuticals have been associated with nepotism and corruption in some countries. This may be due to the complex nature of this business. It is understood by experts only and hence is largely out of reach for informal public control mechanisms. Buying decisions are usually made under the influence of experts (doctors or pharmacists), who may have financial interests that interfere with their role as trusted advisors. Manufacturers may try to influence regulatory decisions or to get preferential market access in exchange for favors.

Thus, before investing in local pharmaceutical manufacturing, there should be an assessment of governance structures and related risks for the sustainability of operations on one side, and future health care cost trends on the other.

HIV/AIDS and the politics of manufacturing

The AIDS crisis and the need to treat large numbers of infected individuals with anti-retrovirals (ARVs) has spurred a number of manufacturing initiatives in developing countries, based on the assumption that it would be cheaper to make drugs “at home” than to buy them from a foreign manufacturer. Whether this assumption is true is difficult to establish, in particular since global deals with drug makers have brought prices for first-line treatments down significantly. However, given the unprecedented scale of the public health crisis caused by HIV/AIDS, the political aspects of local manufacturing should be given special consideration. Local manufacturing has the potential to strengthen political support for treatment programs, mobilize resources to overcome health system bottlenecks, and align political leaders behind the cause of fighting HIV/AIDS. Pride in a national industry and political pressure to make it work may be significant assets in achieving the ultimate treatment goals – more important than potentially slightly higher costs per unit.

Strategic policy options under different scenarios

Countries should take into account their economic conditions and health services infrastructure capacity when deciding on an appropriate strategy for evaluating investments in the local pharmaceutical industry. Both health and industrial policy objectives should be explicit and balanced so as to be consistent with the overall development strategy. The following classification is somewhat simplified in order to provide a clear differentiation. In the real world, some countries might find themselves in more than one scenario at the same time. Or there may be a rationale for a different sequence of steps in order to adjust to the dynamics of an emerging society.

For countries with a sizeable home market and an existing competitive industry, such as India, Brazil, South Africa:

- Strengthen governance and the regulatory framework to ensure that the local industry can produce for the global market.
- Gradually abandon subsidies or preferential market access to fully expose local industry to global competition at a pace that allows it to adapt and become stronger.
- Open the market to foreign companies willing to invest in the local industry, encouraging the introduction of new technology and development of R&D capacity to further improve competitiveness.

For countries with a medium sized or small home market, or an existing industry with questionable competitiveness:

- Strengthen governance and the regulatory framework to ensure safety of drugs in circulation.
- If the local industry is used to a protected environment, allow two to three years for adaptation, but implement a clear path towards full enforcement of GMP standards and a market that is open for globally operating competitors.
- Encourage collaboration and mergers between companies; invite foreign companies to take over local manufacturers. The goal should be to eliminate substandard manufacturing but keep as many jobs as possible.
- Assist the local industry in exploring export markets.

For countries with a medium sized home market, no relevant local industry, but good infrastructure:

- Focus resources on developing an efficient procurement system, distribution chain and payment systems with incentives for rational use of pharmaceuticals.
- Develop strong regulatory capacity to secure safety of drugs in circulation.
- Explore willingness of larger global companies to invest in local pharmaceutical manufacturing, but consider the incremental costs of upgrading the governance and regulatory framework.
- If subsidies are considered for industrial policy reasons, they should neither become a burden on the health budget nor lead to higher drug prices.

For countries with a small or medium sized home market, or with limited infrastructure:

- Focus resources on developing an efficient procurement system, distribution chain and payment systems with incentives for rational use of pharmaceuticals.
- Develop strong regulatory capacity to secure safety of drugs in circulation.
- Shut down substandard manufacturing operations; assess the possibility of changing the business model from manufacturing to pharmaceutical wholesale and distribution.

Example: Jordan - Pros and Cons of having a strong national drug industry

Jordan is a middle income country with a small population (5.4 million), but a sizeable and profitable pharmaceutical industry. 18 companies make a wide range of mostly branded generics, of which 73% are exported. This industry is an important element of the local economy, with over 8000 jobs directly or indirectly depending on it.[5] Because of their role in the economy, local companies have a strong say in the country's national drug policy. There are significant entry barriers for low-cost manufacturers from other countries (such as India and China), and a price regulation system that leads to relatively high prices for multi-source products. The national industry depends on "good prices" at home in order to get similarly profitable prices in export markets (the so called "country-of-origin" method for drug pricing is still common in many parts of the world). The question arises: Does the indirect subsidy from health care spending (through higher prices compared to global benchmarks) generate an overall positive effect on the economy through export income that otherwise might not have been earned?

For additional information, resources

FDA documents on pharmaceutical manufacturing and quality assurance:

<http://www.fda.gov/cder/guidance/6419fnl.htm>
<http://www.fda.gov/cder/guidance/cGMPs/default.htm>
<http://www.fda.gov/cder/gmp/index.htm>

EMA guidelines on GMP:

<http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm>

WHO GMP guidelines:

<http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html>

European Federation of Pharmaceutical Industry position:

http://www.efpia.org/4_pos/access/localprod.pdf

Report on manufacturing for pharmaceutical executives (commercial):

<http://www.pdci.on.ca/reports/manufacturing.htm>

World Bank support:

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