# Local Production and Access to Medicines in Low- and Middle-Income Countries

## A literature review and critical analysis

Intellectual Property and Trade
R&D, Innovation
Technology Transfer
Improving Access
Financing
Monitoring and Reporting

World Health Organization

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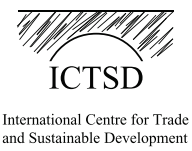


Prepared for the WHO Department of Public Health, Innovation and Intellectual Property by Warren A. Kaplan (Center for Global Health & Development, Boston University, United States).

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All reports associated with this project are available for free download from the following website: http://www.who.int/phi/en/

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# Contents

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## List of abbreviations

| | |
|---|---|
| API | active pharmaceutical ingredient |
| ARV | antiretroviral |
| CQS | chloroquine-sensitive |
| CQT | chloroquine tablets |
| FDI | foreign direct investment |
| FTA | free trade agreement |
| GNI | gross national income |
| GTZ | Deutsche Gesellschaft fuer Technische Zusammenarbeit, |
| HAART | Highly active antiretroviral therapy |
| IPR | intellectual property rights |
| LDC | least-developed countries |
| LMIC | low- and middle-income countries |
| LP | local production |
| MOH | ministry of health |
| NEML | national essential medicines list |
| NGO | nongovernmental organization |
| OECD | Organization for Economic Co-operation and Development |
| OTC | over-the-counter |
| PAHO | Pan-American Health Organization |
| PPP | public–private partnership |
| R&D | research and development |
| SEC | Securities and Exchange Commission |
| TB | tuberculosis |
| UN | United Nations |
| UNCTAD | United Nations Conference on Trade and Development |
| UNDP | United Nations Development Programme |
| UNIDO | United Nations Industrial Development Organization |
| WHO | World Health Organization |
| WHO/PHI | World Health Organization Department of Public Health Innovation and Intellectual Property |
| WTO | World Trade Organization |

# 1. Introduction

## 1.1 Balancing industrial and health policies

For the pharmaceutical sector, policy-makers around the world continually struggle to balance health policy objectives (e.g., access to affordable and essential medicines) with those of industrial policy in the pharmaceutical sector (e.g., promoting innovation and local research and development (R&D) activity).[1] Tensions particularly arise over pricing and reimbursement. Limited health care budgets – and competing demands for scarce resources – force governments to set limits on which medicines to provide or subsidize, for whom and at what price. What ministries of health and/or health plans view as necessary to maintain equitable access to medicines, industry may view as detrimental to R&D and innovation.

## 1.2 Purpose of this report

This report explores the interface between industrial and health policies. Based on a literature review in the field, the report summarizes previous theoretical and empirical work on local production (LP) of biomedical products, and its potential impact on access to medicines. By 'products' we mean medicines and devices, including diagnostics. The report:

- Assesses to what extent the linkages between LP and access were explored in previous studies;
- Critically analyzes whether the methods employed in the literature were sufficient to suggest a robust relationship between LP and access;
- Evaluates whether results obtained could be directly applied to LP conditions in low- and middle-income countries (LMICs).

It is not primarily a review of LP, nor is it an extensive policy discussion on improving LP in LMICs.

## 1.3 Definitions

### 1.3.1 'Local production'

#### *Jurisdictional component*

Local production can take several forms:

1 As an example of the balancing required, Australia has implemented a range of generic programmes and policies to promote, attract and support domestic investment in R&D. Key components of the industry development agenda include direct government support for basic science, research infrastructure and higher education through a combination of grants, tax concessions, venture capital and import/export programmes. Between 1988 and 1999, the government allowed medicine manufacturers undertaking new R&D or value-added production in Australia to receive premium prices under their reimbursement scheme (PBS). Premiums were to be valued at a maximum of 25% of the additional research or production activity. Between 1999 and 2004, firms were required to undertake additional manufacturing and R&D activity in Australia in exchange for higher prices for medicines listed on the PBS (Morgan et al., 2008).

1. Local subsidiary of, or joint venture with, a multinational pharmaceutical company selling branded medicines in local and regional markets (i.e. Glaxo Smith-Kline, Pfizer, etc.);
2. Generic manufacturer producing medicines for the local and global markets (i.e. Ranbaxy, Cipla, etc.);
3. Generic manufacturer producing medicines for predominantly the local market; and
4. Locally–owned, small-scale manufacturers serving a portion of the domestic market (Mercurio 2009).

Some manufacturers cut across more than one of the categories, as branded medicine companies now operate their own generic companies and successful, large-scale generic companies are also developing branded medicines. For the purposes of the current review a jurisdictional definition has been adopted, rather than one based on ownership. If production occurs within a country to produce one or more of the materials listed below (see *Product component*), this is regarded as 'local production'. Most foreign direct investment (FDI) in low-income countries remains in the non-productive sectors. Hence, this form of multinational corporation subsidiary activity will tend to be minimal in the case of LMICs.

### *Product component*

The focus of this review is on biomedical products including pharmaceutical products, vaccines and medical devices, for example. With regard to pharmaceuticals, primary LP is the manufacture of active pharmaceutical ingredients (APIs) and intermediates from basic chemical and biological substances. Secondary LP includes the production of finished dosage forms from raw materials and excipients (inactive substances). Tertiary LP is limited to packaging and labelling finished products, or repackaging bulk finished products. In relation to vaccines and LP, many vaccines are currently derived from viral particles developed in eggs. Technology is specific for each vaccine product and may include isolating viral particles, producing vaccine 'seed' viruses, bulk manufacture, and assembling polyvalent vaccines. With regard to medical devices, the product component can be extraordinarily complex as a medical 'device' can be anything from a bed to a magnetic resonance imagery machine.

## *1.3.2 'Low- and middle-income countries'*

According to United Nations (UN) nomenclature, there is no established convention for the designations 'developed' and 'developing' countries. The World Bank classifies countries according to income, although it should be noted that classification by income does not necessarily reflect development status. Significantly, countries defined as LMICs by the World Bank are considered to be 'developing' under the UN classification. For the purpose of this report, countries have been classified according to the World Bank system,[2]

2 *How we classify countries*. World Bank website: http://data.worldbank.org/about/country-classifications

which divides countries according to 2009 gross national income (GNI) per capita, as follows:

- Low-income: GNI of US$ 995 or less;
- Lower-middle-income: GNI of US$ 996–3945;
- Upper-middle-income: GNI of US$3946–12 195.

According to the World Bank system, all other countries are considered to be high-income countries (GNI per capita US$ 12 196 or more).

Some Central and Eastern European countries are not classified as LMICs by the World Bank nor are they considered 'developing' by the UN system. Some are high-income countries, for instance Hungary. Middle-income countries such as Brazil, India, Mexico South Africa and Taiwan, China have been called 'emerging markets' using other classification systems, however, the classification based on income is more widely used.

Aggregating LMICs in this way masks differences in the unique social, economic, political and health characteristics and contexts of countries and their effects on industrial and health policy. However, for the purpose of this report we use this approach to separate LMICs from those that are characterized by more resources, a longer tradition of promoting and evaluating industrial and health policies, and organizational structures – such as insurance systems – that facilitate policy.

### *1.3.3 'Access to medicines'*

The linkages between LP and 'access to medicines' may initially appear to be relatively simple connections between production, competition and lower prices for medicines, implying that LP provides lower prices through: increased competition, increased economies of scale and/or simple geographical access. However, access is a broader and more complex phenomenon, influenced by more factors than lower prices. In the early stages of the production operations, manufacturers in LMICs might not be able to capture essential economies of scale, which are often only realized in the medium term. Hence a more dynamic medium-term perspective of local production may be required.

Moreover, 'access to medicines' is multi-faceted and includes:

- lower prices (and greater affordability);
- greater availability through the presence of local branded generic medicines;
- local adaptation of pharmaceutical products by local firms (through incremental innovation efforts of local firms);
- new forms of innovative medicines and medical products developed by local firms that may/not be tailored to the local population(s);
- greater availability through better distribution networks of local firms (e.g., in some LMIC settings, local firms may be able to improve penetration of rural markets).

# 2. Methodology

## *2.1 Search strategies*

Building on the experience of a previous literature review on local production (Kaplan and Laing, 2004), the search strategy was founded on two main assumptions:

- Studies showing a robust relationship between 'local production' and access to medicines would be sparse or even non-existent, so capturing different aspects of the issue as possible was essential.
- Much of the local production-related literature occurs in the grey literature. Issues related to local production of biomedical products are often cryptically labelled since 'local production' is not a term in common academic use. Because of its cross-cutting nature, reference to local production may be found in relation to innovation capacity, science and technology, industrial and pharmaceutical policy, IPR analysis and health economics.

As a result, local production is a wide-ranging and challenging subject to search systematically using relatively standard search terms.

Literature searches were performed using keywords and their common synonyms (i.e., 'local', 'national', 'regional' and 'domestic' variously combined with 'production', 'manufacturing' and 'pharmaceutical', 'medicine', 'diagnostic', and searching in both title and/or abstract fields. Search terms also varied according to keywords and search terms permitted by respective databases (Annex 1). Specifically, medical subject headings (MeSH) were used for PUBMED and major subject headings were used for EMBASE, CSA/PAIS and POPLINE. The search strategies were intended to identify information regarding high income countries as well as LMICs.

In addition, there is a large literature comparing multinational corporations and local producers in various countries in relation to finances, foreign direct investment and labour productivity. Local production is not an economic term, so further searches were completed within literature on comparative economics and related performance. Databases were searched using combinations of terms such as 'comparison', 'foreign', 'multinational', 'domestic', 'local', 'performance', 'price', 'pharmaceutical', 'emerging market' etc. This particular search was neither systematic nor exhaustive.

We further distinguished the literature into different categories depending on the kind of study identified (e.g., case studies, econometric models, surveys etc.) and the subject matter (e.g., access, IPR, innovation, supply chains etc.).

## *2.2 Databases*

### *2.2.1 Peer-reviewed articles*

Literature reviews were conducted using various databases:

AfricaWide Information; PUBMED (including the Health Services sub-category; CINAHL; EMBASE; Thomson Reuters (formerly ISI); Web of Science; EconLit; CSA International Bibliography of Social Science; International Network of Rational Use of Medicines (INRUD); PAIS International; POPLINE (One Source); Google Scholar.

### *2.2.2 Grey literature*

To search the grey literature more specifically the following websites were reviewed: the Organisation for Economic Co-operation and Development (OECD); the World Bank; the World Health Organization (WHO); the Pan American Health Organization (PAHO); the Medicines Transparency Alliance (MeTA); the United Nations Industrial Development Organization (UNIDO), the United Nations Development Programme (UNDP); LexisNexis; e-medicine archives; Google; and Google Scholar.

For the Google searches, we also looked for specific countries: Argentina, Bangladesh, Brazil, Egypt, Ghana, Jordan, Mexico, South Africa and the United Republic of Tanzania. We reviewed the most relevant articles up to the first 20 search results. The most relevant search result was then searched for all hyperlinked related articles. We repeated this search twice, once for 'medicines' and again for 'diagnostics' (see Appendix 1).

For all Google searches that were not specified to a given country, the total number of initial results was enormous, and active review was limited to the first 100 references identified. All databases and searches that retrieved relevant references are listed in Appendix 1.

### *UNCTAD case studies on local production and technology transfer*

The United Nations Conference on Trade and Development (UNCTAD) recently completed a series of case studies examining the transfer of technology and local production of pharmaceuticals in different regions, highlighting characteristics such as firm structure, the means by which they obtained and developed the technological capacity to produce medicines, and the types of products handled (UNCTAD, 2011). These case studies were searched to identify the terms 'access', 'availability' and in order to answer the question: "What kinds of evidence exist in these documents that technology transfer improves access to biomedical products?"

### *2.2.3 The primary objective: Inclusion criteria*

The primary objective of this review was to identify operational or implementation/analytical studies identifying linkages between local production and access to biomedical products in LMICs.

The nature of evidence that would clearly satisfy this objective is summarized below, in Table 1.

***Table 1** Criteria for robust evidence regarding local production and access to biomedical products in LMICs*

| Criteria | Explanation |
|---|---|
| Study objective | Define the relationship between local production and access to biomedical products (medicines and/or diagnostics) |
| Study designs | Interrupted time series analysis; and/or<br>Repeated measures studies; and/or<br>Controlled or uncontrolled studies before and after local production. |
| Study sites | LMICs<br>Public and/or private health care institutions; and/or<br>Pharmaceutical retail sector; and/or<br>Public or private biomedical manufacturing sites. |

### *2.2.4 The secondary objective*

A secondary objective of this review was to identify descriptive literature and case studies summarizing the general benefits of local production of pharmaceuticals or diagnostics. The purpose was to gain inferences about the kinds of information that might be needed to satisfy the primary objective.

# 3. Results

## 3.1 A note on the search strategy and results

It cannot be unequivocally stated that the sources identified in the current review are the only potentially useful and reliable sources of information on the subject. Although an attempt was made to implement a systematic search strategy, additional materials could almost certainly be identified using a free form search. The search strategy employed has not covered the entire literature on local production, given its cross-cutting nature, but covers sufficient ground to provide a substantive starting point.

## 3.2 Barriers to local production in LMICs

In most of the LMICs under consideration in this review, local production operates in the context of the following key factors that often tend to disfavour innovation and access to medicines.

- *Human resource constraints*

  In the United Republic of Tanzania, senior management posts in the entirely private local producer (i.e., Shelys) are filled with overseas staff, while the middle and lower tiers of management are filled with local personnel. Both of the local producers (i.e., TPI and Keko), which operate under public–private partnerships (PPPs), are staffed almost entirely by local personnel (Chaudhuri, 2008; Mhamba and Mbirigenda, 2010).

- *Inadequate infrastructure*

  Poor roads, poor communication infrastructure and lack of transport.

- *High operating costs*

  Due, in part, to poor infrastructure to support development. In many cases, there is a lack of industrial zones where utilities could be easily provided for all businesses.

- *Weak links between local and international suppliers*

  Such linkages could reliably source ingredients and raw materials, obtain relevant packaging, access support for specific equipment that requires regular servicing and calibration, and help obtain spare parts for equipment and machinery.

- *High cost of local commercial capital*

  Including limited access to commercial credit.

- *Poor price controls*

  policy framework and government structures so that systems and processes do not guarantee any particular price to the consumer

- *Industry fragmentation*

  This leads to weak competition and poor economies of scale. For example, sub-Saharan African manufacturers generally produce at a cost disadvantage to larger Asian generics manufacturers. Scale efficiencies

generally plateau around 1.0–1.5 billion tablets in blister packaging per year. Production at most sub-Saharan African formulation sites is far below that level. For example, it is estimated that a third of the 30–40% cost disadvantage that a leading Ghanaian manufacturer suffers versus high-scale Indian manufacturers is attributable to scale.

- *Low production quality standards*

  Because of low production quality standards, local producers may only be granted market authorization for one or two years, while imported medicines are generally granted market authorization for four or five years. As a result, transaction costs for importing wholesale traders are likely to be much lower than the costs for the local producers.

Various binding constraints on innovation exist in many countries, including not creating incentives for productive entrepreneurship, lack of provision of adequate skills to the work force, poor transmission of information and ideas, and weak financing opportunities for start-ups, upgrades and commercialization.

### *3.2.1 Protection of local producers*

Disadvantaged by one or more of the above factors in most LMIC settings, local producers can potentially benefit from regulatory support in one or more of the following forms: (1) preferential policies for public tenders (price advantage); (2) tax benefits on raw materials, intermediates and final products; and (3) import bans on selected essential medicines (for example, in Ghana and Nigeria, imports of the seven largest volume products are banned).

More particularly, the Government of Nigeria has previously used pharmaceutical import bans to support increased production by domestic manufacturers. While the medicines banned are those currently manufactured locally, if there is not enough capacity to meet aggregate demand, prices for any available medicines will be prohibitively high. In Pakistan, as of 2002, all importing firms in the private sector had to resister as importers with the government. US-based pharmaceutical manufacturers also faced differential application of the internal sales tax between some of the imported pharmaceutical raw materials (taxed at 15%) and the same domestically-produced raw materials (exempt from taxation). (US Government Printing Office, 2002).

In the Philippines, investors in certain industries were subject to specific laws that required local sourcing. Some laws have required that pharmaceutical firms purchase semi-synthetic antibiotics from a specific local company, unless they could show that the landed cost of imported semi-synthetic antibiotics is at least 20% less than that produced by the local firm (US Government Printing Office). Finished products that compete with locally-produced goods faced high tariffs of 15–30 %. As one last example, in Malaysia the level of tariff protection was generally lower on raw materials and increased for those goods with value-added content or that had undergone further processing. A sales tax of 10% was also levied on most imported goods.

In general, these protectionist policies aid the competitive position of local producers. As local manufacturers increase their production capabilities, it is possible that governments will extend this support to new products or segments of the supply chain (International Finance Corporation, 2011).

### *3.3 The linkages between local production and access to medicines*

A study by Chen et al (2010) clearly illustrates the tension between industrial and health policies, and the complexities of isolating the factors that determine how local production impacts on access to biomedical products.

Chen et al. (2010) investigated the manufacturing, purchasing and prescribing of essential medicines in two provinces in China. In 2007, they conducted surveys of all manufacturers (n=253), and of 59 purposely selected retail and 63 hospital pharmacies, in Shandong and Gansu provinces in order to assess production and supply of products on the 2004 National Essential Medicines List (NEML), as well as factors underlying decision-making about production and supply. They also reviewed prescriptions (n=5456) in health facilities to calculate standard indicators of appropriate medicines use.

Local manufacturers in Shandong and Gansu produced only 62% and 50%, respectively, of the essential medicines they were licensed to produce. Of a randomly selected 10% of NEML products, retail pharmacies stocked up to 60% of imported products. Apparently, manufacturer and retail pharmacy managers based their decisions about medicines production and stocking on economic considerations, while hospital pharmacy managers cited clinical need. Many essential medicines are not perceived as profitable because of low demand, as well as price and mark-up controls. The Chinese pricing authority strictly controls the price of generic medicines, while allowing higher prices for branded generics and much higher prices for originator products. To avoid price controls, manufacturers have shifted registration and marketing to branded generics. In addition, hospitals and doctors have few incentives to use relatively inexpensive generic essential medicines. Health facilities generate greater profits through prescribing of medicines with high mark-ups that are not subject to price control. The more medicines doctors prescribe, the higher the income hospitals and doctors receive.

The authors of the study concluded that there were competing interests between the pharmaceutical industry profit orientation and the government objective of securing access to affordable essential medicines for the public. Over the past three decades, provincial and municipal governments have promoted the pharmaceutical industry as a pillar for economic growth and job creation without emphasizing its responsibility in helping to secure access to essential medicines.

If that this apparent disconnect between industrial and health policies exists elsewhere, no specific, measurable link should be observed between local production and access to medicines.

### *3.3.1 Other illustrative themes highlighted by the review*

As part of the review, three further observations were made:

a. There is extensive business and economics literature covering the comparative economics and strategic planning of multinational corporations and domestic firms. There are fewer references with regard to emerging markets or LMICs, and even less in relation to comparing local and multinational pharmaceutical corporations.
b. The series of UNCTAD case studies on technology transfer as a useful resource base; and
c. The relatively sparse, and mostly descriptive literature on the benefits of local production.

#### *a. Comparing the behaviour of domestic and foreign producers in-country*

There is an extensive literature providing evidence that multinational corporations (MNCs) and local firms are different, primarily based on the fact that the former tend to be relatively more intensive in R&D and advertising than domestic producers (see Dunning, 1988, 1993; Markusen, 1991). The fact that MNCs possess these firm-specific, ownership-based assets in relatively large amounts implies that they are likely to be relatively efficient compared to non-MNC. Correspondingly, MNCs are also likely to be relatively more profitable than other firms if they face similar demand-related conditions. In addition, the marketing networks of MNCs are often more concentrated in international marketing than those of non-MNCs, making it easier for the former to exploit international trade opportunities.

There are two rather distinct areas of economic literature relevant in this regard. One stems from the theoretical aspects and attempts to explain why MNCs exist despite their disadvantage relative to local firms due to inferior knowledge of domestic markets. In addition, economic theories focus on how MNCs overcome these disadvantages as a result of two major factors: they possess relatively large amounts of firm-specific proprietary and knowledge-based assets, as well as generally intangible ones related to production techniques and processes, marketing networks and/or management ability.

Kirim (1986) assessed the comparative performances of MNCs and local pharmaceutical firms in Turkey. Five main issues were reviewed: (i) technologies, (ii) marketing practices, (iii) products, (iv) prices, and (v) the relative export performances of MNCs and local firms.

Comparison of the product structure of MNCs and that of local firms with the prevalent national pattern of disease burden – as well as with the pattern of drug consumption by specific groups of medicines – indicated no significant difference between the two groups of firms in terms of the products they produce and market. Significantly, both the MNCs and the large comparable local drug firms similarly relied more heavily on the production of medicines that do not provide cures for the major causes of mortality in Turkey. The authors could not conclude that the presence of local firms in the Turkish

pharmaceutical industry had been beneficial, because " …all the negative aspects of pharmaceutical production and exchange which the critics have attributed solely to MNCs have been similarly reproduced by local firms in the pharmaceutical industry in Turkey." Local firms were equally involved in overpricing activities. It was argued that, due to the existing pricing legislation, all firms in the industry were motivated to inflate their costs, and hence, final product prices, The available evidence indicated, however, that MNCs overpriced to an even higher extent than local firms.

Additional analysis and conclusions of comparative studies of domestic firms' and MNCs' behaviour are summarized in Table 2. Interestingly, most of the available comparative information of this kind is not from the pharmaceutical sector.

***Table 2**: Comparative behaviours of local firms and multinational corporations*

| Country | Context of study | Analytical method | Conclusion(s) | Reference |
|---|---|---|---|---|
| India | Pharmaceutical | Firm-level data from National Statistics Office: Econometric study | Domestic firms, most of which are controlled by family-based structures, enjoy higher efficiencies (operating profit margins, net profit margins, fixed asset turnover, working capital, inventory holding period, and many others) than affiliates of MNCs. | Saranga and Phani (2009) |
| Bangladesh | Pharmaceutical/ Chemical | Stock exchange data: Econometric study | Domestic production cost advantage over large MNCs gives local products a price advantage. MNCs have more advantageous infrastructures, technology, finances and administration. | Ahmed (2008) |

*Continues…*

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| Country | Context of study | Analytical method | Conclusion(s) | Reference |
|---|---|---|---|---|
| Viet Nam | Pharmaceutical | Literature review and interviews | Local companies enjoy a low-cost advantage: locally-produced drugs are less expensive that those imported from the West, Malaysia or Thailand. Antibiotics, cold remedies, painkillers and vitamins make the bulk of the domestic production. | Simonet (2008) |
| China | Electrical industries | Qualitative: questionnaire<br>Quantitative: correlations | Strategic choices of foreign and local firms differ even when they directly compete. MNCs have superior technological and organizational skills and local firms a have more favourable institutional environment. | Luo and Tan (1998) |
| Thailand | Automobile industry | Firm-level data from National Statistics Office: Econometric study | Foreign plants have high labour productivity, but this is not due to ownership but to other factors. Small size of the Thailand automobile market prevents both foreign and local plants from exploiting economies of scale. | Ito (2002) |
| Viet Nam | All industries | Firm-level data from National Statistics Office: Econometric study | Foreign MNC were larger with higher labour productivity, capital intensity, wage levels, investment and trade than local firms. Results regarding profitability were mixed. | Ngoc and Ramstetter (2004) |

*Continues…*

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| Country | Context of study | Analytical method | Conclusion(s) | Reference |
|---|---|---|---|---|
| Malaysia | All industries (mining, manufacturing, utilities) | Firm-level data from National Statistics Office: Econometric study | No significant difference in labour productivity between wholly foreign-owned and locally-owned establishments. MNCs have significantly lower levels of labour productivity than locally-owned establishments in Malaysia. | Khalifah and Adam (2009) |
| Global | Various industries | Reviews and summarizes the results of selected empirical studies on performance gaps between MNCs and their domestic counterparts | Performance gaps arise in such fields as productivity, profitability, wages, skills and growth but foreign ownership *per se*, is not a factor in this. | Bellak (2004a) |
| Pakistan | Various industries | Firm-level data from National Statistics Office: Econometric study | Foreign firms use more skill and technology intensive techniques than local firms, leading to a labour productivity advantage. | Mahmood and Hussain (1991) |
| Spain | Various industries | Firm-level data from National Statistics Office: Econometric study | Subsidiaries of MNCs invest less in external R&D than domestic firms. Both kinds of firms have similar internal R&D investments. | Un and Cuervo-Zazzura (2008) |

*Continues…*

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| Country | Context of study | Analytical method | Conclusion(s) | Reference |
|---|---|---|---|---|
| Thailand | Food, electronic, automobile, chemical and textile industries | Supply chain surveys | Supply chain operational performance is significantly influenced by industry type and ownership conditions. MNCs have a higher supply chain 'score' than locals. Chemical industry score was near the bottom. Local and foreign chemical firms had the same supply chain "score". | Yaibuathet, Enkawa and Suzuki (2006) |

## *b. Technology transfer and local production: UNCTAD case studies*

Some of the information derived from the eight UNCTAD case studies, including use of the terms 'diagnostic', 'access', 'afford' and 'avail' (and their various versions as noted by the wildcard '*') are summarized in Table 3. Several examples were also noted in these case studies of assertions that could not be substantiated. This illustrates the difficulties in identifying corroborating evidence in studies based mostly on interviews.

***Table 3**: UNCTAD case studies on technology transfer*

| Country | 'Access' and/or 'availab*' and or 'afford*' (# related to biomedical products)† | 'diagnostic' | Examples |
|---|---|---|---|
| 1 | 15 (3) | 5 (0) | The relationship with MNC has provided Y with early access to therapeutics that are new to the country or regional market or have few competitors.<br>Some firms have attained a level of sophistication and technical capacity that contributes to greater access to medicines through discovery and development of new medicines and vaccines. |

*Continues…*

*Continued from previous page*

| Country | 'Access' and/or 'availab*' and or 'afford*' (# related to biomedical products)† | 'diagnostic' | Examples |
|---|---|---|---|
| 2 | 25 (3) | 0 | A competitive market with a large number of medium- and large-sized companies is theoretically sufficient to provide ample space for price-based competition that is essential for greater access to medicines. This does not seem, however, to be the case.<br><br>From an access to medicines perspective, the study shows that both long- term and short-/medium-term considerations have to be taken into account.<br><br>Access to affordable and quality medicines through local production depends on the availability of scientific and technological capacities. |
| 3 | 14 (3) | 4(0) | Implementation of a universal health care system has allowed the creation of a public market for generic products that dramatically expanded access to medicines.<br><br>Rise of local generic production and the complementary importation of other drugs by multinational firms have resulted in 86% of population having access to medicines. |
| 4 | 10 (0) | 1(0) | |
| 5 | 11 (2) | 0 | Locally manufactured non-branded generic medicines are the most affordable.<br><br>A decree mandating all medicines be produced locally is problematic from an access viewpoint as high cost, low volume imports may be barred. |
| 6 | 7 (1) | 6(0) | Company X facility elsewhere in Africa operates as a going concern, and contributes to providing access. |

*Continues…*

*Continued from previous page*

| Country | 'Access' and/or 'availab*' and or 'afford*' (# related to biomedical products)† | 'diagnostic' | Examples |
|---|---|---|---|
| 7 | 24 (3) | 0 | Presently, the drugs produced by company X are approximately 20% more expensive than other branded drugs that are available in the local market for the treatment of the HIV. |
| 8 | 20 (0) | 0 | |

† . Total number of times the word appeared in the document (total number of times the word was related to a biomedical product).

## *c. The putative benefits of local production*

In our attempt to identify linkages between local production and access to medicines, we can also look at its putative benefits. In principle, these benefits may be able to provide: 1. a framework for the types of information that could be collected in a robust monitoring and evaluation project, in order to quantify these links; and 2. a way to assess the gaps that exist in other countries with regard to their technical, financial and regulatory contexts.

We have obtained a document summarizing these presumed benefits in some detail. It is a 2010 filing with the United States Securities and Exchange Commission (SEC) [1] of a company (Vantage Health) wishing to build a facility to manufacture APIs in South Africa. Other examples from the literature are shown that also address these benefits.

### Direct benefits

*a. Potential cost savings*. According to the Vantage Health (SEC) document, a dedicated ARV–API facility in South Africa would be competitive against the lowest cost international producers on the basis of improved process technology, continuous (as opposed to batch) processing, and better economies of scale. The extent of the cost saving depends on which APIs are being manufactured and what processing steps are required.

However, the following general comments can be made about this potential benefit: 1. Most APIs are produced in batch chemical plants that are highly inefficient from an asset utilization perspective. Such plants are generally oversized for the required capacity and operate according to long batch processing cycles. A dedicated facility, which has been explicitly designed to manufacture only a few APIs, would likely provide a lower cost platform for ARV–API production. 2. Secondly, the process technology itself has been considerably improved over the last few years through innovative technology. Many of the established producers are constrained by old processes and

3 The US Government authority that maintains fair and efficient financial markets and facilitates capital formation (see http://www.sec.gov/about/whatwedo.shtml)

technologies; new entrants have greater flexibility to innovate and select more efficient process routes.

*The United Republic of Tanzania:* Mackintosh and Mujinja (2008) surveyed four rural districts in the United Republic of Tanzania and found that nearly half (46%) of recorded observations of various tracer medicines were locally made; the most widely available basic medicines, including paediatric suspensions, basic antibiotics and antimalarials, and analgesics, were all available and widely stocked in Tanzanian versions. Only four companies – Shelys, TPI, Keko and Zenufa – produce antibiotics (simpler ones such as amoxicillin, ampicillin, chloramphenecol, and not the more advanced ones such as cepholosporins). The Shelys product range consists mainly of simple antibiotics, cough and cold preparations, analgesics and antipyretics, sedatives, nutritional supplements and/or treatments, anthelmintics and antimalarials. TPI has started producing fixed-dose combinations of three ARVs (Chaudhuri, 2008). Only the injectable antibiotics, some chronic illness medicines, and one antibiotic were solely available as imports. First-line combination ARVs were just beginning to be locally produced and were found in some hospitals. India supplied a larger proportion (27%) of the items recorded than Kenya, the other major import source (20%), and India was the sole non-European source of the injectable antibiotics. There were no significant differences between prices of medicines from the three main countries of origin, suggesting a competitive pricing process among the three suppliers with no apparent advantage given to the Tanzanian products Mackintosh and Mujinja (2008).

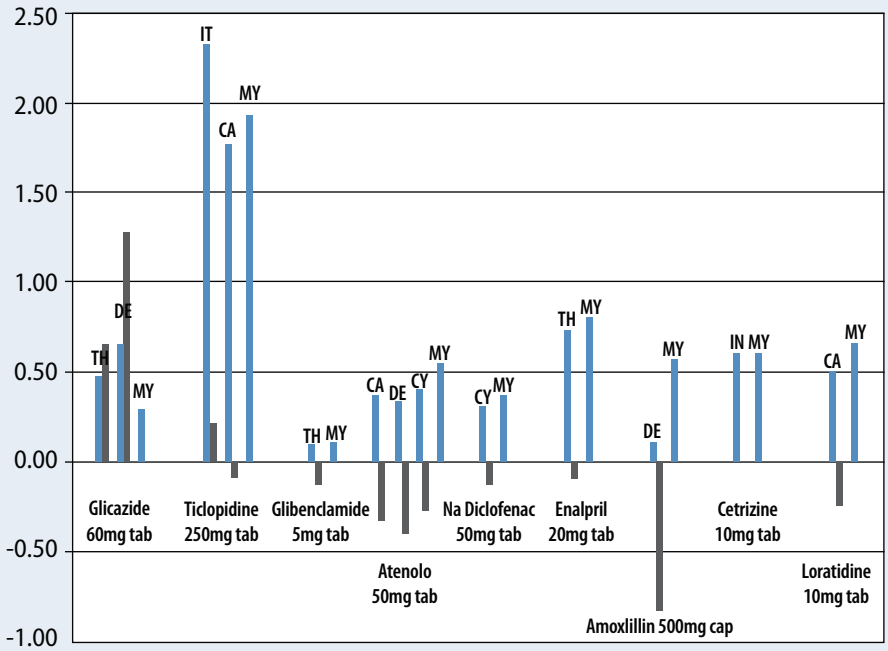
- *The United Republic of Tanzania*: Chaudhuri (2008) found that local production supplies approximately 30% of private and public markets. These authors assert that "...this figure underestimates the importance of local manufacturing for sustaining access to medicines in Tanzanian rural areas." Various tracer medicines included in their qualitative survey in four rural districts were widely available in shops and nongovernmental facilities. Of these medicines, an average 66% were locally made by Tanzanian manufacturers. In rural health facilities, paediatric suspensions, basic antibiotics, antimalarials and analgesics from Tanzanian suppliers were all widely stocked. Only injectables, some chronic illness medicines and one antibiotic were available solely as imports. Many Tanzanian products had wide familiarity and labels that included information in Kiswahili. These authors concluded that "… local production is currently a key contributor to access to essential medicines in rural Tanzania."
- *Modelling study:* Guimier et al. (2004)) created an economic model to test whether domestic production of a variety of medicines could have a modest impact on medicine affordability. By 'modest' the authors meant between a 1–26% reduction in *ex works* price. The higher range may seem impressive but this price reduction was found to be very sensitive to increases in API prices or a loss of (or failure to reach) market share and could easily negate price reductions. The size of the mark-ups that are subsequently added during distribution in both the public and private sectors is likely to outweigh the reduction in *ex works* prices in a large proportion of

sub-Saharan African countries. This could diminish the primary contribution of domestic production to access if the distribution system does not pass on the savings. This may be less of a risk in the case when medicines bought by the government are distributed by public networks, but mark-ups are also added in the public sector and can still add significantly to medicine prices (Guimier 2004).

- *Brazil:* Nunn et al. (2007) compared Brazilian prices for locally-produced generic ARVs to the lowest international prices meeting global pharmaceutical quality standards. They found that as of 2006, prices for Brazil's locally-produced generic medicines were generally much higher than corresponding global prices, and noted that these prices have risen in Brazil while declining globally. They estimated the total excess costs of Brazil's locally produced generics totalled US$ 110 million from 2001 to 2005.
- *India:* Chaudhuri et al. (2006) used an econometric model with detailed product-level data on monthly pharmaceutical prices and sales of antibiotics in the Indian market (the fluoroquinolone segment of systemic antibacterials). Their basic theoretical scenarios all involve the withdrawal of one or more of the locally-produced product groups from the market because of patent protection. The idea was that had patents for, e.g., ciprofloxacin, been recognized in India, all domestic products containing ciprofloxacin would not be present in the market, leaving only the foreign ciprofloxacin product group in the market. Using such a model, the authors simulated prices and market shares and were able to calculate the additional expenditure that Indian consumers would incur in light of the domestic product withdrawal(s) and accompanying price and market share changes. Empirically, the component of the consumer welfare loss attributable to the withdrawal of locally- produced fluroquinolones turned out to be significant and was considered an impact on access due to " …differences in the marketing and distribution networks, domestic products being more readily available to Indian consumers than products produced by foreign subsidiaries." Nonetheless, the estimated loss of consumer welfare from the simultaneous withdrawal of all four domestic product groups was more than two times the sum of the estimated losses from scenarios where only one domestic product group is withdrawn. In absolute terms, the authors estimated that in the absence of any price regulation, the prices of foreign patented products would rise between 100% and 400% if local production ceased.
- *Malaysia*: Shafie and Hassali (2008) compared prices of innovator and generic medicines in Malaysia. Some of the generic medicines were made locally and some of them were considerably more expensive than imported counterparts. The authors assumed that retail mark-ups were identical across products and suggested that the local producers may not be "efficiently producing affordable medicines" and are passing the high costs on to the consumer. Figure 1 has been prepared using data from their study.
- The patterned bars show the average price of the listed generic medicines (US$ per pill) for the Malaysian local producers (MY) and the foreign counterparts (DE= Germany, CY= Cyprus, IN=India, CA=Canada, IT=Italy).

The solid bars are the percentage (x100) difference in price between the foreign and locally-produced generics. For all but one of these medicines, at least one foreign generic was somewhat cheaper than the locally-produced version. In particular for atenolol, loratidine and amoxicillin, the foreign versions were significantly less expensive than the locally-produced medicines.

***Figure 1** Comparison of prices of innovator and generic medicines in Malaysia*




- *Bangladesh*: Chowdury and Kabir (2009) studied pricing differences of 35 essential medicines between local producers and multinational pharmaceutical companies in Bangladesh. Local pharmaceutical production in Bangladesh mostly comprises formulation as the majority of APIs and other raw materials are imported. A few active ingredients are being produced by local companies. Only two products (Aspirin 300 mg, Chlorpromazine 25 mg) of the 35 essential medicine products studied had locally-produced unit prices higher than the corresponding imported products. The prices of various locally-produced dosage forms of ibuprofen and paracetamol were only slightly less than foreign versions. All these medicines studies are very common over-the-counter (OTC) products. As most OTC products are used in low doses and generally for short periods, per-pill profits are expected to be high. A higher price can ensure some degree of profitability, for local producers as well as foreign producers.
- The majority of locally-produced anti-infectives, however, were clearly less expensive than their imported counterparts. This may mean that the actual costs of raw materials and production technology for the local producers are less than the foreign producers, but obtaining actual data is likely to be difficult as this would probably be considered proprietary information.

Multinational corporation managers have asserted that their pricing policies in Bangladesh are restricted by parent companies and that they are bound to import raw materials from sources (i.e., European) that are more expensive than the sources of local producers (i.e., Asian). In addition, when asked, managers of the foreign companies stated that the other reasons for their higher prices were their "exclusive production capabilities and exclusive marketing policies" as well as "more expensive and exceptional" promotional campaigns. Five essential medicine products for chronic conditions (Atenolol 50 mg, Glibenclamide, Amitriptyline, Griseofulvin and Salbutamol) had exactly the same prices for locally- and foreign-produced. There may be less of a need for a high per-pill profit when considering medicines for chronic conditions (Chowdury and Kabir, 2009).

- *Viet Nam:* Kuanpoth (2007) studied ARV prices in Viet Nam. Locally-produced ARVs are priced considerably lower than imported ARVs, currently on the Vietnamese market, they are five to seven times higher than the current best offer on the international market. This is caused, at least in part, by the fact that the market for ARVs is very small.

*b. Reliability of supply.* According to the United States Securities and Exchange Commission (2010) document, local production in South Africa would improve the security of supply, and extend procurement options for ARVs.

- We note that various authors have asserted that increased local production can mitigate the inflexibility of supply created by high dependence on imports. In the United Republic of Tanzania, the government procurement agency obtains supplies through one large annual tender (Chaudhuri et al. 2010). For unanticipated requirements, there are provisions for emergency purchases, which presumably can be made rapidly from local producers. However, floating international tenders and arranging supplies from foreign manufacturers can take a substantial time. Particularly in public health crises, this is a bottleneck to ensuring access to medicines. In principle at least, supplies can be more reliable and secure, although empirical evidence for this is difficult to obtain.
- The concept of a 'supply chain' originated in an industrial context, implying the management of process of supply to manufacturers. This is now part of the much wider discussion of supply of medicines to individual consumers/users/patients (Mackintosh 2010). These concepts exist in countries where most people struggle to buy medicines In Tanzania,, there appear to be several competing 'supply chains' (Mackintosh 2010): a 'delivery chain' of mostly ARV and tuberculosis (TB) medicines from only international firms to facilities treating free at point-of-use; the supply chain from local firms and Indian importers to public/nongovernmental organization (NGO) facilities for essential out-of-pocket payments; and a private market without a controlled supply chain, selling both subsidized imports and local and imported commercial supplies.
- The ARV/TB supply chain is probably the most treatment-based and equitable, although there is a high international subsidy and it excludes local suppliers. The private market supply chain is the least equitable as it

is payment based, not treatment-based, although the subsidies do reduce patient exclusion to some extent.

- The supply chain for public/NGO facilities tends to encourage local suppliers, and could lead to upgrading of local industrial capabilities and employment.

*c. Quality standards*. According to the United States SEC (2010) document, local production in South Africa with regular surveillance on quality control issues, in conjunction with health authorities, "would guarantee quality standards" without compromising on cost.

- *Maponga and Ondari* (2003**)** conducted a pilot study to assess the quality of antimalarial medicines (chloroquine and sulphadoxine/pyrimethamine) in seven selected African countries, and to determine whether the quality of these products was related to the level of the distribution chain at which the samples were collected. There were failures of 56% (27/48) among locally made products, compared to 47.2% (17/36) for foreign products for chloroquine tablet active ingredient content, and 28% (7/25) versus 13% (3/23) chloroquine-syrup active ingredient content. Further investigation of this phenomenon will be important since it is easier for national drug regulatory authorities to act and correct problems that involve domestic manufacturers. No clear relationship between the quality of products and the level of the distribution chain was observed. There were failures in quality of antimalarials regardless of whether the product was taken from a teaching hospital, district hospital, pharmacy or household. The reasons for these failures in quality vary: some are due to storage, some to poor quality of imported medicines and others to poor quality of locally-produced medicines.

  Indeed, there was no apparent difference in quality between locally/ manufactured and imported products and one might infer that locally/ produced and imported antimalarials were of equal quality.

*d. Foreign import savings*. According to the United States SEC (2010) document, the average price for the first-line ARVs required to treat HIV/AIDS is US$ 950 to US$ 1100/kg. By 2012, the total annual import bill for the estimated South African ARV procurement programme will be about ZAR4.9 billion (0.68 US$ billion, at 2007 prices; this figure assumes 1.75 million patients are on ARV and based on a fully imported API that is locally formulated). Local production may, to an extent, offset in part this foreign exchange exposure and import deficit. It is estimated that the cost of importing the relevant raw materials is about 55% of the API cost (depending on the API) and hence implies a foreign import saving of at least ZAR2.4 billion (0.33 US$ billion) per annum. The latter figure excludes any foreign currency earnings through the export of ARV APIs to other countries.

- We could find no reference for another country to support this although this supposition could be tested (See Section 4).

**Indirect benefits:**

*a. Development of further innovation capacity*. The need to diversify the pharmaceutical manufacturing sector, and in particular to stimulate production of more profitable, high technology products, has been emphasized by many different countries. Over the past 20 years there has been strong growth within this sector, to the extent that it now forms a major part of the high technology activities of many developed countries, alongside telecommunications and information technologies.

The literature on general knowledge 'spillovers' is relevant in this regard. These are intellectual gains through exchange of information for which a direct compensation to the producer of the knowledge is not given (Kesidou and Romijn, 2008).

Many policy/makers, particularly those in LMICs, have competed rigorously in attracting foreign direct investment (FDI). A common justification for this incentive-based competition is the argument that FDI provides not only capital and additional employment but also new knowledge to recipient economies. The hope is that the new knowledge, transferred from multinational companies to their subsidiaries for example, may spill over entire recipient economies and increase the economic performance of domestic firms. This knowledge spillover has recently been regarded as an important source of productivity growth for LMICs.

In LMICs, dependence on foreign production explains the large number of studies emphasizing the importance of accessing and absorbing international knowledge for acquiring competitiveness and fostering economic growth in these countries, and in particular the important role that international knowledge spillovers could play in that process. The literature is vast and determinants of knowledge spillover vary from sector to sector in line with determinants of technological capacity.

- *Uganda:* Haakonsen (2009 looked at the Ugandan pharmaceutical industry from the viewpoint of global pharmaceutical value chains and found that it operated only in 'downstream' activities; namely, in the local importing, assembly, production and marketing areas. The products are simple, and this strand of the pharmaceutical value chain is price-driven. Inputs for production are obtained from abroad, mainly from industry contacts in India. Likewise, information, technology and machinery for product and process upgrading are facilitated by their upstream linkages. The pharmaceutical industry in Uganda has upgraded during the past 20 years, and did so from imports of finished pharmaceuticals to packaging and assembly. This upgrading took place even though the Ugandan companies were never engaged as suppliers to lead firms in the pharmaceutical value chain.

  The upgrading was facilitated by a combination of their upstream vertical linkages to suppliers, their existing linkages downstream in the chain as importers and retailers of pharmaceuticals for the domestic market, and as a result of government policies. Ugandan companies have upgraded by importing finished technologies and knowledge, not by learning

production methods as such. Production is at a low level technologically and has not increased the companies' technological capabilities in terms of higher prospects for further upgrading.

The machinery and technology for more efficient production are those found in small- and medium-sized companies in other developing countries, primarily India, as there is a huge technology gap between the Ugandan industry and companies in industrialized countries. The market consists of relatively poor people in need of basic medicine, and there is no scope for producing high-value products in Uganda. Likewise, the producers are not introducing new products into the market, but are replacing imports with local production. However, the companies do upgrade their products; for example, by improving packaging materials and product quality.

The notion that Ugandan companies are not introducing 'new' products points to another challenge in this field, namely the definition of innovation. It is unclear what 'new' means in the context of the Ugandan pharmaceutical industry although one might infer that it means development of a novel product.

*b. Exports*. A local API producer could also become a significant exporter. Although the initial intention of a 'local producer' would be to develop itself as a local supplier of a highly strategic product, ultimately this could assist in building a regional production capacity that may benefit, for instance neighbouring countries. From a macroeconomic viewpoint, this may help improve trade imbalances. But this will also depend on the products themselves, their patent cover and the scope of any voluntary license agreements addressing patent issues.

- We found no evidence to support this, for instance in Sub-Saharan Africa, although the supposition could be tested (see Section 4).

*c. Development of human capital*. Most of the essential skills for a successful API manufacturing sector may already be well developed in certain countries (e.g., India, Thailand and South Africa) and within academic institutions (organic chemistry, chemical engineering, mechanical engineering, pharmacology, etc.). At the same time, it may be that experienced professionals with knowledge of pharmaceutical manufacturing within an industrial environment are very limited. The main reason for this gap would be the lack of a local API industry. India is a major exception. In Hyderabad, India, much of the impressive growth of the API manufacturing sector can be linked to the initial commitment of Dr KA Reddy and the establishment of his company 'Dr Reddy's Laboratory' in 1984. The history of the API industry in Hyderabad is an interesting example of how an initial activity went on to snowball into a highly developed, populated and profitable industrial sector.

*The United Republic of Tanzania:* In 2007, Losse, Schneider and Spennemann conducted a situation analysis of Tanzanian local producers and included a study of a major producer whose staff comprised mainly of Indian and British expatriates. Tanzanian staff were still the minority and it was

mentioned by the CEO that this was "... a major problem." The company would prefer to employ Tanzanian staff, but the competency needed for pharmaceutical production is simply not available in the country. In total the company employs 800 people in the United Republic of Tanzania. The Tanzanian employees are unskilled and work in the packaging area, whereas the Indian and British staff are skilled.

# 4. Discussion and conclusions

The arguments linking access to medicines with domestic production of biomedical products in high income countries were not reviewed because such arguments tend not to be explicitly stated. The linkages are *assumed* to exist in the United States and other OECD countries. Such linkages are a complex function of health care and industrial policy, including insurance, generic medicine policies, pricing and reimbursement policies. They are based, at least in part, on the unique characteristics of the pharmaceutical market and products, and the recognized weaknesses in the way this market functions. It has been argued that to remedy these defects, the state (i.e., national/local) in developed countries plays a specific and critical role in establishing controls and regulatory mechanisms designed to overcome information imbalance, moral risks and adverse choices, seeking to guarantee quality of – if not access to –medicines. Innovation in relation to products, services and processes, fuels economic growth through enhancements in productivity. As some share of innovation comes from health-related applications, there is an economic agenda closely tied to innovation in life sciences and health, that is linked to the ability of producers to rapidly disseminate new technologies.

The pursuit of improved access to medicines often coincides with the pursuit of industrial policy in the pharmaceutical sector; the latter relates to the support for the pharmaceutical industry in terms of providing explicit or implicit incentives to locate within national boundaries and invest in innovation. In the United Kingdom, for example, industrial policy is explicitly pursued through supply-side regulation by the Pharmaceutical Pricing Regulation Scheme, which combines free-pricing subject to profit control and R&D incentives. In Germany, industrial policy is implicit through free-pricing of medicines and the implementation of targeted initiatives in certain areas such as biotechnology by the relevant government agencies. In France, industrial policy considerations (such as employment, manufacturing value added, research and exports) are discussed during reimbursement negotiations and are, therefore, linked to reimbursement decisions. In Spain, the government has an agreement with industry to attract investment in certain priority research areas and contributes by channelling funding to these areas. **(**Kanavos, 2011**).**

Of the various putative advantages of local production of biomedical products, these advantages exist, at best, in some countries (mostly larger ones such as India and Brazil) and are either not borne out or the impact is unclear in other countries . Table 4 provides examples of each of these.

***Table 4**: Literature review: Examples of positive, negative and uncertain benefits of local production*

| Potential benefit of local production | Positive impacts | Unclear/negative impacts |
|---|---|---|
| Potential cost savings | Some locally produced medicines **are less expensive** than foreign-made counterparts (Bangladesh, India, UNCTAD study, Palestine) | Some locally produced medicines are **more expensive** than foreign-made counterparts (Turkey, UNCTAD study, Tanzania, Brazil, Malaysia, Vietnam) |
| Reliability of supply | Literature on medicines regulation and quality in high-income countries support this as a positive benefit | Surprising little direct evidence one way or the other for this in LMICs |
| Improved quality standards | Literature on medicines regulation and quality in high-income countries support this as a positive benefit | Surprising little direct evidence one way or the other for this in LMICs |
| Foreign import savings | Little direct evidence from this literature search | Little direct evidence from this literature search |
| Increased local innovation capacity | A vast literature on 'knowledge spillovers' in high-income countries especially, but also in South-East Asia | Little clear evidence from sub-Saharan Africa |
| Development of export capacity | Indian and South African companies are major exporters of ARVs | So far, little clear evidence from sub-Saharan Africa |
| Development of human capital | Essential skills for R&D and manufacturing capacity already developed in Brazil, China and India | Preponderance of expatriate staff in Tanzanian firms |

Indeed these putative advantages exist primarily in high-income countries as the bulk of biomedical products are made there, with India as a major manufacturing hub for generic products and China as a key source of API. More than four-fifths of pharmaceuticals sold globally – totalling about $773 billion in 2008 – are geared towards satisfying the needs of the high-revenue markets of North America and Europe (UNIDO 2010b).

There is no reason, *a priori*, to expect that such advantages of local production would not eventually accrue in LMICs. It has been said that the development of a strong pharmaceutical industry in India may offer some suggestions as to how to build a high-quality manufacturing industry in LMICs (UNIDO 2010b). In brief, there exists in India detailed quality requirements with a firm

timelines. Companies also received time-limited incentives such as working capital credits, interest subsidies and export incentives, which enabled them to invest in the necessary upgrades while remaining competitive. India has a sizeable pool of skilled human resources, a large domestic market, and capabilities to produce many of the inputs within the country.

The barriers to development of a local biomedical product industry are context-dependent in other countries. Challenges are interrelated and their solutions require cooperation and coordination. These barriers have been articulated by others (Kaplan and Laing, 2004; UNIDO 2010a).

We can summarize our main conclusions as follows:

- We note the predominance of case studies and surveys and the relative lack of econometric and time series studies linking local production and access.
- Our brief review of the UNCTAD technology transfer literature does not suggest any robust attempt to link local production and access to medicines but this may not be surprising as technology transfer may be considered industrial rather than health policy, and the case study methodology is not strictly applicable to investigate such a link.
- The business and economic literature that we have seen also is concentrated on the upstream side (e.g., supply side, industrial policy, knowledge spillovers, innovation etc.) with seemingly little information on the downstream issues of local production and access to medicines.
- The public health literature on the subject of local production is directed predominantly towards the issue of intellectual property rights and access to medicines.
- It seems quite remarkable that many of the pricing surveys do not distinguish the price of local versus foreign producers on a product-by-product basis.
- There is an almost complete absence of information on the link between local production and access to medical devices. The reason for this may not be difficult to discern. Modern technology is producing an overwhelming abundance of medical devices at a rate that soon makes even the latest device obsolete. Furthermore, there is an extreme diversity of the medical device arena – diverse in terms of types of devices, degrees of complexity, applications, usage, users and categories. Just as for pharmaceuticals, research in medical devices often not based on public health needs. (WHO 2010) Furthermore, almost all medical devices present in developing countries have been designed for use in industrialized countries. Although beyond the scope of the present document, it is necessary to frame medical devices as part of an agenda to improve global access so that it does not just focus on upstream innovation efforts but also on choosing which medical devices to procure in a rational way, responding to the needs, and in ensuring that they are used as effectively as possible to best improve health. Whether local production of medical devices contributes to improved access to devices is an open question.

## 4.1 Methods employed in the literature are insufficient to prove a robust relationship between LP and access

Table 5 lists the references cited in the text (as well as some others not cited) and the type of study upon which the paper was based.

### *Table 5* References identified and corresponding study types

| Reference | Econometric | Case study | Time series | Survey/Qualitative |
|---|---|---|---|---|
| Samira Guennif | | Brazil, India, Thailand | | |
| Shyama V. Ramani | | | | |
| Anil Hara | | Brazil, Cuba, India | | |
| Haakonsson | | Uganda | | |
| Anil Hara | | LAC | | |
| Nejla Yacoub | | | | Tunisia |
| Nunn et al. | | | Brazil | |
| Teixeira, Bastos | | | Brazil | |
| Veira | | | Brazil | |
| deOliveira | | Brazil | | |
| Chang et al. | | | | China |
| Semin | | Turkey | | |
| Thomas | | India, China | | |
| Orwa | | | | Kenya |
| Kisa | | Turkey | | |
| Chaudhuri et al. | India | | | |
| Losse and Schneider | | United Republic of Tanzania | | United Republic of Tanzania |
| Flynn | | | Brazil | |
| Dinarvand | | | Iran | |
| Maponga and Ondari | | | | 8 African countries |
| Chaudhuri et al. | | | | United Republic of Tanzania |
| Mackintosh and Mujinja | | | | United Republic of Tanzania |
| Kesidou and Romijn | Uruguay | | | Uruguay |
| Pradhan | | India | India | |
| Kuanpoth | | | | Thailand |
| Greco and Simao | | Brazil | | |
| Chaudhuri | | India | | |
| Chaudhury and Kabir | | | | Bangladesh |
| Mhamba and Mbirigenda | | United Republic of Tanzania | | |
| Shafie and Hassali | | | | Malaysia |

Table 6 lists the references (as in Table 5) but with a different focus. Keeping in mind the presumed benefits of local production as it relates to access to medicines,[2] those aspects of 'access' that are the major focus of these papers are summarized. We note the preponderance of papers directed to IPRs.

### *Table 6 References identified and corresponding access to medicines criteria*

| Country | Affordability/ Price | Availability/ Generics | Innovation | Availability/ Distribution | IPRs | Other | Reference |
|---|---|---|---|---|---|---|---|
| India, Thailand, Brazil | | | | | X | % LP and imported medicines inThailand | Guennif, Ramani |
| India, Brazil, Cuba | X (Brazil only) | | | | X | | Hara |
| Uganda | | | | | | | Haakonsson |
| LAC | | | X | | | | Hara |
| Tunisia | | | | | X | | Yacoub |
| Brazil | X | | | | X | | Nunn et al. |
| Brazil | X | | | | X | | Teixeira, Bastos |
| Brazil | | | | | | X-MOH spending | Veira |
| Brazil | | | | | | Survey of LP | deOliveira |
| China | | X | | X | | | Chang et al. |
| Turkey | X | | | | X | Overview | Semin |
| India, China | | | X | | | | Thomas |
| Kenya | | | | | | Quality of medicine | Orwa |
| Turkey | | | | | | Overview | Kisa |
| India | X | | | | X | | Chaudhuri et al. |
| United Republic of Tanzania | | | | | X | Overview | Losse and Schneider |
| Brazil | | | | | | Overview | Flynn |
| Iran | | | | | | Overview | Dinarvand |
| Africa | | | | | | Quality | Maponga and Ondari |
| United Republic of Tanzania | | | | | | Overview | Chaudhuri et al. |

*Continues…*

2 E.g., (a) lower prices (and greater affordability); (b) greater availability through the presence of local branded generics; (c) local adaptation of pharmaceutical products by local firms (through incremental innovation efforts of local firms); (d) new forms of innovative medicines and medical products developed by local firms that may, or may not be, tailored more or less to the population(s); (e) greater availability through better distribution networks of local firms (as in the case of some LMICs where local firms are indeed able to penetrate rural markets better).

*Continued from previous page*

| Country | Affordability/ Price | Availability/ Generics | Innovation | Availability/ Distribution | IPRs | Other | Reference |
|---|---|---|---|---|---|---|---|
| United Republic of Tanzania | X | | | | | | Mackintosh and Mujinja |
| Tanzania | | | | | X | Overview | Chaudhuri |
| Uruguay | | | X | | | | Kesidou and Romijn |
| India | | | X | | | Overview | Pradhan |
| Thailand | | | | | X | | Kuanpoth |
| Brazil | X | X | | | | | Greco and Simao |
| India | | | | | | Overview | Chaudhuri |
| Bangladesh | X | X | | | | | Chaudhury and Kabir |
| United Republic of Tanzania | | | | | | Overview | Mhamba and Mbirigenda |
| Malaysia | X | X | | | | | Shafie and Hassali |

Perhaps the best we can do at the present time is to draw inferences about the links between LP and access to medicines.

There are certain other countries, such as Iran and Bangladesh (where domestic manufacturers dominate the Bangladesh pharmaceutical industry with local companies enjoying an 80% market share (Chowdury and Kabir, 2009) where there is also a very strong inference that LP has improved access to medicines. This information does not take into account geographic heterogeneity of access, however, and this could be extremely important. We should be able to find ways of robustly monitoring and evaluating the link between LP and access to biomedical products.

## *4.2 Factors limiting understanding of the link between LP and access to medicines*

Notwithstanding some national policies in LMICs that support local production, for the most part 'access to medicines' is not a precondition for a local factory to be built. The business and industry pressures to create a local producer will usually overshadow health policy concerns. Also, the links between LP and access to medicines have not been explored because it is harder to make access to medicines a particular concern for individual firms, and at the collective level, accountability is hard to enforce. There are likely to be some observable links between LP and access to medicines, and the absence of evidence is not evidence of absence.

### *4.2.1 Conclusory and contradictory statements with little corroboration*

One key limitation of the both the peer-reviewed and grey literature is that the putative benefits of LP are sometimes referred to in conclusory statements with little supporting evidence. In some cases, the information is contradictory (see Boxes 1 and 2).

### **Box 1**. *Quality Chemicals Ltd. in Uganda: One point of view*

The Quality Chemicals Limited Company in Uganda was established in 2007 in conjunction with technology transfer from Cipla, Ltd. Its purpose is to locally produce generic ARV medicines and WHO pre-qualified the facility in March 2010 so the factory can now both legally manufacture and market generic ARV medicines *locally and internationally*, and make them available in bulk to charitable or donor organizations. Local production of generic ARVs directly benefits patients, as medicines are produced at a lower cost, especially compared to patented ARV medicines imported from foreign pharmaceutical companies. In an interview, the managing director of this facility indicated that locally-produced ARV medicines will be around 30% cheaper than imported versions, which means that the monthly cost of triple combination therapy would become available at around approximately US$ 9 per person: a substantial saving. Thanks to local production, patients will be able to take one tablet twice a day, containing three medicines in one, instead of a cocktail currently consisting of 12 ARV medicines. The factory aims to prevent potential problems associated with the limited availability of ARV medicines by producing 2 million tablets per day, and increasing this amount to 6 million tablets per day or 1.8 billion tablets annually when operating at full capacity (Vermuelen, 2010).

### **Box 2**. *Quality Chemicals Ltd. in Uganda: Another point of view*

Despite expectations that locally-produced medicine will be cheaper than imported ones, a Ugandan medicine maker has stated the contrary. Locally produced essential pharmaceuticals, including ARVs, are around 15% more expensive than those imported from abroad.* ARV makers in Uganda have no shortage of demand. However, there have been reports of closures by some suppliers, although reasons have been withheld. Quality Chemical Industries, which opened for production in January 2009, states that it has to add a 17.9% margin on medicine sales to include the interest rates and development costs from construction of the Ugandan facility. When factored into medicine costs, Quality Chemicals claims that it makes consumer prices relatively higher than the imported medicines (Business Monitor International, 2009).

* Confirmed by UNCTAD Uganda case study

Even if certain medicines are made exclusively by domestic manufacturers or even domestic subsidiaries of multinational companies, it does not necessarily follow that the population has access to affordable, quality-assured medicines.

#### *4.2.2 The dynamic relationship between LP and access to medicines:*

#### *The changing context in Brazil*

Brazil is exemplary in that it has created a viable public health response to AIDS, which serves as an encouraging example of pooled demand power in the developing world. The Brazilian Government fully subsidizes ARV medicines through the Ministry of Health. Free distribution of AIDS medicines became a reality, supported by law, in 1996. Fully 47% of ARV medicines are obtained from national production. Brazil has also resisted pharmaceutical companies,

threatening temporarily to break Roche's patent on an AIDS medicine in 2001, for example, until the company reduced its price (Galvao, 2002).

As of early 2007, the Brazilian strategy to guarantee medicine supply included domestic production of off-patent ARVs and the threat of compulsory licensing for patented medicines. Thus, three factors were critical to this success: legislation for free access to treatment; public sector capacity to manufacture medicines; and strong civil society action to support government initiatives to improve access (do Lago and Costa, 2009). In Brazil, a public agency (i.e., the government) created a pooled demand for free distribution. From 1997 to 2003, AIDS mortality dropped by 40% to 70%, morbidity decreased by 60%, there were 360 000 fewer hospitalizations, and 58 000 thousand new AIDS cases were avoided (Ford et al., 2007).

Were these declines between 1999 and 2001 due to domestic production of off-patent ARVs, despite an increase in the number of patients? This is not categorically provable, but there is a very strong inference that this is the case.

Since 2005, there has been a major increase in expenditure on ARVs. In part, this was due to the emergence of viral resistance, which requires treatment with expensive second- or third-line products. These are patent protected. Imported ARVs now account for a substantial fraction of total Brazilian ARV expenditure (do Lago and Costa, 2009). Nunn et al. (2007) found that prices for Brazil's locally-produced, generic ARVs are generally much higher than corresponding global prices, and noted that these prices have risen in Brazil while declining globally. They estimated the excess costs of Brazil's locally-produced generics to be US$110 million from 2001 to 2005.

The growing need to import high-cost medicines, production of which is protected by patents, imposed a new agenda on the Brazilian state in relation to the sustainability of drug production. This is quite different today than even five years ago. The reality is that the Brazilian pharmaceutical market is presently dominated by a handful of multinational companies. Large manufacturers exert pressure on price formation and wield sufficient power to affect national policies. The market in Brazil contains barriers to entry in the form of patent protection, the need for high investments in R&D, control of the supply of active ingredients, and brand name loyalty to the leading laboratories. (do Lago and Costa, 2009). The share of total ARV supply relegated to Brazilian government laboratories (Far Manguinhos) has decreased continuously between 2001 and 2006 in comparison to the share supplied by private companies.

Several additional factors make the connection between access to ARVs and their local production somewhat problematic in Brazil. It may seem remarkable, but production of APIs and intermediate products for synthesis or use in manufacturing is limited. Nearly all of the intermediate products used by government laboratories are imported from China or India (do Lago and Costa, 2009) Only a few domestic private pharmaceutical companies produce active ingredients for ARVs. The experience of the Brazilian HIV/AIDS Programme shows that the government has assumed the role of providing

"public goods". However, the market position of transnational companies in ARV production is being strengthened.

Demographic transition in Brazil, characterized by the rapid ageing of the population and increasing disposable income, correlates with higher incidences of lifestyle-induced and age-related diseases such as hypertension and diabetes. To the extent that government supply of biomedical products requires that private sector interests and social/health interests be mutually compatible, this balance is being challenged in Brazil.

*LP and access to medicines in India: Weak links between industrial and health policies*

Since India's independence more than 60 years ago, the government's two major objectives have been to: (i) ensure availability of reasonably priced high-quality medicines; and (ii) promote the growth and development of a strong domestic pharmaceutical industry. Indian pharmaceutical companies are major exporters not only to other LMICs, but also to high-income markets. Indian companies contribute to the affordability of medicines in the U.S. Are Indian companies contributing to the affordability of medicines in India? For a host of complex but well documented reasons, India has been able to develop its industry but has difficulty in ensuring availability of medicines (Chaudhuri, 2007).

Government policy has been a key ingredient of its industrial success. Where India differs from other countries is that currently the large firms dominating the industry are not multinational companies but local producers. A distinctive feature of the pharmaceutical industry in India has been the close collaboration between the government laboratories and the private sector (Chaudhuri, 2007). Almost all the top pharmaceutical companies in India – for example, Cipla, Ranbaxy, Lupin, Nicholas Piramal. Wockhardt, Unichem, Torrent, Cadila, Neuland, Sun Pharmaceuticals and Orchid – have used the services of the Indian governmental laboratories (Chaudhuri, 2007). The model that the Indian companies have adopted is to develop new molecules and license out the molecules to multinational companies at early stages of clinical development. As a result the Indian companies are effectively not targeting neglected diseases, but diseases which interest multinational companies (Chaudhuri, 2005). Locally-produced medicines are available, however, for many other diseases that afflict Indian people. What has been a problem has been distributing the medicines to those who need them and ensuring that these are of proper quality. In this regard, there are two main issues:

1. Paradoxically, while multiple sellers for even new medicines have driven down prices to a low level compared to the prices of the patent holders abroad, the result has not been a competitive retail medicines market in India, where substantial price differentials exist. With trimethoprim combinations, for example, there are 53 sellers, but the largest controls 46% of the market and the top four firms control 76.8% of the market (Chaudhuri, 2005). These firms have the market power to set the prices at levels higher than other local firms.

In India, given the absence of product patent protection for most of the most essential medicines, the entire industry might be considered an entirely generic market, yet the larger firms use brand names to create product differentiation. Like the multinational companies, the Indian generic companies target marketing at doctors to prescribe their brands and directly at consumers for non-prescription purchases, spending substantial amounts on sales promotion. Brands of reputed companies sell at substantially higher prices because the products are considered reliable.

2. Most Indian states do not have a proper medicine procurement and distribution system. In India thousands of brands are available in the market. But the vast majority of these are considered to be therapeutically irrational, resulting in tremendous wasteful expenditure. A weak medicine control administration is considered the major reason for such a problem.

## *4.3 A framework for evaluating LP and access to medicines*

A first step towards an evidence-based framework describing the links between LP and access to medicines would be to make a simple distinction between two kinds of methodologies.

### *4.3.1 Static vs. dynamic experimental designs: an introduction*

A *static group* comparison design (i.e., cross-sectional study) is a 'snapshot' of relevant variables (price, affordability, availability) at one point in time. The data are all collected at the same time (or within a short time frame). The surveys of prices described in this document are all examples. It is very difficult to rule out rival hypotheses and determine causality with this approach.

*Dynamic methods* (i.e., longitudinal) may be useful to provide more robust evidence.

Panel data, also called longitudinal data or cross-sectional time series data, are data where multiple cases (e.g., several local and multinational producers) are observed at two or more time points/periods. This should include nationally representative samples of local producers and multinational subsidiaries, or a sample of pharmacies and clinics etc., each surveyed repeatedly over multiple years.

There are two kinds of information in panel data: the cross-sectional information reflected in the differences between subjects (i.e., differences between local producers and multinational companies, between public and private sectors etc. at one point in time) and the time-series information reflected in the changes within subjects over time (changes in ARV production over time from a local producer etc.).

Standard econometric comparisons of domestic firms and multinational companies providing medicines locally could use firm- or plant-level data to model a given activity. Comparisons could be made between the groups of firms or plants. For example, medicine production can be compared between two groups to confirm differences, and the differences can be examined if

they are found to be statistically significant. Another approach is to model the activity in question (e.g. production of medicine, price levels of the produced medicine, extent of local innovation in local producers and multinational companies, availability of medicine produced by each firm etc.) directly as a function of related variables (e.g. size of firm, age of firm, kind of medicine) and a set of dummy variables identifying firms belonging to the group(s) of interest. The significance of the differences in dependent variable among groups, after controlling for differences in the other relevant independent variables, is then revealed.

Unfortunately, there may be very poor access to firm- and/or plant-level data. In short, rigorous comparisons require models that allow relevant control variables and their effects to be identified and isolated before comparisons are made. Small sample size and lack of data on relevant variables often make such modelling impossible.

In such cases, a more appropriate approach is to look at time-series variations in indicators of performance. A time series design collects data on the same variable at regular intervals (weeks, months, years, etc.) in the form of aggregate measures of a population. For example, unemployment rates among local producers, ARV production, consumer price indices etc.

The primary drawback of this time series methodology is that a lack of good quality data may make it impossible to separate the various factors that may be influencing performance. For example, if a region dominated by local producers is observed with a time series showing lower prices than an adjacent 'control' region dominated by multinational producers, lower prices may reflect differences in capital and technology intensity, and prices may be more comparable if differences in capital intensity could be controlled for. In many cases, comparisons of multinational companies and local firms are further complicated by the fact that countries may have severe policy biases that favour state-owned enterprise.

Moreover, from a business perspective, the "firm/establishment" is actually not an economic unit *per se*. It is an accounting unit, quite unlike an individual factory (Bellak, 2004b). A typical "firm" may include plants of different sizes and different ages. With relatively frequent compositional changes over time this makes it difficult to undertake certain types of analysis in a economically meaningful way. This may be less true in reality as in LMICs where the "firm" is likely to consist of a single factory.

A special form of time series, called an interrupted time series (Soumerai et al (2008) may be more useful in studying the linkage between LP and access to medicinesbecause the effect of an intervention on an outcome variable can assume a variety of forms over time. In such circumstances, the intervention is made by someone other than the researcher and it is not normally made for experimental purposes, although the researcher makes use of it for causal analysis. In that sense an interrupted time series can be considered a "natural experiment". Data for evaluating the impact of the intervention usually

comes from existing archives: collections of data gathered routinely across time for administrative purposes.

To give a hypothetical example, in April 2011, country X granted a compulsory license for an important ARV to ELP SA, a local producer of generic pharmaceuticals. Providing such administrative data exists on ARV production, or price or volume, market share etc., a time series can be created beginning from well before the intervention and continuing through and after it. Time-series data can change level and direction for many reasons, some related to the intervention and others due to other factors. Separating potential influencing factors into those essentially related to the intervention and those only coincidentally related is the principal task in analyzing time-series experiments. Having detailed expectations about how the relationship should change in response to an intervention is the best protection against erroneous interpretation of extraneous influences and chance occurrences. In this hypothetical scenario, the ARV price and/or various access markers would change at some point after ELP SA started producing. A 'control' group in country X (i.e., one lacking the intervention) would be ideal.

***Table 7** Summary of static and dynamic experimental designs*

| | **Lower prices (and greater affordability)** | **Greater availability (e.g., more local branded generics** | **Local adaptation of products by local firms (more incremental innovation)** | **Innovative products developed by local firms** | **Better distribution networks of local firms** |
|---|---|---|---|---|---|
| Static | Prices of locally produced vs. foreign-produced generics/branded generics on a product-by-product basis. | Market share/ surveys of local vs. foreign-produced generics/branded generics on a product-by-product basis. | | Patent filings/R&D expenditures/ of local producers vs. Importers/ in-country multinational subsidiaries | |
| Dynamic<br>Time/panel longitudinal<br>Analyses/<br>interrupted time series | Price of various local/imported products prior to, during, and after a major financial investment/a policy change/ factory going "on line" | Market share/ surveys of various local/imported generic products prior to, during, and after a major financial investment/a policy change/ factory going "on line" | | Patent filings/R&D expenditures of local producers/ multinationals prior to, during, and after a major financial investment/a policy change/ factory going on line | |

# Appendix 1: Search terms

| Database(s) | Search term key words for database(s) | Number of initial hits |
|---|---|---|
| Lexis Nexis | Local, production, pharmaceutical, medicine diagnostic | 997 |
| Google/Google Scholar | Local, innovation, pharmaceutical, medicine, diagnostic, access | >1000 |
| Google | Peter Singer Abdallah Daar ethics, local production pharmaceutical, medicine, diagnostic | 54 |
| AfricaWide Information<br>CINAHL | Local production pharmaceutical, medicine diagnostic | |
| OECD | Local production | 68 |
| Health services subset of PUBMED | Local production | 4 |
| POPLINE | medicine / pharmac* / diagnostic & production / manufacture | 21 |
| ECONLIT | | 32 |
| ECONLIT | medicine / pharmac* / diagnostic & production / manufacture | 1127 |
| | Comparative AND (foreign OR multinational) AND (domestic OR local) AND performance OR price AND "pharmaceutical" | |
| CSA | Local production pharmaceutical medicine diagnostic | 13 |
| ISI Web of Knowledge | | 429 |
| CSA | Local production pharmaceutical medicine diagnostic | 818 |
| | Comparative AND (foreign OR multinational) AND (domestic OR local) AND performance OR price | 38 |
| | Same as immediately above AND "pharmaceutical" | |
| BioOne Abstracts and Indexes | (local or domestic or national) and AB=production | 12 |
| PAIS International | and AB=(pharmaceutic* or medicine or diagnostic) | 12 |
| Worldwide Political Science Abstracts | local or domestic or national) and AB=production | 8 |
| | and AB=(pharmaceutic* or medicine or diagnostic) | |
| International Bibliography of the Social Sciences | AB=(local or national or domestic) and AB=production | 22 |
| | and KW=(medicine or pharmaceu*) | |

*Continues…*

AB= abstract; KW= key words

*Continued from previous page*

| Database | Search term key words for database(s) | Number of initial hits |
|---|---|---|
| Google Scholar **country-specific** | 1. Specific country AND pharmaceutical<br>AND with the exact phrase: "production"<br>AND with at least one of these words: "local domestic national regional diagnostic"<br>2. Specific country AND diagnostic<br>AND with the exact phrase: "production"<br>AND with at least one of the words: "local domestic national regional pharmaceutical" | |

# PUBMED search terms

1. (domestic[All Fields] AND ("economics"[MeSH Terms] OR "economics"[All Fields] OR "production"[All Fields])) AND ("pharmacy"[MeSH Terms] OR "pharmacy"[All Fields] OR "pharmaceutical"[All Fields] OR "dosage forms"[MeSH Terms] OR ("dosage"[All Fields] AND "forms"[All Fields]) OR "dosage forms"[All Fields])
2. "medicine industry"[Mesh] AND "medicine"[Mesh]
3. (Medicine[ti] OR Pharmaceutical[ti] OR Diagnostic[ti] OR "Medicines, Essential/supply and distribution"[MAJR]) OR "Medicines, Essential/economics"[MeSH Terms]) AND (Production[tiab] OR Manufacture[tiab]) AND (Local[tiab] OR regional[tiab] OR national[tiab] OR domestic[tiab]) NOT (("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields]) NOT clinical[All Fields])
4. Limits – Humans
5. Developing Countries
   "Developing Countries"[Mesh] OR Africa[Mesh] or "Africa South of the Sahara"[Mesh] or Asia[Mesh] or "South America" [Mesh] or "Central America"[Mesh] OR Africa[tiab] or Asia[tiab] or "South America"[tiab] or "Latin America"[tiab] or "Central America"[tiab]

   "American Samoa"[tiab] or Argentina[tiab] or Belize[tiab] or Botswana[tiab] or Brazil[tiab] or Bulgaria[tiab] or Chile[tiab] or Comoros[tiab] or Costa Rica[tiab] or Croatia[tiab] or Dominica[tiab] or Equatorial Guinea[tiab] or Gabon[tiab] or Grenada[tiab] or Hungary[tiab] or Kazakhstan[tiab] or Latvia[tiab] or Lebanon[tiab] or Libya[tiab] or Libia[tiab] or Libyan[tiab] or Lithuania[tiab] or Malaysia[tiab] or Mauritius[tiab] or Mexico[tiab] or Micronesia[tiab] or Montenegro[tiab] or Oman[tiab] or Palau[tiab] or Panama[tiab] or Poland[tiab] or Romania[tiab] or Russia[tiab] or Seychelles[tiab] or Slovakia[tiab] or South Africa[tiab] or "Saint Kitts and Nevis"[tiab] or "Saint Lucia"[tiab] or "Saint Vincent and the Grenadines"[tiab] or Turkey[tiab] or Uruguay[tiab] or Venezuela[tiab] or Yugoslavia[tiab] or Mayotte[tiab] or "Northern Mariana Islands"[tiab] or "Russian Federation"[tiab] or Samoa[tiab] or Serbia[tiab] or "Slovak Republic"[tiab] or "St Kitts and Nevis"[tiab] or "St Lucia"[tiab] or "St Vincent and the Grenadines"[tiab]

   Albania[tiab] or Algeria[tiab] or Angola[tiab] or Armenia[tiab] or Azerbaijan[tiab] or Belarus[tiab] or Bhutan[tiab] or Bolivia[tiab] or "Bosnia and Herzegovina"[tiab] or Bosnia[tiab] or Cameroon[tiab] or China[tiab] or Colombia[tiab] or Congo[tiab] or Cuba[tiab] or Djibouti[tiab] or "Dominican Republic"[tiab] or Ecuador[tiab] or Egypt[tiab] or El Salvador[tiab] or Fiji[tiab] or "Georgia (Republic)" [tiab] or Guam[tiab] or Guatemala[tiab] or Guyana[tiab] or Honduras[tiab] or "Indian Ocean Islands"[tiab] or Indonesia[tiab] or Iran[tiab] or Iraq[tiab] or Jamaica[tiab] or Jordan[tiab] or Lesotho[tiab] or "Macedonia" [tiab] or "Marshall Islands"[tiab] or Micronesia[tiab] or "Middle East"[tiab] or Moldova[tiab] or Morocco[tiab] or Namibia[tiab] or Nicaragua[tiab] or Paraguay[tiab] or Peru[tiab] or Philippines[tiab] or Samoa[tiab] or "Sri Lanka"[tiab] or Suriname[tiab] or Swaziland[tiab] or Syria[tiab] or Thailand[tiab] or Tonga[tiab] or Tunisia[tiab] or Turkmenistan[tiab] or Ukraine[tiab] or Vanuatu[tiab] or "Cape Verde"[tiab] or Gaza[tiab] or Georgia[tiab] or Kiribati[tiab] or Macedonia[tiab] or Maldives[tiab] or Palestine[tiab] or "Syrian Arab Republic"[tiab] or "West Bank"[tiab]

Afghanistan[tiab] or Bangladesh[tiab] or Benin[tiab] or "Burkina Faso"[tiab] or Burundi[tiab] or Cambodia[tiab] or "Central African Republic"[tiab] or Chad[tiab] or Comoros[tiab] or "Democratic Republic of the Congo"[tiab] or "Cote d'Ivoire" [tiab] or Eritrea[tiab] or Ethiopia[tiab] or Gambia[tiab] or Ghana[tiab] or Guinea[tiab] or Guinea-Bissau[tiab] or Haiti[tiab] or India[tiab] or Kenya[tiab] or Korea[tiab] or Kyrgyzstan[tiab] or Laos[tiab] or Liberia[tiab] or Madagascar[tiab] or Malawi[tiab] or Mali[tiab] or Mauritania[tiab] or Melanesia[tiab] or Mongolia[tiab] or Mozambique[tiab] or Myanmar[tiab] or Nepal[tiab] or Niger[tiab] or Nigeria[tiab] or Pakistan[tiab] or "Papua New Guinea"[tiab] or Rwanda[tiab] or Senegal[tiab] or "Sierra Leone" [tiab] or Somalia[tiab] or Sudan[tiab] or Tajikistan[tiab] or Tanzania[tiab] or East Timor[tiab] or Togo[tiab] or Uganda[tiab] or Uzbekistan[tiab] or Vietnam[tiab] or Yemen[tiab] or Zambia[tiab] or Zimbabwe[tiab] or Burma[tiab] or Congo[tiab] or Kyrgyz[tiab] or Lao[tiab] or "North Korea"[tiab] or "Solomon Islands"[tiab] or "Sao Tome"[tiab] or Timor[tiab] or "Viet Nam"[tiab]

"developing country"[tiab] OR "developing countries"[tiab] OR "developing nation*"[tiab] OR "less* developed country"[tiab] OR "less* developed countries"[tiab] OR "under developed country"[tiab] OR "under developed countries"[tiab] OR "poor* country"[tiab] OR "poor* countries"[tiab]

"middle income country"[tiab] or "middle income countries"[tiab] or "low income country"[tiab] or "low income countries"[tiab]

lmic[tiab] or lmics[tiab]

(#1) OR (#2) OR (#3) OR (#4) OR (#5) OR (#6)

Japan[tiab] OR "United States"[tiab]

# POPLINE

Developing Countries:

Developing countries / Afghanistan / Bangladesh / Benin / Burkina Faso / Burundi / Cambodia / Central African Republic / Chad / Comoros / Democratic Republic of the Congo / Cote d'Ivoire / Eritrea / Ethiopia / Gambia / Ghana / Guinea / Guinea-Bissau / Haiti / India / Kenya / Korea / Kyrgyzstan / Laos / Liberia / Madagascar / Malawi / Mali / Mauritania / Melanesia / Mongolia / Mozambique / Myanmar / Nepal / Niger / Nigeria / Pakistan / Papua New Guinea / Rwanda / Senegal / Sierra Leone / Somalia / Sudan / Tajikistan / Tanzania / East Timor / Togo / Uganda / Uzbekistan / Vietnam / Yemen / Zambia / Zimbabwe / Burma / Congo / Kyrgyz / Lao / North Korea / Solomon Islands / Sao Tome / Timor / Viet Nam / Albania / Algeria / Angola / Armenia / Azerbaijan / Belarus / Bhutan / Bolivia / Bosnia and Herzegovina / Bosnia / Cameroon / China / Colombia / Congo / Cuba / Djibouti / Dominican Republic / Ecuador / Egypt / El Salvador / Fiji / Georgia Republic / Guam / Guatemala / Guyana / Honduras / Indian Ocean Islands / Indonesia / Iran / Iraq / Jamaica / Jordan / Lesotho / Macedonia / Marshall Islands / Micronesia / Middle East / Moldova / Morocco / Namibia / Nicaragua / Paraguay / Peru / Philippines / Samoa / Sri Lanka / Suriname / Swaziland / Syria / Thailand / Tonga / Tunisia / Turkmenistan / Ukraine / Vanuatu / Cape Verde / Gaza / Georgia / Kiribati / Macedonia / Maldives / Palestine / Syrian Arab Republic / West Bank / American Samoa / Argentina / Belize / Botswana / Brazil / Bulgaria / Chile / Comoros / Costa Rica / Croatia / Dominica / Equatorial Guinea / Gabon / Grenada / Hungary / Kazakhstan / Latvia / Lebanon / Libya / Libia / Libyan / Lithuania / Malaysia / Mauritius / Mexico / Micronesia / Montenegro / Oman / Palau / Panama / Poland / Romania / Russia / Seychelles / Slovakia / South Africa / Saint Kitts and Nevis / Saint Lucia / Saint Vincent and the Grenadines / Turkey / Uruguay / Venezuela / Yugoslavia / Mayotte / Northern Mariana Islands / Russian Federation / Samoa / Serbia / Slovak Republic / St Kitts and Nevis / St Lucia / St Vincent and the Grenadines

Title and Abstract:

medicine / pharmac* / diagnostic & production / manufacture

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