Project no. 513396

WP3.9 / Deliverable D391

A literature review on local production of medicines and access to health-care

Davide Consoli

Institute of Innovation and Knowledge Management (INGENIO, CSIC-UPV),
Polytechnic University of Valencia (Spain)
Manchester Institute of Innovation Research (MIoIR), Manchester Business School (UK)

1. Introduction

According to the World Health Organization (2005) large shares of populations in Least Developed Countries (LDCs) lack access to medicines that are essential to meet primary health-care needs. This phenomenon has several instantiations which for ease of narrative lead to distinguish between: (i) health problems that are common both to developing and developed countries; within this group one may further distinguish between diseases for which medicines are available, and are not patented, and those for which effective cures are being perfected, and whose therapies are subject to some kind of property rights regime, like HIV/AIDS; and (ii) neglected diseases that are common in the developing world and for which existing medicines are not adequate, for example malaria and tuberculosis in Sub Saharan Africa, South America and South-East Asia. Two issues are central to this debate. The persistence of barriers to access existing medicines raises questions about the 'right' mix of investment production and trade activities that may enable LDCs to escape the "disease trap"; the substantive question therefore concerns the institutional set-up that is most conducive to achieving and maintaining that mix. The second issue is the systematic under-investments in therapies for neglected diseases like malaria and tuberculosis, and raises questions about the pathways that are needed to create incentives while preserving affordability.

One particular thread in this intricate debate concerns whether creating local production facilities for necessary medicines might be a viable solution for LDCs. Two main arguments have been put forth either in favour, within the health policy arena, or against, from the industrial policy perspective, the motion. This review offers a (necessarily) selective review of the theoretical arguments and the empirical evidence that contribute this particular debate. The first section lays out basic empirical evidence and conceptual issues; the second part introduces basic elements of the economics of pharmaceutical production and related aspects of intellectual property right regimes; the third part reviews the recent history of the pharmaceutical industries of India, Brazil and China to appreciate some characteristics of emerging competitors in an evolving global pharmaceutical industry. The last section offers some final considerations, reflects critically on where the boundaries of the debate have been traced and hints at possible, hitherto unexplored, directions to move forward the research agenda.

2. Access to essential medicines

The Alma-Ata Declaration of 1978 is a major milestone for public health in that it reaffirms primary health care as the key to the attainment of the goal of Health for All. It is to that occasion that the World Health Organisation (WHO) first spoke explicitly about essential medicines as "(…) those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility".[1]

Accordingly the WHO articulates the degree of access to essential medicines and health services along four dimensions: geographical accessibility; affordability; cultural acceptability; availability of care on a continuing basis.[2] In broad terms 'access' is a supply side dimension indicating the level of service which is made available by the health care system to individuals. In practice this notion is contingent on the context: in countries where health is offered in return of payment or on a private

[1] http://www.who.int/topics/essential_medicines/en/

[2] For a review of the key conceptual issues see the background document on pagg. 83-118. Online at http://www.msh.org/seam/reports/Access_Meeting_Ferney_Voltaire_1.pdf

basis, the key to "access" is whether individuals have insurance or not; in systems where all citizens receive free health-care access refers to the ability to secure a specified range of services at a specified level of quality subject to a specified maximum level of personal inconvenience and cost (Goddard and Smith, 2001). This conceptual structure based on the traditional public-private divide has been further articulated by the OECD in a comparative study (1992) on models of health-care delivery differing on the basis of (i) type of finance (voluntary or compulsory) and (ii) method of paying providers (out of pocket by consumers with or without insurance, indirectly by third parties via arm's length contracts and via budgets and salaries within an integrated organisation). Further differentiations exist within segmented health-care systems in Latin America and Asia where the more affluent have service provision through private insurance, social insurance caters for those in formal employment and the public sector covers the low-income classes (see Londoño and Frenk 1997 and Suárez-Berenguela 2001, cited in Mackintosh, 2007). As far as the various dimensions of access to health-care the "Rational Pharmaceutical Management Plus" expands on the WHO framework by taking into account factors like determinants of User location, determinants of pricing and other dimensions sketched in Figure 1.

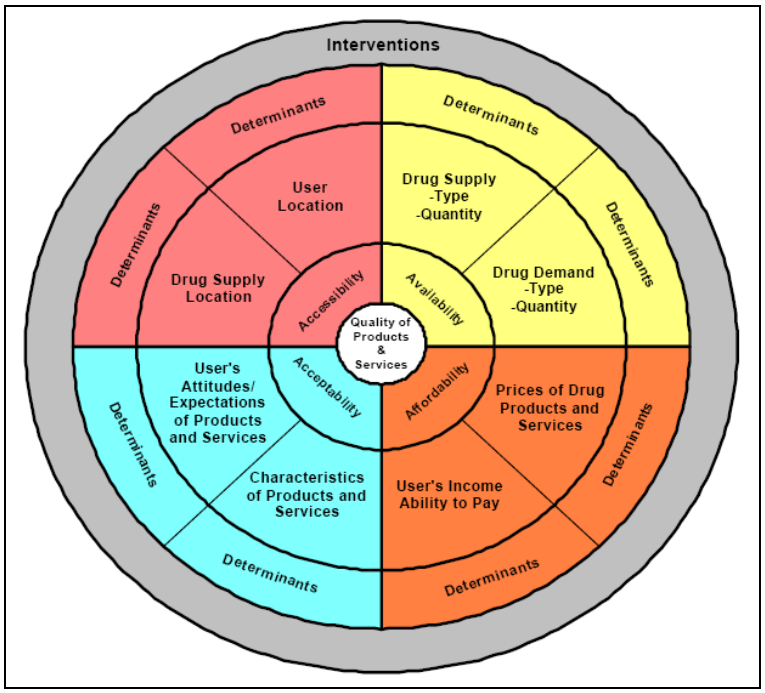

Figure 1: Measuring dimensions of access to essential medicines
Source: "Rational Pharmaceutical Management Plus"

Lack of access to essential medicines is a source of health-related mortality in several LDCs, and a multifaceted phenomenon which does not lend itself neither to simple definitions nor to all-inclusive indicators. Let us take a quick look at the available evidence. The World Health

Organisation (WHO) estimates that the share of world population lacking access to essential medicines has been decreasing during the 1970s and 1980s but stabilised at roughly one third in the mid-1990s (Figure 2). The figure rises to about 50% in poorest countries within Sub-Saharan Africa and South-East Asia as opposed to 0.3% in high-income countries: as Figure 3 shows lack of access is most severe in Africa and India, which together account for 53% of the world population with no or limited access to drugs (WHO 2004). Statistics on HIV, Malaria and Tuberculosis (Table 1) are stark evidence on the magnitude of the health emergency that is plaguing Africa and South-East Asia.

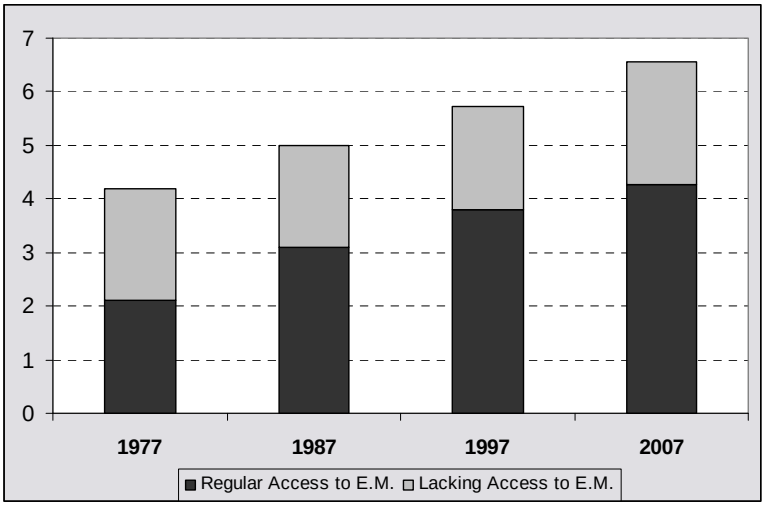

Figure 2: World Population and Access to Essential Medicines (bn)
Source: World Health Organisation

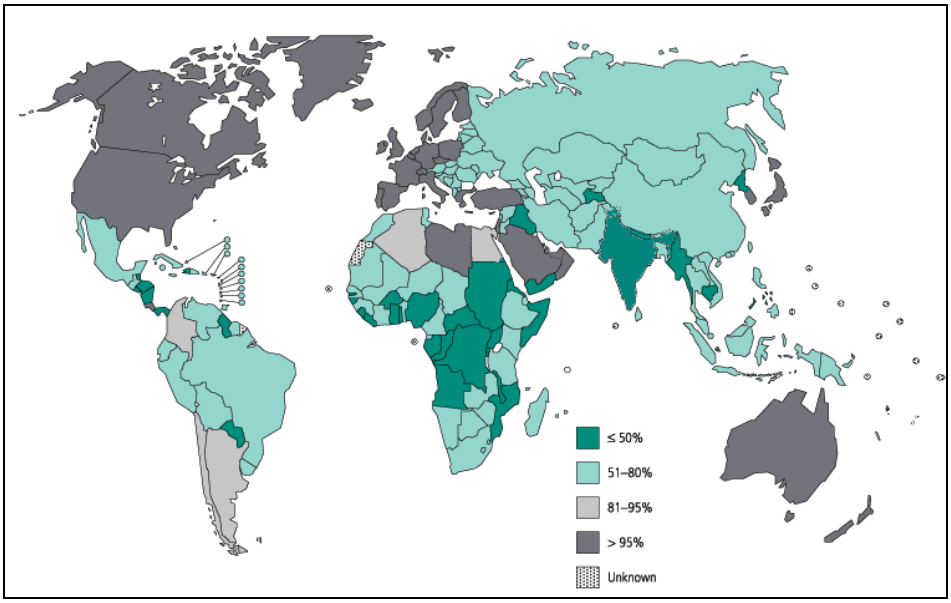

Figure 3: Population of the world with regular access to E.M. (%)
Source: World Health Organisation

	HIV/AIDS	Malaria	Tuberculosis
Africa	2,905,000 (81%)	1,136,000 (89%)	348,000 (22,22%)
Americas	103,000 (2,87%)	1,000 (0,07%)	46,000 (2,93%)
South-East Asia	436,000 (12%)	65,000 (5,11%)	599,000 (38,25%)
Europe	36,000 (1%)	2,000 (0,15%)	69,000 (4,41%)
Eastern Mediterranean	44,000 (1,22%)	57,000 (4,48%)	138,000 (8,81%)
Western Pacific	61,000 (1,7%)	11,000 (0,86%)	366,000 (23,37%)

Table 1: Death Statistics, Year 2002
Source: World Health Report 2004

The most common type of institutional response for countering such health-related emergencies are public facilities for providing access to medicines at low cost or free of charge. A study by the United Nations (2008) however shows that drug availability is as low as 35% in the public-sector and 37% in private health facilities in several LDCs (Fig. 4). Looking at level of financing, another crucial factor in determining availability of medicines in the public sector, the same study finds wide variation in national per capita spending on medicines by the public sector – between $0.04 and $187.30 among LDCs – as well as among countries of similar economic status, expenditures ranging from $26.67 to $505.46 across developed countries and from $0.04 to $16.30 across developing countries (Figure 5).

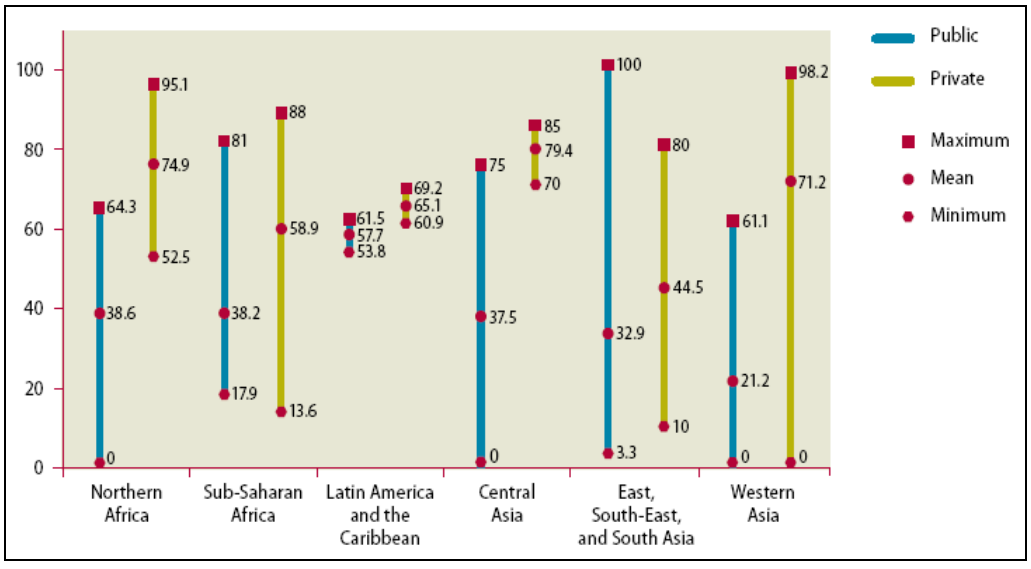

Figure 4: Availability of Selected Essential Medicines (%)
(Source: WHO Survey of medicine prices and availability, 2008)

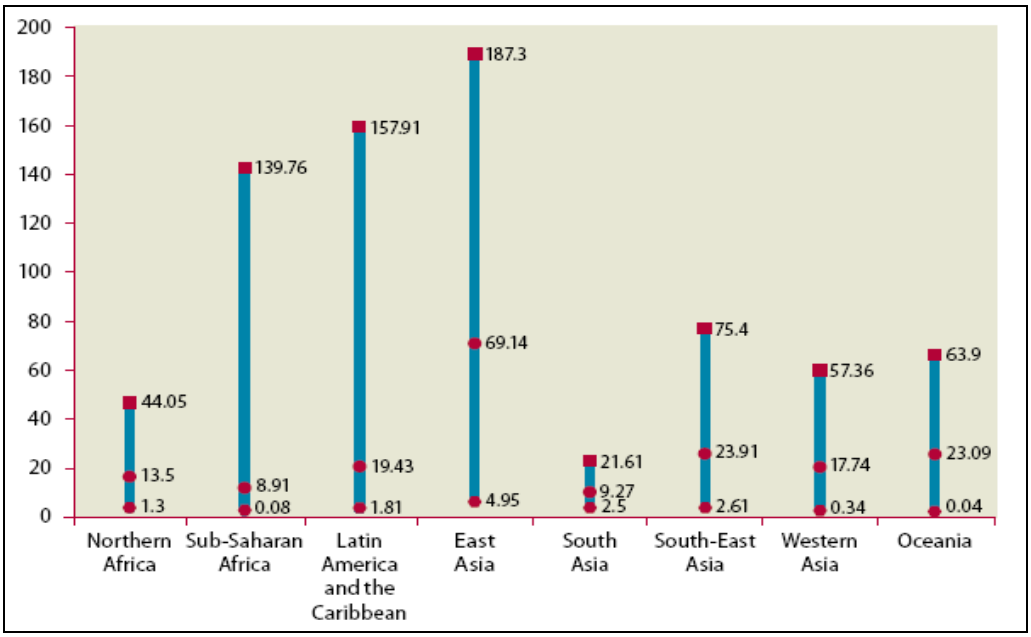

Figure 5: Public per-capita expenditure on medicines
(Source: WHO Survey of medicine prices and availability, 2008)

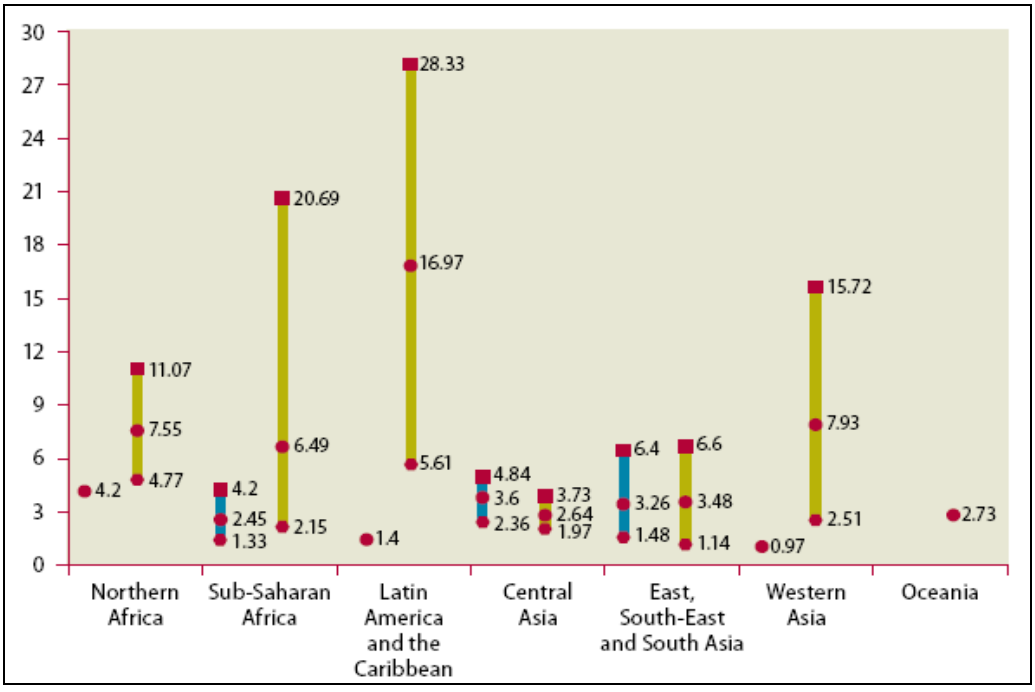

Figure 6: Ratio of consumer prices to International Reference Prices for selected generic medicines in public and private health facilities
(Source: WHO Survey of medicine prices and availability)

Other important determinants for availability of medicines include procurement of high-priced products, such as originator brands, and the efficiency of the supply chain; in relation to these the UN study finds that generic medicines are costlier in 33 LDCs compared to the International Reference Prices (IRP) both in the private (6 times higher) and public sectors (2,5 times). Figure 6 provides a breakdown of these figures across macro-regions.

Higher prices in the private markets are due to mark-ups that are added to the cost of the production of medicines as they move through the supply and distribution chains. Empirical results from a selection of countries show that these add-on costs are substantial in both the public and the private sectors (Table 2).

Country	Public Sector Mark-up	Private Sector Mark-up
China	24-35	11-33
El Salvador	165-6	894
Ethiopia	79-83	76-148
India	29-694	
Malaysia	19-46	65-149
Mali	77-84	87-118
Mongolia	32	68-98
Morocco	53-93	
Pakistan	28-35	
Uganda	30-66	100-358
United Republic of Tanzania	17	56

Table 2: Margin between producer and consumer prices (%)

Besides affordability other factors play a crucial role in determining access to medicines, especially availability of adequate, sustainable and equitable financing. International aid programmes such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States President's Emergency Plan for AIDS Relief (PEPFAR), UNITAID and Advance Market Commitments for vaccines (AMC) respond to the rationale of channelling resources for the purchase of drugs and vaccines. While some diseases are stronger catalyst for such programmes, further support is needed for other chronic, non-communicable diseases such as cardiovascular disease, cancer, diabetes and chronic respiratory disease which are estimated to be responsible for 35 million deaths (60% of all deaths) in low- and middle-income countries. In 2008 Roger England (chairman of Health Systems Workshop a health-policy charity) raised the controversial question "Are we spending too much on HIV?" on the authoritative British Medical Journal. Dr. England (2008a,b) points out that AIDS receives about a quarter of global health aid but accounts for "only 5% of the disease burden in low- and middle-income countries"; in his view efficiency improvements in health systems would

be more effective if aimed at broader goals like tackling other diseases and by means of less inexpensive interventions such as immunisations, mosquito nets and family planning.

Further evidence on cross-country disparities from a study by the Economic and Social Commission for Asia and the Pacific (UNESCAP) (2007) shows that per capita spending on pharmaceuticals ranges from less than $20 in low- and middle-income countries to $528 in high-income countries. The key point is that differences are also significant in the distribution of research and production capacity (see Table 4) which are a key cause for the neglect of high-incidence tropical diseases. In fact only the share of new medicines for such diseases only account for 0,3% of total drug local production.

Stage of Development	**Country**
Sophisticated industry, sophisticated research	Japan
Innovative capability and well-developed industry	China, India, Australia, Republic of Korea, Russian Federation
Ability to produce active ingredients and products	Indonesia, Thailand, Pakistan, Philippines, Bangladesh, Malaysia, Turkey, Singapore, New Zealand
Finished products from imported raw materials	Sri Lanka, Myanmar, Vietnam, Nepal, some Central Asian countries
No manufacturing capacity	Pacific Island countries, Bhutan, Cambodia, Lao PDR, Maldives

Table 4: Degree of development of Pharmaceutical industries in Asian countries
Source: Economic and Social Commission for Asia and the Pacific, 2007

The UNESCAP study finds also that global drug supermarkets like China and India cater for very little local demand and that, in fact, companies based in either country are responsible for an associated health issue, namely the commercialisation of counterfeit and substandard drugs. A policy remedy to this is increasing the use of quality-assured generic medicines and improving the affordability of medicines by allowing pharmacists to dispense generics in place of the originator brand listed on the prescription. Figure 7 shows however that legal provisions for generic substitution is rather common among developing countries though with significant differences like, for example, East Asia (100% of countries) compared to South and Western Asia (40%).

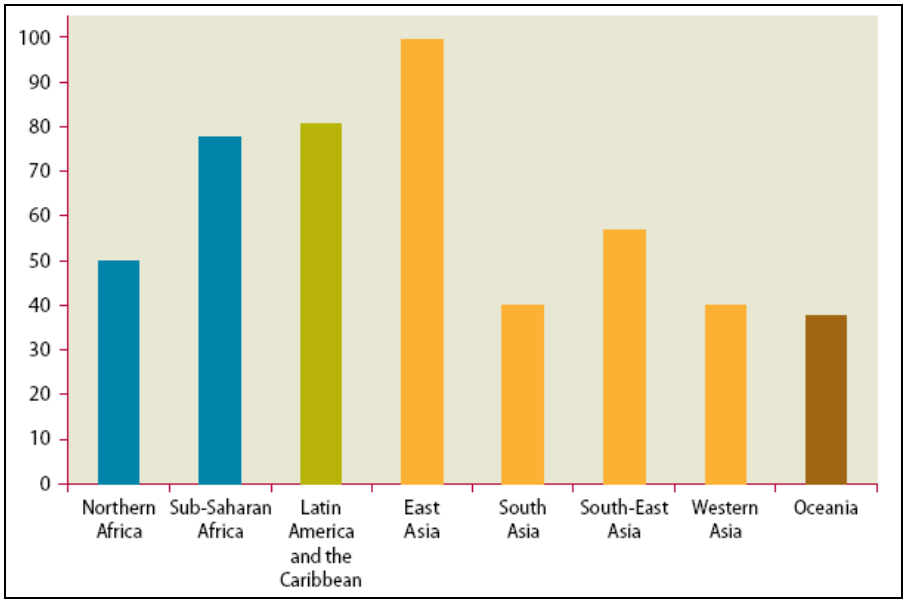

Figure 7: Countries with legal provisions for generic substitution in the private sector in 2007 (%) (Source: WHO Survey of medicine prices and availability, 2008)

The phenomena to which this evidence refers to fuel the scholarly debate in two directions concerning how to increase access to affordable existing medicines, and hot to stimulate drug development for poverty-related diseases. In relation to this the Working Group on Access to Essential Medicines for the UN Millennium Project distinguishes barriers to existing medicines from barriers to the development of new medicines. Very synthetically, the most common barrier to existing medicines have been found to be (1) inadequate political commitment to making healthcare a priority both at national and local levels; (2) scarce commitment to create human resources for health through education and training as well as retaining of skilled workers; (3) poor engagement by the international community with the challenges of the poverty-disease trap; and (4) insufficient donor funding and aid coordination to avoid unnecessary duplications. Conversely, the main barriers to the development of new medicines are two: compliance to Trade-Related Aspects of Intellectual Property Rights (TRIPS) and inadequate incentive structures for R&D investments on health priorities within LDCs (WHO and IFPMA 2001). But besides financial political and institutional circumstances, other factors play a crucial role. Most developing countries feature substantial internal inequalities which are exacerbated by debt burdens and operational constraints imposed by foreign financial and political organisations; in addition, as already anticipated, competition in the pharmaceutical sector is replete with mismanagement, corruption and predatory behaviour. At heart of these problems is what many describe as the paradox of health-care in LDCs where the forces of health-care commercialisation prevail on the will to

operate according to egalitarian principles[3] (see e.g. Hanson and Berman 1998; Bennett et al 1997; Leonard 2000; Söderlund et al 2003; Mackintosh and Koivusalo 2005, cited in Mackintosh, 2007).

Empirical work by Mackintosh (2006, 2007) shows that patients in poorer countries most likely incur in out-of-pocket spending; the same studies also find that practices aimed at creating, expanding or reinforcing independent, small scale, largely unregulated primary provision tend to spread in contexts where private insurance is underdeveloped and social insurance is restricted. The upshot is that citizens of the poorest countries end up spending a much larger proportion of their incomes on health care than those living in high-income countries, and are exposed to impoverishment, loss of income-earning capacity and exclusion. Mackintosh (2006: 397) offers a thorough articulation of the pathways through which 'cash and carry' health care and inequality mutually reinforce one another, which include loss of income-earners; social divisions; social hierarchies in the health system; weakening aspirations to health care; loss of public sector capacity; abuse, exclusion and impoverishment. Besides targeted regulatory improvements and ad-hoc solutions like international aid programmes, Mackintosh (2007) concludes, health-care reforms require direct government intervention aimed at integrating both the development of market processes with the expansion of access to citizens. These considerations therefore suggest that inefficient institutional set-up is a crucial piece in this complex jigsaw.

3. Production of Pharmaceuticals

One of the suggested pathways towards the removal of barriers to essential drugs is the development, or strengthening, of local production systems. In some low-resource settings activities are limited to compounding and packaging, repacking, and processing bulk medicines into dosage forms using imported raw materials; in the few countries where production takes place it is mostly for generic medicines and aimed at a small proportion of domestic demand. It is clear that the viability of such local production system depends on a variety of economic, social and institutional factors.

The key activities involved in the production of pharmaceutical drugs include:

- Manufacture of products by chemical synthesis;
- Production and separation of medicinal chemicals (e.g. antibiotics and vitamins from microorganisms);

[3] See Price (1999) for a case study on South Africa, Pannarunotai and Mills (1997) on Thailand and Falnkingham (2004) on Tajikistan. See also a literature review on the economic literature on health-care charges by McPake (1993).

- Manufacture of botanical and biological products by extraction of organic chemicals;
- Formulation of bulk pharmaceuticals into dosage forms that can be taken by the patient (e.g. tablets, capsules).

Availability of medicines depends on a combination of production and trade activities mixed in different dosages along the following continuum:

- No manufacturing and total dependency on imports;
- Packaging of formulated medicines and small-scale local production;
- Formulation of drugs in final dosage form and some production from imported intermediates;
- Production from imported intermediates and manufacture of some intermediates from local materials;
- Production of active substances and processing to produce the required pharmaceutical dosage forms.

This spectrum of operations entails a division of labour among three main typologies of firms (see Balance et al, 1992). First are large multinationals which engage all stages of the process of production and leave the distribution to subsidiaries and licensees; these firms manage large portfolios of products and tend to be highly concentrated in a small number of developed countries. The second group include companies that produce mostly patent-expired drugs and invest very little in research and development activities. The last type of firm, most common in developing countries, are those that lack in-house research capacity and purchase active ingredients to produce medicines either under brand names or under international non-proprietary names as generics.

Considering the possibility of inter-firm alliances and partnerships, the following scenarios are possible:

- Uni-national pharmaceutical companies with sales activities that only occur within the country;
- Multinational pharmaceutical companies with a single corporate headquarters within the country;
- Multinational companies with relatively large research and development and sales activities within a country and corporate headquarters in another country;

- Multinational companies with corporate headquarters in another country, and with a relatively large manufacturing plant or technical development laboratory and sales activity within the country; however, no major research and development group exists within the country;
- Multinational companies with corporate headquarters in another country, and only relatively small operations for technical development, research, or manufacturing, in addition to sales activity, within the country;
- Multinational companies with only sales activities within the country.

The issue of viability of production is tightly related to intellectual property protection in the pharmaceutical industry. The debate concerning the rationale of patenting in fact goes back 50 years and finds its main justification in the costly R&D investments that are required for discovering, developing and gaining regulatory approval for a drug (see Scherer, 2004). Several empirical studies demonstrate strong correlation between profitability and R&D investments in the pharmaceutical industry (Vernon, 2005). A company operating in the sector will typically engage several parallel projects knowing that most drug candidates will fail to reach the market; to be precise less than 1% of the compounds examined in the pre-clinical stage are cleared for testing on humans, and just about 20% of the compounds that are actually used in clinical trials obtain approval from the US Food and Drug Administration (Di Masi et al, 1995). Besides being costly, the process is also lengthy and involving successive trials of considerable organizational and scientific complexity. These premises illustrate why only financially capable firms can undertake investments decisions in this sector. Two interrelated factors add to the above. Drug manufacturing is expensive, especially when specific production requirements prevent reaping scale advantages[4] while imitation costs are low relative to the innovator's costs for discovering and developing a new product. It is clear that weak or absent intellectual property protection stimulates free-riding and, in so doing, discourages new drug development.

A key piece of legislation for developing countries is the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), negotiated at the end of the Uruguay Round of the General

[4] It is worth drawing attention also to empirical evidence showing that economies of scale are limited in pharmaceutical production (see e.g. Jensen, 1987; Graves and Langowitz, 1993; Cockburn and Henderson, 1996; 2001); it is also shown that R&D activities generate economies of scope by sustaining diverse portfolios of research projects that capture internal and external knowledge spillovers (Cockburn and Henderson, 1996; 2001).

Agreement on Tariffs and Trade (GATT) in 1994 to create global minimum standards for protecting all intellectual property – including pharmaceuticals. Prior to the agreements countries like Brazil, China and India would bypass patent protection and manufacture domestically generic versions of high cost drugs patented in developed countries at lower costs.[5] The standard TRIPS regime forbids generic competition during the life of a patent save exceptions under special circumstances[6] such as public health emergencies. This applies clearly to LDC which are, in principle, granted permission to issue licences for necessary medicines. There is however mixed evidence on the effectiveness with which domestic regimes have adapted to implement compulsory licensing; India and Brazil and Tanzania are perhaps the extremes of this spectrum of experiences (Chauduri, 2007).

Since its inception the TRIPS legislation has been under scrutiny for what concerns operational shortcomings in the requirements for issuing compulsory licenses.[7] The World Health Organization (2004) has repeatedly pointed out critical aspects of the implementation of TRIPS rules. First, whether national governments would effectively use safeguards or not depends on relations with traditional manufacturers and international trade partners. Second, and relatedly, the decision to bypass patent protection depends on the cooperation between generic producers and research-based industries. As a matter of fact patent-holders have a strong incentive to enter into voluntary licensing agreements after the generic manufacturers benefit from TRIPS safeguards. A third critical issue concerns the extent to which broader institutional conditions within LDCs support or thwart the development of local production capacity. Experiences from South African countries are a testimony to the fact that even if voluntary licences are issued, insufficient manufacturing capacity or deficient administrative infrastructures are significant obstacles (see e.g. Chauduri, 2008).

---

[5] The advantage of a process patent system is that any small change in the steps used to create a drug allows a generic producer to sidestep the patent. The goal is for several manufacturers to produce the same drug by using different methods, thereby stimulating competition and lowering drug prices.

[6] Compulsory licensing enables a competent authority to license the use of an invention to a third party or government agency without the consent of the patent-holder. Parallel importation promotes competition for a patented product by allowing importation of equivalent patented products marketed at lower prices in other countries. Article 8 of TRIPS specifies that countries can "adopt measures necessary to protect public health and nutrition and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provision of this Agreement". The original text however authorised for supply of the domestic market only of a "manufacturing" country which de facto excluded a large number of developing countries. The text was subsequently amended by the WTO in 2003.

[7] As James (2003) points out, for example, an importing country is obliged to assess its generic industry's capacity to produce the medicine locally, and only if this is deemed insufficient it must notify the WTO and explain and justify its decision. The importing country must also notify a potential exporter who must seek a voluntary license from the patentee; if that fails then the exporter must seek a compulsory license from its own government on a single-country basis.

According to Kontic (2008) compulsory licensing is most practical when production is aimed at domestic needs, like the case of patented drugs for HIV/AIDS in Brazil or China.

At first sight the downward pressure on prices exerted by TRIPS agreements seemingly enhances the bargaining power of low-income countries under strain from health emergencies due to HIV/AIDS, malaria and tuberculosis. Indeed the cost of treatment with antiretroviral drugs declined from around US $ 30 per day per person in 1998 to $1 at the end of 2002 (Economist, 2002). Further down the line, however, two critical issues deserve greater attention. First, the decline of prices for antiretroviral drugs and the related higher availability in the global distribution network do not entail health benefits de ipso facto. A clear example is the mixed picture of HIV/AIDS prevalence after the emergence of combined therapies in the mid-1990s: while life expectancy increased in high-income countries such as Denmark, United Kingdom and United States (Lohse et al., 2007; Walensky et al, 2006; Beck et al, 2008) still in 2003 only 1% of patients in need in Sub-Saharan Africa had access (Ito and Yagamata, 2007). On a similar note, the latest UNAIDS report (2008) estimates that between 2000 and 2007 the rate of new HIV infections has outpaced the availability of AVRs therapies by 2,5 to 1; in short, the gap in mortality rates between high- and low-income countries for patients under AVR therapy remains at around 30% (Antiretroviral Therapy in Lower Income Countries Collaboration, 2006). This reaffirms that medical advances are necessary but not sufficient conditions to alleviate health emergencies.

A second important issue is that lower prices may address the comparative static problem of balancing demand and supply of drugs, but matters are more complicated in the case of diseases that are prevalent only in resource-limited settings, like malaria or tuberculosis. On the one hand it is clear that LDCs do not possess techniques and know-how that are necessary to undertake intensive R&D activities aimed at catering for their own health needs. On the other hand, eroding profit margins limit the incentives of those with adequate R&D capacity, like large pharmaceutical companies, to invest in the development of new drugs for diseases that are prevalent in low-income countries, and for which therefore demand is high but resources are scarce. Ito and Yagamata (2007) show that over the last twenty years private pharmaceutical firms have outperformed public ones in terms of the number of patent applications for treatments for HIV/AIDS and tuberculosis, prevalent in both developing and developed countries, but also for malaria, which is instead rare in developed countries. By contrast the deceleration of HIV/AIDS-related patenting after 2001 seems to indicate that large pharmaceutical companies have shifted their R&D away from these areas (Nitta, 2005). These remarks lead to the following question: what institutional architecture can best encourage the private sector to continue developing new drugs for diseases that are most prevalent in least profitable markets within LDCs?

4. Production of Pharmaceuticals in LDCs: selected cases

The debate concerning health emergencies within LDCs revolves mostly around the question of whether creating local systems of production is a viable solution or not. Let us now take a look at the main arguments presented in favour and against this motion, and at selected experiences of pharmaceutical industry development.

A World Bank report by Lashman (1986) argues against the local manufacturing argument on the grounds that the prevailing conditions within LDCs do not meet minimum operational and technical standards that are necessary to set up local production of medicines. Notable exceptions were countries with large local markets and potential to produce Active Pharmaceutical Ingredients (APIs)[8] such as China, India, Thailand, Brazil, and Argentina. Another study by Balance et al (1992) estimated that LDCs accounted for about 20% of world drug production at the end of the 1980s. The report provides a detailed breakdown, namely: countries with sophisticated pharmaceutical industry and research base (e.g. USA, UK, Switzerland, Germany and France); countries with innovative capabilities (e.g. Australia, Canada, Denmark, China and India); countries producing both Active Pharmaceutical Ingredients (APIs) and finished formulations (e.g. Brazil, Cuba, Indonesia, Romania and Turkey); countries producing only finished formulations (e.g. Afghanistan, Bangladesh, Cambodia, Ethiopia, Kuwait and Morocco); and finally countries without any pharmaceutical industry, mostly in Sub-Saharan Africa e.g. Bhutan, Chad, Laos, Qatar, Suriname. A recent study by Chauduri (2008) finds that the gap has actually grown over the last two decades and that the share of global pharmaceutical exports of South-Africa is historically low, at 14%.

A study by Kaplan et al (2003) elaborates a “threshold” level of industrial competitiveness for ascending countries above which the volume of production does not vary significantly. The implication is that close to the frontier further improvements depend on structural factors other than economies of scale, such as for example backward linkages with polymer, plastic and container manufacturers, or forward linkages with the distribution channels (shipping and trucking industries). In addition only countries with a “positive” pharmaceutical trade balance are likely to develop sustainable local production above the competitive threshold. The study also looks at the impact of educational and vocational system on the supply of skilled workers for the pharmaceutical industry and finds a correlation between the growth of India and China and the

[8] Active Pharmaceutical Ingredients of a drug are the biologically active components which impart the therapeutic effect.

large supply of skilled workers as opposed to the case of Ukraine, Egypt, Russia, Poland and the Philippines.

Kaplan et al (2003), Chauduri (2008) and Loureiro et al (2007) concur that recent changes in the global economy place countries like China, Brazil, Korea and India in a better position to compete on a global scale (also) in pharmaceutical production. A different picture emerges for Sub-Saharan African countries where structural deficiencies are still persistent and a significant obstacle to escape the poverty trap. Besides structural deficiencies in financial and human resources local pharmaceutical markets suffer from lack of regulation and government supervision which reduce the prospects of industrial expansion (Chauduri, 2008). A study by the World Health Organisation reiterates that growing pressure from foreign competition forced scaling down activities of local pharmaceutical industries in 38 countries of Sub-Saharan Africa (WHO, 2005).

The broader point is that poverty tends to be a self-reinforcing process aggravated by circumstances such as shortage of skilled labour, scarcely developed financial sectors, low levels of foreign direct investment, inefficient systems for financing, taxes and regulation, corruption and generally weak legal and regulatory regimes. The challenge of competing within a global pharmaceutical market adds other factors to that list: restrictions from intellectual property right regimes, wide fluctuations in cost per unit, ineffective measures against unfair practices like dumping, add to these factors (see Kaplan et al, 2003; Chauduri, 2008). The strong message coming from the specialised literature is that government action is deemed both indispensable and, at the same time, crucial for avoiding the self-reinforcing spiral of low development. This point is advanced forcefully by a study Mackintosh and Tibandebage (2007) on the adverse effects of market dynamics in Tanzania where the diffusion of unregulated competition lowers incentives to provision of skilled patient care; where local small businesses are thwarted by systematic instability; and where fragmentation is a leading cause of insufficient and unequal access to health-care for large parts of the population. These concerns are at root of a wider debate as on how to integrate policies aimed at stimulating innovation with those aimed at ensuring the widest spread of the associated social benefits (see Mackintosh, 2006; Mackintosh et al, 2007).

The juxtaposition of globalization, double disease burden and increasing health-care costs is held by many at root the gap between demand and supply of essential medicines in LDCs. Notwithstanding the persistence of these disparities, the geography of pharmaceutical production has changed significantly over recent decades. Growing competitive pressure has pushed large drug developers to establish partnerships with firms operating in areas with abundant work force

and low costs. The next subsections will look at the ascent of India, Brazil and China against the backdrop of a global pharmaceutical industry in continuing evolution.

4.1.1 - India

The value of India's pharmaceutical market has grown at an annual growth rate of 15% (compared to global 6%) between 1998 (U.S. $3 billion) and 2005 ($10 billion) (in 2001 U.S. $) (Clark, 2004). At the same time average per capita expenditure on pharmaceuticals remains low, $3 compared to $412 in Japan, $222 in Germany and $430 in the U.S. Part of this gap is explained by the prevalence of alternative healing methods in parts of the country but most of it stems from systematic government intervention aimed at fostering a collaborative climate for development and innovation through government laboratories, public sector companies and support to Indian universities (Chauduri, 2007; 2008).

The domestic Indian pharmaceutical industry, which as of 2002 was the largest producer of generic drugs in the world in terms of volume, is representative of middle-income countries with large numbers of small and medium sized firms with significant imitative capabilities to produce and market domestically drugs that are under patent protection. Within the Indian private sector operate domestic manufacturers together with foreign-controlled importers of bulk drugs and producers of formulations. A sustained expansion process after the 1970s allowed Indian domestic firms to achieve sufficient in-house R&D capacity for developing new drug molecules and producing bulk drugs in the 1990s and, later, to gain importance in the map of global trade. Not only Indian pharmaceutical companies export to other LDCs, their supply actually contributes to keep drugs affordable in developed countries (Chauduri, 2005). By and large this success has propelled large Indian firms to become global corporations leaving smaller businesses to brand building and collaborating with universities and research labs to survive (Dhar and Rao, 2002). According to Chauduri et al (2003) patent enforcement will eventually erode the space of domestic products whose active pharmaceutical ingredients are protected by (foreign) patents.

In recent years the Indian pharmaceutical industry has expanded the production of both generic drugs and specialised medicines – including antiretroviral for HIV/AIDS. A key question is whether the advent of TRIPs has effectively changed the rules of the game for this expanding industry. Empirical works on this are scarce. An exception is the study by Chauduri et al (2003) on the impact of TRIPS on the Indian pharmaceutical industry. The latter articulates contextual features of demand for drugs in a low-income economy where health insurance is rare and medical expenses are met mostly by out-of-pocket payments. The analysis by Chauduri and co-authors shows that the 'adverse' effects of TRIPS on the local industry are low, mostly mitigated by the availability of

close therapeutic substitutes in the domestic market. In other words, when patents on drugs are enforced consumers would rather opt for locally produced, and cheaper, drugs based on different molecules rather than costlier foreign products with the same molecule. In this framework large welfare losses are limited to the extreme case of simultaneous withdrawal of all domestic products, which is rather unlikely.

The case of India is also exemplary of the paradoxes that are common among fast-growing economies in which unregulated competition fosters successfully the emergence of a large market for low-cost bulk drugs but fails to cater for domestic health needs. As Govindaraj and Chellaraj (2001) note the expansion of the Indian pharmaceutical industry contrasts with persistent failures in providing domestic access to essential medicines. To give an idea, only 3% of drugs produced in India are aimed at domestic needs while the bulk of its output is for markets in industrialised countries. Indian suppliers cater for about 50% of the global demand for antiretroviral medicines for HIV/AIDS. Before the emergence of Indians firms the cost of the drugs exceeded US$10,000 per person per year, while now it is less than US$150 (Medecins Sans Frontieres, 2006 – cited in Chauduri, 2007), and yet an estimated 50–65% of the population did not have regular access to essential medicines in 1999 (WHO, 2005, cited in Chauduri, 2007).

4.1.2 - China

The Chinese drug industry has been growing by an average of 17.5% per year since 1979, after the enactment of economic reforms and the adoption of open-door policies. A number of persistent features corroborate the perception that this industry is still in its infancy, namely the small-scale volume of production; the geographical dispersion of key players; the diseconomies in the production processes; and the persistence of obsolescent manufacturing technologies and management structures (Yuanjia et al, 2005). The industry currently caters for only 1.5 % of global demand, with domestic market worth around US $ 10 billion in 2007 (Marketavenue, 2008) and consisting for 97% of generic drugs. Within it operate about 3,500 small domestic firms – down from 5,000 units a decade ago – 35% of which are owned by the government, while the remaining are either private (35%) or aided by foreign funds (29%). Perhaps unsurprisingly, the industry lacks a record of patented pharmaceuticals developed in-house. Notwithstanding these weaknesses the growth of foreign investments into production facilities formerly owned by the state has shifted the focus of pharmaceutical companies from generic production to development of new drugs

(Arayama and Miyoshi, 2004; Yuanjia et al, 2005). As a result China made it in the list of countries which possess "innovative capability" for medicine production (WHO, 2004b)[9].

A triggering event for the Chinese pharmaceutical industry was the HIV outbreak of the late 1990s which the government attempted to contrast by spurring domestic production[10] and by making ARV medicines freely available to citizens who could not afford them. Despite these measures, however, the situation was exacerbated by inarticulate IPR protection over fixed-dose combinations which led domestic manufacturers to provide incorrect drugs combinations, triggering toxic reactions and virus resistance among patients.[11] It is diffuse opinion that the Chinese government on that occasion was unable to organise a concerted response to the health emergency comparable to that of Brazil.

China became a member of the WTO in 2001, but voluntarily amended its patent legislation to become TRIPS compliant several years before. Although many of the first-line ARV medicines received international filing dates several years before patent laws were amended, China allowed "administrative protection" for several of the common ARV medicines. Despite the removal of legal restrictions and the achievement of manufacturing ability for domestic purposes, generic companies in China produced either no ARV medicines or low quality illegal versions. This has changed over the last five years as Chinese generic firms started producing state licensed first-line ARV medications both in response to growing domestic need as well as opportunities in the international markets. However, more than the final formulation the crucial step in manufacturing ARVs is producing the APIs for the final formulations (Tanner, 2006). APIs require substantial inventories of raw ingredients and costly laboratory equipment. Both China and India have become world leading producers of APIs which are primarily targeted for export to Brazil, Thailand and the Republic of Korea.

Strategic motives lie behind China's preference for investment in APIs production. One of them is avoiding patent infringement and trade violations which may exacerbate tensions with foreign countries.[12] Another reason is that the production of generic drugs in China does not always meet quality production standards established by the WHO, and this may lead to financial penalty fees.

---

[9] This means that at least one new pharmaceutical has been discovered and marketed in China between 1961 and 1991 (Balance et al, 1992). To give an idea, Brazil has "reproducer capability" status, that is, maker of both active ingredients and finished products.

[10] People's Daily On-line English version, "China-made anti-AIDS medicine benefiting developed countries"(May 23, 2004). Online: http://english.people.com.cn/200405/23/eng20040523_144142.html

[11] The owner of the patents Glaxo Smith Kline refused voluntary licensing.

[12] China is in the U.S. list of countries that practice trade violations.

Yet one more important aspect is that the WTO has removed prior restrictions and opened up the market for foreign multi-national drug companies which can now import pharmaceuticals in China and therefore erode margins for domestic producers. It is also important to note that China is the only developing country that exports most of its pharmaceuticals to industrialized countries. Consequently, without a steady source of demand for ARV medicines from African countries, Chinese manufacturers will not find a lucrative market. Only domestic need for ARV medicines may initiate more Chinese production of these drugs. In the face of privatization and a market-based economy, a key policy challenge for China is prioritizing production of ARV medications.

4.1.3 - Brazil

The history of domestic production of generic ARV medicines in Brazil is closely tied to the severe HIV/AIDS outbreak of the mid-1990s.[13] Starting from inadequate structures and limited financial resources the government has been able to set up a concerted institutional response based on stimuli to the local manufacturing capacity; rationalise commercial distribution; open up access to health-care; and revise international trade agreements. The goal of removing barriers to the public health system eventually proved efficient for providing essential medicines in the face of a crisis as well as cost-effective for the health-care budget.

The bulk of pharmaceutical production in Brazil retained a distinct local dimension until the liberalisation of imports in the early 1990s. This change encouraged subsidiaries of multi-national corporations to increase foreign imports. Brazil has since become the 11th largest pharmaceutical market in the world as per drug sale figures (Cohen, 2000). As a result of the increase of imports domestic suppliers catered less than 20% of the total market at the end of the decade. In 1999 the government took steps to stimulate domestic production by establishing guidelines that supported the introduction of quality generic drugs as well as domestic competition for non-brand drugs.[14] The number of Brazilian of generic drugs manufacturers grew to 56 in 2005 and domestic companies supply 80% of the demand for generic drugs in Brazil, and 30% of the global market for generics (Nobergal et al, 2007).

Until patent protection for pharmaceutical products was not granted in Brazil in 1997 local companies produced a small number of ARV medicines in accordance with international

[13] Martin Foreman, "Patents, Pills and Public Health – Can TRIPS Deliver?" (2002) Panos Report No. 46 at 35. Online: http://www.panos.org.uk/PDF/reports/TRIPS_low_res.pdf

[14] The legislation states that if a generic and patented drug cost the same amount, the Unified Health System (SUS) shall give purchasing preference to the locally produced generic drug.

agreements but without regulatory standards on copied medicines and non-brand name products. After joining the WTO the patent legislation was modified in accordance with the TRIPS Agreement to integrate technical standards and norms for generic, innovative, reference and 'similar' drugs[15]. The legislation also attributed supervisory power to the newly created Federal Sanitary Surveillance Agency (ANVISA) and endorsed local production through public procurement.[16]

The expanding generic manufacturing industry in Brazil continues to rely heavily on foreign imports. In fact, domestic firms cannot legally produce all of the first-line ARV medicines and nearly 80% of the special HIV/AIDS budget was spent to purchase patented medicines in 2004.[17] Despite having a large domestic industry, patents on several drugs prevent its generic manufacturers from producing the entire first-line regimen – or 'fixed-dose combination'. According to WHO recommendations in resource-limited countries a single first-line regimen should be provided to the majority of new patients. Such a regimen consists of 2 nucleoside analogs and either a non-nucleoside or Abacavir, or a protease inhibitor. A second line regimen should be chosen to substitute first line regimens when needed (for toxicity or treatment failure).[18] The problem is that Brazilian manufacturers are only able to produce the first component of the fixed-dose combination, and all the drugs that formulate the second component are under patent protection. To provide complete first-line therapy, therefore, Brazil needs to import several drugs and is unable to export complete first-line therapies.

In 2004 the Brazilian Ministry of Health announced that should negotiations with the patent owners fail the alternative plan would be to support local manufacturing of generic ARVs. Previously the government negotiated reduced drug costs with multi-national companies under Article 68 of the Industrial Property Law which allows compulsory licensing in the case of 'abusive' use of patent rights.[19] This provision enables issuing a compulsory license to a local manufacturer to produce the drug or allow parallel importation from the cheapest international source without

---

[15] A generic drug, as defined by the Generic Law, must have the same presentation and dosage as the patented drug (must be interchangeable) and it must be approved by ANVISA in relation to its effectiveness, safety and quality.

[16] James Love, "Brazil Considers Compulsory Licenses, Defends Doha P6 Deal" IPS news article, September 6, 2003. Online: http://lists.essential.org/pipermail/ip-health/2003-September/005237.html

[17] Mario Osava, "New Offensive Against Drug Patents" IPS News article, Nov 30, 2004. Online: http://www.ipsnews.net/africa/interna.asp?idnews=26494

[18] See: www.who.int/hiv/topics/arv/en.

[19] Richard Elliot, "US Files WTO Complaints against Brazil Over Requirement for "Local Working" of Patents" (2000) 5(4) Canadian HIV/AIDS Policy and Law Review. The United States filed a complaint with the WTO in 2001 alleging that the "working requirement" violated the rules set out in the TRIPS Agreement.

the patents holder's consent. Negotiations for voluntary licenses with Merck (Efavirenz), Abbot Laboratories (Lopinavir and Ritonavir), and Gilead (Tenofovir) had a mixed record, and in 2007 in the face of disagreements with Merck & Co. the government issued a compulsory license to produce domestically the Efavirenz drug.[20] It is estimated that this drug is necessary for 75% of HIV/AIDS patients and a generic version would save about $240 million until the expiry of Merck's patent in 2012.

The relative successes of Brazil and India have not escaped the focus of the scholarly community. Both countries feature focused industrial policy in support of industrial development and prompt government action to the opportunities and the challenges brought about by a changing patent regime. Wogart et al (2008) propose an interesting comparison between the National Health Governance in Brazil and in South Africa over the battle against the respective HIV/AIDS epidemics. The visible data concerns the difference between Brazil's falling prevalence rate, 0.6 % of its population in 2007, versus South Africa's persistent 18% (Brazilian Ministry of Health, 2008). The comparative summary of Table 5 illustrates interesting similarities and differences between the two countries.

Item	Brazil	South Africa
Trajectory	HIV-infected people 1992: about 770,000 or prevalence-rate < 1%	HIV-infected people 1990: < 1%
	Actual HIV prevalence 2006: 0.61%; i.e., 620,000 HIV-infected people	HIV prevalence 2006: 11% (5.54 million HIV-infected people)
Per capita income	US$3000 (2006)	US$3630 (2004)
Income distribution	Seriously unequal (Gini-Index: 59.3—2005)	Seriously unequal (Gini-Index: 57.8—2005)
Public health expenditures	7.3% of federal budget with additional state and municipal spending	11.5% of total public budget
ARV distribution free of charge (year of implementation)	Since 1988, DST-medication; since 1991, AZT; since 1996, ARV distribution	Since April 2002, legal entitlement for HIV-positive mothers (Nevirapine); since November 2003 for all citizens
HIV/AIDS treatment policy at federal level (year of implementation)	Since 1985: National HIV/ AIDS Program	1994: National AIDS Plan

Note: Gray-colored cells indicate major divergences between Brazil and South Africa.

Table 1 (Source: Wogart et al, 2008)

Although in the mid-1990s' the two governments could tap into a similar resource base to contrast the disease, different attitudes influenced the strategy and their outcomes. Despite greater

[20] This followed Thailand's prior steps in overriding patents on three anti-AIDS drugs, which resulted in the country being added to the United States list of copyright violators.

exposure to external debt, Brazil provided an aggressive response with the supply of ARVs free of charge in 1996 while a similar program surfaced in South Africa only in 2003. Another important, and differentiating, factor in favour of Brazil was the strong drive provided by both civil society groups and close collaborations between the government and NGOs – especially in the early days (Galvão, 2003; 2005). Over time the role of civil society organizations proved crucial to manage the International AIDS Project strategically, and to limit the influence of the main funder, the World Bank. This gave the Brazilian government a stronger role and an opportunity to keep its comprehensive program of prevention and treatment coherent (Calcagnotto 2007). The South African government instead engaged very mildly with global actors, preoccupied as it was not to add to the debt burden. Throughout the 1990s the South African government accepted external offers of financial or technical assistance just up to 1% of the annual health budget (Schneider and Gilson, 1999). This bland strategy led to deteriorating health conditions within the country, and forced a change of attitude – arguably late especially if compared to Brazil: in 2005 the American organization President's Emergency Fund for AIDS Relief (PEPFAR) provided US$221.5 million for treatment, prevention, care of orphans, and palliative care to both the national government and civil society organisations (United States Global AIDS Coordinator 2005). With an estimated 5.7 million South Africans living with HIV in 2007 this country has the second highest prevalence in the world. Most alarmingly although the supply of antiretroviral drugs has grown most people in need do not have access, and the epidemic de facto outpaces the rate at which drugs are delivered.

Overall it is not surprising that Brazil's experience in curtailing the national health emergency is reaching out to other LDCs in the form of advice, technology transfer, training of medical personnel and drugs.[21] Through the International Cooperation Program for HIV and AIDS Prevention and Control Activities for Other Developing Countries, launched in 2001, Brazil provides direct and indirect assistance to patients in various African countries as well as South America.[22] It is worth stressing that the paradigm of HIV response in Brazil is now under scrutiny as the end of the transition period in 2005 puts the sustainability of the whole program under strain. Orsi et al (2006) outline the combination of factors that underlie this situation. First, despite the best efforts of the national HIV campaign domestic capabilities for synthesising molecules are still inadequate; a second critical factor is the need of updating local production and to integrate the newer generation ARVs. Combined together these factors imply strong dependency on suppliers who are

[21] Brasilia, Ministry of Health, Press Release issued December 19, 2002. Online: http://www.cptech.org/ip/health/c/brazil/brazil12192002.html

[22] "Brazil Exporting HIV Treatment to Six Countries", ACAN-EFE (translated from Spanish to English by World News Connection) August 26, 2004. Dialog® File Number 985 Accession Number 194500771

TRIPS-compliant such as India and China and therefore greater exposure to the pricing strategies that Brazil had hitherto managed to bypass.

5. Beyond the demand and supply scheme

A growing wealth of gray literature assesses the viability of local drug production in resource-limited settings vis-à-vis the emerging scenario of global competition and trade legislation, and proposes various policy indications. The previous section indicates four areas for policy intervention, namely (i) encouraging rational selection and use of essential medicines; (ii) ensuring affordable prices; (iii) engaging programmes for sustainable financing; and (iv) creating and monitoring reliable supply systems.

In an attempt to tackle the issue of access to essential drugs the World Health Organisation in 2005 has laid out key principles and action point to facilitate the development of local pharmaceutical production at sub-regional and regional levels. By and large the proposed strategy hints at the construction of 'south-south' collaborations built upon public and private partnerships, and monitored regularly by specialised assessors. Government policies should be aimed at encouraging intraregional trade and production of competitive products at national, sub-regional or regional level through existing communities such as the Economic Community of West African States, Southern African Development Community, and Common Market of Eastern and Southern Africa. According to the WHO medicine and vaccine production is best left to the private sector while governments should promote a favourable environment through regulation. More specifically, governments' responsibilities include:

(a) Create an enabling policy and economic and regulatory environments for technology transfer, and facilitate the development of local production capacity for essential medicines;

(b) Use regional economic integration to improve local production and encourage countries to join regional economic communities;

(c) Enhance collaboration among the various ministries (health, trade, industry, finance), patent offices, private sector and other development partners;

(d) Undertake economic appraisals of alternative options to ensure sustained supply of essential medicines;

(e) Enhance pharmaceutical research and development, especially using locally-available medicinal plants and other raw materials, in order to generate data on safety, efficacy and quality needed for large-scale production;

(f) Build regulatory capacity to enable implementation of Good Manufacturing Practice and TRIPS safeguards such as compulsory licensing.

It is, in turn, responsibility of the World Health Organization to support countries to:

(a) Build medicine regulatory capacities and implement Good Manufacturing Practice;

(b) Implement national medicine policies, patent laws and regulations; play an advocacy role; and monitor the impact of globalization on access to medicines.

Development partners also have various roles. It is envisioned that they would:

(a) Mobilize resources to support the development of local production of essential medicines;

(b) Identify countries with potential for success in local production and advise them on making informed decisions on the development of an economically-viable pharmaceutical industry;

(c) Assist countries to effectively implement TRIPS safeguards.

Another policy orientation argues for supports the integration of local production systems with technology transfer implemented by means of ad-hoc associations like: the Regional cooperatives of manufacturers PHARMESA, the Common Market of East & South African (COMESA), the Economic Community of West African States (ECOWAS), and the Pharmaceutical Manufacturers Association.

As already anticipated the foregoing policy debate is both inspired and delimited by the conceptual boundaries of the TRIPS framework. Some authors have stepped outside of that realm and explored alternative routes.

Gaslandt et al (2001) ascribe the undesirable effects of the current regime to (i) lack of incentives to develop new treatments for endemic diseases in low-income countries; (ii) provision of drugs at low prices in LDCs generating negative externalities on patients in higher-price countries who effectively contribute to recover fixed R&D costs. In view of this, neither pharmaceutical companies nor their patients may be expected to accept costs of distribution and development; (iii) pharmaceutical firms chronically under-supplying medicines in poor countries because of limited patent protection and of adverse effects of parallel trade. To address these issues Gaslandt and co-

authors propose the alternative of “Developing Economies’ Fund for Essential New Drugs” (DEFEND) program, built upon the following criteria. The first action point is the separation between incentives for development of new drugs and distribution of existing drugs whereby the latter should be based on cost-based pricing while new drug development should be funded by a scheme with fixed lump-sum payments for new innovations. The fund would be partly subsidized by the industrialized countries with a long-term guarantee to the pharmaceutical companies that they will receive reasonable returns on their investment in new and effective drugs. The fund would also be used to buy licenses to produce and sell patented essential drugs in least-developed nations that choose to adhere to the program. The second provision is that the coverage of inexpensive distribution should be limited to a clearly-defined geographical area, with official restrictions on parallel imports enforced by an independent supervisor, like the WHO. The program would be open primarily to countries in Sub-Saharan Africa, and any government, international organization or non-governmental organization would be allowed to use the license in the participating countries under three conditions: the original patent is respected in non-participating markets, the distribution is restricted to patients in the participating countries and parallel trade to other markets is prohibited. The portfolio of licenses managed by the international fund should be limited to the most essential drugs. Finally, the implementation of the program should be gradual and start with priority areas such as HIV/AIDS treatment. The initial step would be the purchase of a portfolio of five or six licenses for the most important drugs. Gaslandt and co-authors estimate that a reasonable payment for these licenses in Sub-Saharan Africa would be in the range of $500 million to $1 billion/year with an overall program cost of about $8.2 to $12.1 billion/ year. They also estimate that this commitment would correspond to 0.03 – 0.05% of total GDP (at 2000 levels) among the OECD countries.

A recent work by Nitta (2005) captures similar aspects, namely the dual effects of generalised price decrease for essential medicines, specifically AVRs. To counter the weakening of incentives to develop new medicines Nitta proposes the Green Intellectual Patent (GIP) system which is based on a complex Trust Fund financed by reserves, taxes, and premiums in the patent system. Reserves are a special budget for the Trust Fund; the tax would be paid by successful patentees when they earn patent incomes including royalties and infringement compensations; the GIP premium would be an insurance fee paid by patent beneficiaries to guarantee patent incomes. The idea is that in return for the premium, when low-income countries apply for compulsory licenses for essential medicines, the GIP system would offer financial aid for royalties and a subsidy to purchase the medicines.

A number of conceptual alternatives have emerged also in the scholarly research arena. One of the strongest arguments has been made by Mackintosh (2007) in relation to the divide between research on poverty-related health issues, such as access to services and medicines and the extent to which public health initiatives reach the poor and research on industrial innovation in pharmaceuticals. Mackintosh et al (2007) argue that traditional ingredients of innovation research such as the analysis of changing market and non-market structures based on the notion of systemic feedback are an appropriate terrain for the integration of social and industrial policy. Equity and efficiency need not be orthogonal in search of problem-solving strategies that foster efficient institutional intervention to support growth and innovation as well as preserving or improving social equilibrium. Conversely, research in social policy needs to accept that social sectors are both productive and distributive. The link between social sectors and growth is often understood only in terms of their demand for industrial inputs, and even then, the link between, for example, effective health policy and industrial innovation is rarely made. But social sectors contain large numbers of businesses that form key elements of local production and innovation systems. Social policy for poverty reduction needs to associate its distributional concerns on the ways in which both social sector interventions and broader social policy frameworks such as labour regulation can contribute to and help to sustain technological capabilities.

6. Concluding remarks

The stark contraposition between Health Policy scholars, who advocate that LDCs should develop local facilities for pharmaceutical production, and the Industrial Policy camp, that this solution would not meet the criteria for efficiency can be ascribed, at least initially, to ontological differences in assigning primacy to either equity or economic efficiency. A new research agenda could reconcile the two positions by resorting to a Systems of Innovation approach. To do so, however, the conceptual focus should be adapted since the question of whether LDCs should develop or not local systems for the production of medicines overlooks two important issues.

First, disease prevalence and incidence differ across countries due to a mix of natural and infrastructural conditions. Contrary to this, the Health Policy and Industrial Policy discourses share a tendency to cram health emergencies and geographical regions in a homogenous mould, thus losing view of the interplay between disease-specific features and local institutional dynamics. It is clear that the characteristics of each disease call for a specific response across the entire health-care board, from the scientific knowledge needed to understand the causes to the capabilities that are necessary to organise the provision of patient services. The stories of China and Brazil are

strong reminders of how local health emergencies can become focussing devices for institutional response as well as of the extent to which context-specific factors can hinder or support the extent of such a response. The broader point is that a coherent and alternative research agenda, one that aspires to inform policy design, would carefully articulate health-care emergencies by type (e.g. common vs rare diseases) and by geographical location.

A second issue concerns the narrow scope of the debate over the pharmaceutical production which is admittedly a subset of the vast health-care universe. The availability of medicines at affordable prices is a necessary but not sufficient condition for tackling rare or common diseases. As the evidence reviewed here shows, effective solutions to health problems ultimately require a sound system for the provision (other than production) of health-care. This in turn calls for accurate consideration of organisational and institutional aspects which are not part of the analytical weaponry deployed by either Health Policy or Industrial Policy. The narrow focus on creation or support of drug production systems does not contemplate issues such as cultural bias or structural inefficiency as co-causes of high incidence and mortality rates of some particular diseases in LDCs. Again, the different performances of South-Africa and Brazil are testimony of the extent to which factors besides the economic sphere play a critical role in the workability of health solutions. A broader perspective would look beyond the viability of those production systems and focus on the build-up of an institutional infrastructure that adequately support the diffusion of health-related information, therein including the culture of prevention, as well as improving the facilities.

It is difficult, and to some extent perilous, to draw broad policy conclusion from scattered evidence about the disparate mix of institutional, economic, social and cultural processes that concur in this complex area. However there is scope to at least reflect as on whether macro-regions featuring similarities in epidemiological patterns due to geographical proximity (e.g. malaria in Sub Saharan Africa; HIV in South-America) might benefit from plans enacted at three levels: (1) At local level, by improving provision and ensuring equitable access; (2) Within each macro-regions by coordinating specifically designed trade patterns; and (3) at international level by seeking to resolve sensitive issues. This division of institutional labour would require the development of different yet complementary capabilities, distributed according to local endowment whereby international authorities based in advanced economies are likely to be better geared (although there conflicts of interest) at monitoring IPR issues while national authorities are in arguably better shape to evaluate and promote local priorities.

Acknowledgements

The author wishes to thank Luigi Orsenigo for valuable guidance, and Maureen Mackintosh for pointing out important issues and bibliographic references. The usual caveat applies. The research leading to the above results has received funding from the European Community's 6th Framework Programme, project number 513396.

Bibliographic references

Arayama, Y. and Miyoshi, K. (2004) Regional Diversity and Sources of Economic Growth in China. The World Economy 27(10): 1583-1607.

Balance, R. Pogany, J., and Forstner, H. (1992) *The Worlds's Pharmaceutical Industries*. England: Edward Elgar Publishing Limited.

Beck, E.J., Mandalia, S., Youle, M., Brettle, R., Fisher, M., Gompels, M. Kinghorn. G. McCarron, B., Pozniak, A., Tang, A., Walsh, J. Williams, I. and Gazzard, B. (2008) "Treatment Outcome and Cost-effectiveness of different HAART regimens in the UK 1996-2002". *International Journal of STD & AIDS* 19: 397-404.

Bennett, S. and McPake, B. and Mills A. (eds.) (1997a) *Private Health Providers in Developing Countries: Serving the Public Interest?* London, Zed Books

Brazilian Ministry of Health (2008) "Targets and Commitments made by the Member-States at the United Nation General Assembly. Special Session on HIV/AIDS". http://data.unaids.org/pub/report/2008/brazil_2008_country_progress_report_en.pdf

Brunetti, A., Weder, B., and KIsunko, G. (1997) *Institutional Obstacles to Doing Business: Region-by-Region Results from a Worldwide Survey of the Private Sector*. World Bank Working Papers: Governance, Corruption, Legal Reform, Working Paper No. 1759. http://wbln0018.worldbank.org/research/workpapers.nsf/.

Calcagnotto, G. (2007) "Consensus-Building on Brazilian HIV/AIDS Policy: National and Global Interfaces in Health Governance", in: Hein, W., Bartsch, S., Kohlmorgen, L. (eds.) *Global Health Governance and the Fight Against HIV/AIDS*. New York: Palgrave Macmillan.

Center for Pharmaceutical Management (2003) "Defining and Measuring Access to Essential Drugs, Vaccines, and Health Commodities". Report of the WHO-MSH.

Chaudhuri, S. (2005) *The WTO and India's Pharmaceuticals Industry: Patent Protection, TRIPS and Developing Countries.* New Delhi: Oxford University Press.

Chauduri, S. (2007) The Gap Between Successful Innovation and Access to its Benefits: Indian Pharmaceuticals. The European Journal of Development Research, Vol.19, No.1, pp.49–65.

Chaudhuri, S (2008) "Indian Generic Companies, Affordability of Drugs and Local Production in Africa with Special Reference to Tanzania". Open University Research Centre on Innovation Knowledge and Development, Working Paper No. 37.

Chaudhuri, S., Goldberg, P., Panle, J. (2003) "The Effects of Extending Intellectual Property Rights Protection to Developing Countries: A Case Study of the Indian Pharmaceutical Market". Columbia University, Department of Economics Discussion Paper Series, No. 0304-08, 2003: http://www.nber.org/papers/w10159

Clark, T. (2004) "The Indian Pharmaceutical Market". *Pharma Marketing News* 3(8): 1-5.

Cohen, J.C. (2000) "Public Policies in the Pharmaceutical Sector: A Case Study of Brazil". World Bank LCSHD Paper Series. http://www.healthpolicy.cn/rdfx/jbywzd/gjjy2/bx/yjwx/201002/P020100227605123706712.pdf

Dhar, B., and Rao, C. (2002) *Transfer of Technology for Successful Integration in the Global Economy: A Case Study of Pharmaceutical Industry in India*. UNCTAD Global Programme for Globalization.

DiMasi J.A., Hansen R.W., Grabowski H.G., Lasagna L. (1995) "Research and development costs for new drugs by therapeutic category: a study of the US pharmaceutical industry". *Pharmacoeconomics* 7: 152-69.

England, R. (2008a) "Are we spending too much on HIV?" *British Medical Journal* 334: 344 (17 February).

England, R. (2008b) "The writing is on the wall for UNAIDS". *British Medical Journal* 336: 1072 (10 May).

Falkingham, J. (2004) "Poverty, out-of-pocket payments and access to health care: evidence from Tajikistan". *Social Science & Medicine* 58(2): 247-258.

Galvão J. (2003) "Community mobilization and access to medicines: the Brazilian non-governmental responses for the HIV/AIDS epidemic". Paper presented at: Harvard Forum on Human Rights in Brazil, Brazil Human Rights Series: Rights to Health; November 3, 2003; Boston, Mass.

Galvão, J. (2005) “Brazil and Access to HIV/AIDS Drugs: A Question of Human Rights and Public Health”. *American Journal of Public Health* 95(7): 1110-1116.

Ganslandt, M., Maskus, K.E. and Wong, E.V. (2001) “The Developing and Distributing Essential Medicines to Poor Countries: the DEFEND Proposal”. The Research Institute of Industrial Economics Working Paper.

Goddard, M., and Smith, P. (2001) “Equity of access to health care services: Theory and evidence from the UK”. *Social Science & Medicine* 53 (9): 1149-1162.

Govindaraj, R., and G. Chellaraj (2002) *The pharmaceutical sector in India: Issues and options*. World Bank, Washington, DC.

Graves, S.B., Langowitz, N., 1993. Innovative productivity and returns to scale in the pharmaceutical industry. Strategic Management Journal 14, 593–605.

Gross, A. (1999) “New Trends in India’s Pharmaceutical Market” Pacific Bridge, Inc. http://www.pacificbridgemedical.com/publications/new_trends_in_India's_pharmaceutical_market_1999.pdf

Hanson, K and Berman P. (1998) ‘Private health care provision in developing countries: a preliminary analysis of levels and composition’ *Health Policy and Planning* 13: 195-211

Henderson, R. and I. Cockburn (1996) Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery. The RAND Journal of Economics 27(1): 32-59.

Henderson, R. and I. Cockburn (2001) Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research Journal of Health Economics 20: 1033–1057.

Ito, B. and Yamagata, T. (2007) “Who Develops Innovations in Medicine for the Poor? Trends in Patent Applications Related to Medicines for HIV/AIDS, Tuberculosis, Malaria, and Neglected Diseases”. The Developing Economies, Institute of Developing Economies, 45(2): 141-171.

James, J.S. (2003) “WTO Accepts Rules Limiting Medicine Exports to Poor Countries” AIDS Treatment News: www.findarticles.com/p/articles/mi_m0HSW/is_394/ai_108394861

Jensen, E.J., 1987. Research expenditures and the discovery of new drugs. Journal of Industrial Economics 36, 83–95.

Kaplan, W.A., R.O. Laing, B. Waning, L. Levison, and S.D. Foster (2003) “Is Local Production of Pharmaceuticals a Way to Improve Pharmaceutical Access in Developing and Transitional Countries? Setting a Research Agenda." World Bank, Washington, DC. http://www1.worldbank.org/hnp/hsd/documents/LOCALPRODUCTION.pdf.

Kontic, S. (2008) “An Analysis of the Generic Pharmaceutical Industries in Brazil and China in the Context of TRIPS and HIV/AIDS”. http://www.law.utoronto.ca/accesstodrugs/documents/TRIPS%20Sasha%20Kontic-trips%20final.doc

KPMG (2006) “The Indian Pharmaceutical Industry: Collaboration for Growth”. Industry Report.http://www.kpmg.com/IN/en/WhatWeDo/Industries/Documents/IM/Indian%20Pharma%20Outlook.pdf

Lashman, K.H. (1986) “Pharmaceuticals in the Third World: An overview”. PHN Technical Note 86-31, World Bank, Washington, DC.

Leonard, D. (ed) (2000) *Africa’s Changing Markets for Health and Veterinary Services.* London, Macmillan.

Lohse, N., Hansen, A.E., Pedersen, G., Kronborg, G., Gerstoft, J. Sørensen, H.T. Væth, M., and Obel, N. (2007) “Survival of Persons with and without HIV Infection in Denmark, 1995-2005”. *Annuals of International Medicine* 146: 87-95.

Londoño, J.L. and Frenk, J. (1997) “Structured pluralism: towards an innovative model for health system reform in Latin America”. *Health Policy* 41: 1-36.

Loureiro, S., Simões, B., Aragão, E., Mota F., Moura, H., and L. Damasceno (2007) “Diffusion of Medical Technology and Equity in Health in Brazil: an Exploratory Analysis”.The European Journal of Development Research 19 (1): 66–80.

Mackintosh, M. (2006) “Commercialisation, inequality and the limits to transition in health care: a Polanyian framework for policy analysis”. *Journal of International Development* 18: 393–406.

Mackintosh, M. (2007) “Planning and market regulation: strengths, weaknesses and interactions in the provision of less inequitable and better quality health care”. IKD Working Paper No. 20.

Mackintosh, M. and Koivusalo, M. (eds.) (2005) *Commercialization of Health Care: Global and Local Dynamics and Policy Responses* Basingstoke, Palgrave.

Mackintosh, M. and Tibandebage, P. (2007) “Competitive and organisational constraints on innovation, investment and quality of care in a liberalised low income health system: evidence from Tanzania”. *European Journal of Development Research* 19(1): 81-99.

Mackintosh, M., Chataway, J. and Wuyts, M. (2007) “Promoting Innovation, Productivity and Industrial Growth and Reducing Poverty: Bridging the Policy Gap”. *The European Journal of Development Research* 19(1): 1–12.

McPake, B. (1993) “User charges for health services in developing countries: A review of the economic literature”. *Social Science & Medicine* 36 (11): 1397-1405.

Marketavenue (2008) "2007-2008 Annual Report on the Development of China's Pharmaceutical Industry". Industry Report.

http://www.marketavenue.cn/Reports_Sample/MAHY211108003.PDF

Medecins Sans Frontieres (2006) “Too Little For Too Few: Challenges for Effective and Accessible Antiretroviral Therapy”. Briefing Document, August.

Nitta, I., (2005) “Proposal for a green patent system: implications for sustainable development and climate change”. *Sustainable Development Law and Policy*, 5. American University, Washington College of Law, Washington, D.C., pp. 61-65.

Nóbrega1, O.T., Marques, A.R., Gomes de Araújo, A.C., de Oliveira Karnikowski, M.G., de Oliveira Silva Naves, J., Dee Silver, L. (2007) “Retail prices of essential drugs in Brazil: an international comparison”. *Pan American Journal of Public Health* 22(2): 118-123.

Organization for Economic Cooperation and Development (1992) “The reform of health care. A comparative analysis of seven OECD countries”. *Health Policy Studies No. 2*. Paris.

Orsi, F., d’Almeida, C., Hasenclever, L., and Coriat, B. (2006) “Trips-Post 2005 in Southern Countries: the Sustainability of Public Health Policies at Stake”. Conference Paper. http://www.dime-eu.org/files/active/0/Orsi%20et%20al.pdf

Pannarunothai, S., and Mills, A. (1997) “The poor pay more: Health-related inequality in Thailand”. *Social Science & Medicine* 44 (12): 1781-1790.

Price, M. (1997) “The consequences of health service privatisation for equality and equity in health care in South Africa”. *Social Science & Medicine* 27(7): 703-716.

Scherer, F.M. (2004) “The Pharmaceutical Industry. Prices and Progress”. *New England Journal of Medicine* 351: 927-932.

Schneider, H., and Gilson, L. (1999) *The Impact of Free Maternal Health Care in South Africa. Safe Motherhood Initiatives: Critical Issues*. Reproductive Health Matters - Blackwell Science.

Söderlund, N. Mendoza-Arana P.and Goudge J. (eds.) (2003) *The New Public Private Mix in Health: Exploring The Changing Landscape* Alliance for Health Policy andSystems Research, Geneva.

Suárez-Berenguela, R M. (2001) “Health system inequalities and inequities in Latin America and the Caribbean”. In: Pan American Health Organization. *Investment in Health: Social and Economic Returns* Scientific and Technical Publication No.582, PAHO, Washington DC.

Tanner, J.A. (2006) “WTO TRIPS and its effect on the supply and development of medicines in China”. Hong Kong Medical Association. http://www.hkmj.org/article_pdfs/hkm0602p84.pdf

The Economist (2002) “Cheap Cures”. August 15th.

Tybout, J. (1998) *Manufacturing Firms in Developing Countries How Well Do They Do, and Why?* World Bank, Washington, D.C., Policy Research Working Paper No. 1965

UNAIDS (2008) Report on the Global AIDS epidemic. United Nations Programme. http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp

UNESCAP (United Nations Economic and Social Commission for Asia and the Pacific) (2007) "Development of Health Systems in the Context of Enhancing Economic Growth towards Achieving the Millennium Development Goals in Asia and the Pacific". Report. http://www.unescap.org/esid/hds/pubs/2449/2449.pdf

UNIDO (1980) *Appropriate industrial technology for drugs and pharmaceuticals*. United Nations Industrial Development Organization. New York, NY, Monographs on Appropriate Industrial Technology.

United States Global AIDS Coordinator (2005) "Engendering bold Leadership: The President's Emergency Plan for AIDS Relief". First Annual Report to Congress. Washington, DC: United States Global AIDS Coordinator.

United Nations (2008) "Strengthening the Global Partnership for Development in a Time of Crisis". Millennium Development Goal. MDG Gap Task Force Report 2009 http://www.un.org/esa/policy/mdggap/mdg8report_engw.pdf

Vernon, J.A. (2005) "Examining the Link between Price Regulation and Pharmaceutical R&D Investment". *Health Economics* 14(1): 1–16.

Walensky, R.P., Paltiel, A.D., Losina, E., Mercincavage, L.M., Schackman, B.R., Sax, P.E., Weinstein M.C. and Freedberg K.A. (2006) "The survival benefits of AIDS treatment in the United States". *Journal of Infectious Diseases* 194: 11-19.

Watts, H. (2004) "Bill C-9: The Complaints of the Generic Drug Manufacturers and the Perspective of Developing Countries": http://www.dww.com/articles/bill_c-9.htm

Wogart, J.P., Calcagnotto, G., Hein, W. and von Soest, C. (2008) "AIDS, Access to Medicines and the Different Roles of the Brazilian and South African Government in Global Health Governance". GIGA Working Paper No. 86. http://ideas.repec.org/p/gig/wpaper/86.html

World Health Organization (WHO) (2004) "Policy Perspectives on Medicines — Equitable access to essential medicines: a framework for collective action". http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.4.pdf

World Health Organization (WHO) (2004a) "World Health Report". http://www.who.int/whr/2004/en/

World Health Organization (WHO) (2004b) "The World Medicines Situation". http://apps.who.int/medicinedocs/es/d/Js6160e/

World Health Organization (WHO) (2005) "Local Production of Essential Medicines, Including Antiretrovirals: Issues, Challenges and Perspectives in the African Region". Report of the Regional Committee for Africa.

World Health Organization (WHO) (2005) "Summary Country Profile for HIV/AIDS Treatment Scale Up: India". http://www.who.int/hiv/HIVCP_IND.pdf

World Health Organization (WHO) (2008) "Measuring medicine prices, availability, affordability and price components". http://www.haiweb.org/medicineprices/manual/documents.html

Yuanjia, H., Ung, C., Ying, B. and Yitao, W. (2007) "The Chinese pharmaceutical market: Dynamics and a proposed investment strategy". *Journal of Medical Marketing* 7: 18–24.