Producing medicines for chronic disease in less developed countries

Lessons from the global response to HIV/AIDS

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International Policy Network

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International Policy Network (IPN) is a non-governmental, educational and non-partisan organization whose mission is to encourage better public understanding of the role of the institutions of the free society in social and economic development. IPN achieves this goal by interacting with thinkers and commentators in many countries and across many disciplines.

IPN conducts, commissions and disseminates research, directly and indirectly with partner organizations, in the realms of health, environment, trade and development. IPN hopes that as a result of its programs, individuals will be better able to achieve their aspirations, regardless of race, color, creed, nationality or human condition.

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Executive summary

Chronic conditions such as diabetes, cancers and heart disease are gradually displacing infectious diseases as the greatest health problem in lower-income countries. The long-term nature of these diseases, combined with ageing populations, will pose enormous problems for overstretched state health systems.

In responding to this challenge, there is some indication that governments may copy some of the policies which have informed the response to HIV/AIDS, including taking steps to reduce the cost of producing drugs. This paper is an attempt to see what lessons for the production of medicines for chronic disease can be drawn from the international response to HIV/AIDS.

To date, the international community has centred its response to HIV on increasing the availability and uptake of generic ARVs, particularly by encouraging manufacturers in lower-income countries. This has taken place through a mixture of voluntary licenses, compulsory licenses and unlicensed manufacture of copies of patented drugs by companies in India and certain African countries. Meanwhile, innovator companies have pursued "tiered pricing" strategies, which involve selling their patented ARVs at a discounted price in lower-income countries.

In principle, generic medicines make valid alternatives to innovator drugs providing they are bioequivalent, safe and efficacious. Many of the major government-backed procurement programmes and their advisors in the World Health Organization, however, have judged that the need to rapidly expand ARV coverage outweighs the need to rigorously test and certify all generics. Also, many of the generic ARVs being manufactured in India and certain African countries have not received any form of quality approval.

As a result, there is a possibility that many of the ARVs in circulation in sub Saharan Africa do not meet the strict bioequivalence requirements necessary to minimise drug resistance and clinical failure. An examination of the literature relating to ARV quality in lower and middle-income countries suggests wide variations in the quality of drugs available, and high levels of drug resistance in some areas. The few studies that exist for Africa also raise questions about the quality of the drug supply.

As chronic diseases become more prevalent in lower-income countries, it is vital that public authorities do not repeat these mistakes, and sacrifice the quality of medicines in the sometimes ideological and clinically irrational promotion of generic medicines. As such, the differential pricing schemes pursued by some manufacturers seems a viable way of improving access while maintaining quality, as do properly administered voluntary licenses for generic production.

Finally, donors should not be distracted by debates on intellectual property from the major barriers to access to medicines, which are insufficient health infrastructure and trained personnel.

Producing medicines for chronic disease in less developed countries

Introduction

Chronic diseases such as cancer, diabetes and cardiovascular conditions are rapidly becoming the biggest health problem facing low and middle income countries. Improving living conditions and longer life-expectancies mean that chronic diseases already account for 60 per cent of all deaths globally, with 80 per cent of these occurring in low and middle income countries – double the number of deaths caused by infectious diseases such as HIV/AIDS and malaria.

As chronic diseases displace infectious diseases as the biggest health problem in poorer countries, health ministries are facing enormous economic challenges as more people require protracted and costly treatment and disease management, often for the duration of patient's life. At the same time, new medical technology is becoming increasingly expensive. This combination of factors is creating a major problem to cash-strapped health ministries in lower income countries.

This situation is not unprecedented, however. The HIV/AIDS pandemic has affected large numbers of the general population in parts of sub-Saharan Africa and, like many chronic diseases, HIV is a long-term affliction that requires complex diagnostics and treatment, often involving hospitalisation and lengthy inpatient care. As is also the case with modern oncology and cardiovascular drugs, antiretroviral medicines (ARVs) are evolving at a rapid rate, but are becoming increasingly costly to develop. Providing universal access to ARVs in the worst affected regions is proving to be a major financial, logistical and political challenge. All this provides a foretaste of what to expect as chronic diseases tighten their grip on the developing world. In formulating policy responses to chronic disease, there may therefore be interesting lessons to learn from the international community's response to the AIDS pandemic.

One of the defining features of this response has been the promotion and mass roll-out of generic medicines by international agencies such as WHO and the Global Fund for Aids, Tuberculosis and Malaria. This has occurred due to a perception that global intellectual property rules have made modern ARVs prohibitively expensive to poor countries, and that governments and aid agencies should therefore intervene to override property rights and promote generic medicines.

Since 2001, steps have been taken to dilute the global intellectual property rules administered by the World Trade Organization (the TRIPs agreement) and promote the use of generic medicines. Meanwhile, global aid and health agencies have pushed generic ARVs to the forefront of their AIDS treatment plans, and these drugs now form the backbone of drugs on the World Health Organization's Pre-Qualification list. Likewise, the world's largest HIV funding agency, the Global Fund, also prefers that grantees procure generics with its funds. In many cases, rights-holders have willingly allowed generics companies to produce their products via "voluntary licenses"; in other cases governments have issued or threatened "compulsory licenses", which forcibly abrogate intellectual property rights so that generic competition can start before patent expiry. Many generics companies manufacture copy ARVs without permission from the license holder.

It is very possible that international agencies will also attempt to place generic medicines at the heart of the global response to chronic diseases, given that the numbers of patients involved are so much higher. Thailand's 2007 decision to issue compulsory licenses for a number of chronic disease therapies is perhaps an

augury of how governments may respond to this epidemiological shift.

Methodology

This working paper attempts to analyse and distil lessons from the production of ARVs for the developing world, in order to inform future policy responses to chronic disease. This is the second part of a three phase programme of work. The first phase examined funding for HIV/AIDS, while the third will examine delivery of treatment. For this second study, IPN conducted a review of relevant literature to provide a snapshot of current thinking and evidence on the production of ARVs, including:

- Price regulation
- Voluntary licenses
- Compulsory licenses
- Differential pricing
- The quality of generic ARVs
- Barriers to access to medicines

A search was conducted in major social science databases on phrases related to the topics above. This series of papers will hopefully flag up mistakes and successes in the response to HIV/AIDS, in order to inform better the future response to chronic disease.

Different policies for increasing access to ARVs

The prioritisation of generic medicines by international aid and development agencies is informed by a simple premise: the temporary marketing monopolies conferred by drug patents raise the price of medicines to a level that is unaffordable by poorer patients in lower and middle income countries. On this basis it has been widely argued that there is a compelling welfare case for overriding patents on ARVs to improve access in poorer countries.

The notion that patents are responsible for driving up prices in poor countries is common in the literature. Cohen et al. (2005); DFID (2006); Saggi (2007); Ford et al. (2007) all claim that the temporary marketing monopolies created by patents unnecessarily raise prices, and therefore represent a barrier to access. Nevertheless, the purpose of a patent is to raise prices temporarily for some consumers, in order to recoup R&D costs.

Policy responses to the high price of patented medicines fall in four broad areas: price regulation, market segmentation, voluntary and compulsory licenses.

Price regulation

Government-imposed price controls are a widely used method of attempting to increase access to medicines by moderating drug prices. However, standard economic theory suggests that price controls will lead to shortages, especially of higher quality branded medicines, as suppliers of such medicines become unable to recoup sufficient revenues to cover their costs and make a profit. Research by Danzon et al (2003) appears to bear this out, showing that manufacturers delay the launch of innovative drugs into smaller, price-controlled markets. This is especially relevant for the launch of new ARVs, which are both expensive to produce and are often most pressingly required in smaller markets.

For generic medicines, there have been many media reports in India on the relationship between the Drug Price Control Order and the emergence of harmful 'irrational' fixed-dosed combination drugs.[1] These are combinations of drugs that have no clinical rationale and have not been properly tested, but avoid the price controls. But this area has not yet been subject to academic scrutiny, despite the potential massive harm that is being done to Indian patients. Although these concerns have been raised mainly in relation to other common medicines, many fixed-dose combination ARV drugs have not been rigorously tested to see if they work on the body in exactly the same way as the originator drug (so-called "bioequivalence"), and may be having similarly unquantified effects on patients.

Voluntary licenses

Another method for improving access to ARVs in poor countries is the use of voluntary licenses, which allow generic companies to manufacture the medicines in

return for a small royalty payable to the innovator. These licenses usually come with certain restrictions, for example the manufacturer may only export the ARVs to those countries permitted by the rights holder. This would ensure that profits are not eroded by exports to high income countries. This strategy was suggested by Friedman et al, (2003) and there are now many examples. In South Africa ARV rights-holders routinely out-license their ARVs to local generic manufacturers, and the practice is becoming more widespread in India which has significant generic manufacturing capacity. Licenses have also been issued to smaller African manufacturers.

Voluntary licenses are particularly attractive in that the rights-holder has a strong reputational incentive to ensure the licensee maintains its own standards of manufacturing and testing. According to Chien (2007), the majority of 2nd-line ARVs in use in sub-Saharan Africa are made by innovator companies, often in collaboration with local generics manufacturers via a voluntary license.

Although many voluntary licenses for manufacturing generic ARVs have been granted, they do not always result in drugs being manufactured and shipped to patients. Initial desk research conducted for this paper, using publically available internet sources, shows numerous other examples of voluntary licenses granted but not actually resulting in manufacture. For example, Gilead has granted numerous voluntary licenses for its Tenofovir to Indian generics manufacturers. Despite being granted these licenses, there is no evidence that Strides Pharmaceuticals, Shasun, Medchem or Alkem are manufacturing Tenofovir. Similarly, GSK has issued numerous voluntary licenses for Combivir to, amongst others, Biotech Labs, Feze and Sonke and Thembalani. None of these companies appear to be manufacturing the product. It could be that the costs of scaling up production, marketing and distributing a product are too high for many generic manufacturers to turn a profit.

Differential pricing

A perhaps more sustainable way of increasing the availability of quality ARVs is for innovator companies to sell their medicines at marginal cost in low-income markets, and higher prices in richer markets. In theory, so-called "differential pricing" achieves the twin aim of increasing access for the poor while allowing the innovator to recoup from richer countries the development costs plus a profit.

The ability to sell a product at different prices to different consumers enables companies with a degree of market exclusivity to ensure that their products reach as many consumers as possible while still maximising revenue. If a company is able to segment markets precisely according to each individual's willingness to pay, then every consumer willing to pay at least the marginal cost of production for the product should be able to purchase that product. This would both maximise the number of people who benefit from the product and would also maximise revenue to the company, which in principle would enable more to be spent on R&D. Perfect market segmentation means that the number of consumers served and the price paid by the poorest consumer are the same as that which would exist in a perfectly competitive market.

In practice, market segmentation is costly to enact -primarily because of the need to prevent low price purchasers reselling to higher-price purchasers – and the larger the number of market segments, the greater the cost. So, firms weigh up the benefits of adding a segment with the cost of enforcing the additional segmentation. Typically, firms segment markets first by overall market (which is usually a country or trading bloc) and then by sub-categories, such as: individuals (which may be further segmented by age and income), businesses, charities, and governmental bodies. So, for example, drug prices in South Africa are far lower than in Europe and the US. This means that market segmentation can be particularly beneficial for patients in poorer countries.

Where the overall market for a product is very large and where that market is readily segmented (i.e. the cost of enforcing the segmentation is low compared to the benefits), companies may set the lowest price close to the marginal cost of production. In the context of a disease such as HIV/AIDS, where the total market for medicines is massive and the humanitarian case for widespread distribution is great, companies may even choose to sell below marginal costs in some markets, provided that sufficient profit is recouped in others.

However, this strategy depends on the ability of manufacturers to maintain the separation of different market segments, which could be undermined by richer countries re-importing drugs earmarked for poorer markets (Danson & Towse, 2003; Barton, 2004) or by issuing compulsory licenses. Effective market segmentation therefore depends on respect for intellectual property, including trademarks. R&D companies have long pursued this strategy by selling ARVs into African markets at prices well below those of the developed world. In 2008 drug manufacturer GSK announced plans for tiered pricing across its entire product range. In 2009, its sales in emerging markets rose by 20%,[2] suggesting greater sales volumes – and, by implication, greater numbers of patients getting access to their products.

Compulsory licenses

Despite the potential for increasing the supply of quality medicines presented by both differential pricing and voluntary licensing, many commentators advocate as a preferred solution the outright abrogation of intellectual property rights via compulsory licenses. Bradford, Kerry & Lee (2007); Satyanarana (2007); Mendis et al. (2007) and Cohen, Kohler & Lipkus (2008) all claim that patents act as a barrier to access and call for the use of "TRIPS flexibilities" (i.e. compulsory licensing) and local manufacture in order to reduce drug prices. In practice, few compulsory licenses for ARVs have actually been issued, with the exception of those of Thailand in 2006 and 2007, Brazil in 2007 and Ecuador in April 2010. Governments' reticence to use this policy measure may be partly to do with the risk to foreign direct investment that would result from compulsory licenses (Bird & Cahoynn, 2008).

One high profile instance of compulsory licensing has been largely abandoned. The Canadian Access to Medicine Regime, enacted in 2004, hoped to take advantage of TRIPs flexibilities in order to export low-cost copies of patented medicines. However, the law resulted in only one shipment of compulsory licensed medicines from Canada to Rwanda, with the only manufacturer involved ruling itself out of any further participation.[3]

Quality of medicines

What would happen to quality if the governments of low-income countries abrogate pharmaceutical patents wholesale? It is highly likely that innovators will cease supplying that country, taking with them their manufacturing and importation supply chains. This happened to a considerable degree in India from 1972, when the government significantly diluted intellectual property rights. In order to counter this, opponents of pharmaceutical patents call on lower-income countries to break patents, bolster local production and increase supplies of low-cost generic medicines manufactured by foreign countries like India (Shadlen, 2007). Local production of generic medicines is supported by the African Union, the G8, the Global Fund, the German development agency GTZ, and United Nations Industrial Development Organization.[4]

In principle, generic ARVs should make a valid alternative to innovator drugs; to do so, they must be safe, and bioequivalent to the original product. Generic ARVs that do not meet these criteria have the potential to do enormous harm. For instance, generic drugs that are not bioequivalent may be less effective and accelerate the emergence of drug-resistant strains of HIV. This is a particular risk if the drug contains sub-therapeutic levels of active ingredients. Non-bioequivalent generics also increase the risk of adverse side-effects and clinical failure (Bartlett & Muro, 2007). Uncontrolled ARV resistance has an enormous potential macroeconomic burden, as more patients will require a lifetime of costly second line treatment, which requires greater monitoring, follow-up and hospitalisation (Adelman, et al, 2005).

Most generic drugs found in Western markets meet these high standards. A review and meta-analysis of 47 studies on generic cardiovascular drugs (Kesselheim et al, 2008)found that nearly all the generic drugs studied (mainly in the US) were similar in clinical outcomes to the originator. All the drugs had been certified as bioequivalent by the US regulator, the Food and Drug Administration (FDA). Patients in developed markets can be reasonably certain, therefore, that their generic medicines are both safe and efficacious.

However, the picture is not so clear for lower-income

countries. Many generic ARVs used in Africa are distributed on the basis that they are expected to behave like the originator product, even though they frequently have not undergone rigorous bioequivalence and clinical testing – this is particularly true of the Fixed Dose Combination drugs promoted by the World Health Organization's Prequalification programme, and financed by the Global Fund and UNITAID. These organisations appear to have decided that the need to rapidly scale-up treatment in lower-income countries, which does not allow for the time and expense of testing every new generic drug, outweighs the risks of delivering substandard medicines to patients.

The WHO's Prequalification programme has become especially influential in determining which kinds of drugs are used in the treatment of HIV in low-income countries that do not have sufficient regulatory capacity to determine the safety and efficacy of generic drugs. The programme makes its judgments on candidate medicines by evaluating dossiers submitted by manufacturers and factory visits. While the Prequalification programme claims to maintain standards as high as those of a stringent regulatory authority, WHO has admitted that in some cases dossier evaluations are substituted for site visits. It also issues a disclaimer stating that it cannot guarantee the safety of any of the drugs it recommends in treating HIV.[5]

The Prequalification programme's claims that it maintains the highest standards on drug quality were somewhat undermined in 2004, when 18 ARVs where "de-listed" for not properly demonstrating bioequivalence (although some drugs were subsequently reinstated). In addition, many of the fixed-dose combination drugs recommended by WHO have never undergone proper clinical evaluation, and are therefore technically "experimental" drugs.

Additionally, there are many commonly used generic ARVs made under voluntary license that have not received any form of quality approval from either WHO or a stringent regulatory authority. For example, one Kenyan pharmaceutical company has licenses from two R&D companies to manufacture generic copies of patented ARVs, although none of its products appear on either the WHO's Prequalification list or the FDA's list of approved or tentatively approved generic ARVs. It is not clear how many of these drugs of indeterminate quality are circulating in Africa.

ARV quality in low and middle income countries

Although drug resistance can be accelerated by a number of factors, including poor prescribing and improper adherence to regimens, drug quality is also extremely important. Maintaining the quality of first line drugs should be an overriding public health concern, in order to avoid the acceleration of drug resistance, which already at stood at around 5.5% in Africa in 2007 (Shekelle et al, 2007) -- a relatively high rate considering mass treatment has only been available in this region since the early to mid 2000s.

Despite the massive potential public health and macroeconomic implications of inadequate drug quality, there are few independent studies of bioequivalence, clinical outcomes of generic medicines, or rates of drug resistance amongst HIV patients in lower and middle income countries. Many of the bioequivalence studies available are limited by their use of small samples, and are not designed to assess clinical outcomes. Nevertheless, some of the studies available give some indication as to the potential quality of the ARV supply and associated outcomes.

For middle-income countries, the quality of generic ARVs varies from country to country. Narang (2004) studied the uptake of Cipla-manufactured Stavudine in healthy South African volunteers, and concluded the drugs were bioequivalent to the originator. Huang et al (2009) found a "reassuringly low" prevalence of pre-therapy drug resistance in the patients studied in the Free State, South Africa, many of whom had been taking generic nevirapine. South Africa is notable for adhering to its own treatment protocol, rather than following that recommended by WHO.[6] Brazil's universal AIDS programme is based on generic medicines either manufactured locally and approved by the regulator ANVISA, or imported from overseas and recommended by the World Health Organization (do Lago & Costa, 2009). Few studies are available on the quality of these medicines, but Dos Reis Serra et al (2008) present data demonstrating that locally manufactured Zidovudine is

bioequivalent to its reference product. However, Ferreira et al (2010) discovered high rates of primary ARV resistance amongst a cohort of treatment-naïve HIV+ Brazilian children, with mutations detected in four out of the 41 (9.8%) children in the sample. Based on this finding, the study recommends that testing for drug resistance should be introduced for all newly diagnosed children. The study also cites literature showing resistance rates to be between 3.6% and 19% in Brazil. Brazil, a middle income country, appears to have a problem with generic quality and other factors that affect drug resistance.

India is a major manufacturer of generic ARVs, and its medicines form the basis of the WHO's prequalification programme, and by extension the supply for many African countries. Monif et al (2007) determined that the Indian manufactured stavudine studied was bioequivalent and could be used interchangeably in medical practice. However, a bioavailability study of Indian-manufactured generic versions of Ritonavir and Lopinavir/Ritonavir in a dog model found broad variability in relative bioavailability. Although dog models are not strictly comparable to human beings, the authors suggest that some of these generics copies may not be as efficacious as the originator product (Garren et al, 2009). Some of these products were added to the WHO Prequalification list in 2009.

Meanwhile, Gupta et al (2010) found very high rates of drug resistance in private clinics in Mumbai, and conclude that this underlines the need for greater viral load and resistance monitoring, and use of optimal ARV combinations. The study did not disclose whether those patients with resistance had been receiving generic or brand name medicines.

Thai studies also apparently show locally manufactured drugs to be interchangeable with originator products. A study by Chompootaweep et al (2006) showed locally-manufactured Antivir to be interchangeable with the reference drug. However, an investigation into ARV drug resistance among treatment naïve Thais infected between 2003 and 2006 showed that annual drug resistance increased from 0 to 5.2%, a rise described as 'alarming' by the authors (Apisarnthanarak et al, 2008). This timeframe coincides with the establishment of the National Access to ARV Programme, based on the use of the locally manufactured triple combination copy drug, GPO-vir.

One of the ingredients of GPO-vir is stavudine, which WHO removed from its Prequalification list in November 2009 because of "long-term, irreversible" side-effects in HIV patients including wasting and a nerve disorder.[7] GPO-vir has been found to cause lipodistrophy and hyperlactatemia (Tin et al, 2005). All these side-effects make it difficult for patients to continue physical work, such as agriculture, yet the drug remains widely in use in Africa, despite being de-listed by the WHO.

There are few studies available on the quality of ARVs in Africa, but some studies raise concerns about the quality of stavudine in circulation in Africa. Hosseinipour et al (2007) showed Triomune (a Fixed Dose Combination of which stavudine is a component) not to be strictly bioequivalent to its innovator cousins in a study in Malawi. Byakika-Tusiime et al (2008) showed that Indian-manufactured Triomune was also not strictly bioequivalent in their research in a cohort of HIV-infected adult Ugandans. A study conducted by Gottlieb et al (2009) found multi-class drug resistance to be common amongst a cohort of patients in Senegal being treated with nucleoside reverse-transcriptase inhibitor and Indinavir-based regimens.

Other barriers to access to high quality medicines

Despite the fact that policymakers have gone to great lengths to increase the supply of generic ARVs in sub-Saharan Africa, there is no clear evidence that patents reduce access to these drugs in the first place. In 2001, Attaran and Gillespie White showed that few ARVs are on patent anywhere in Africa, while Attaran (2004) showed that fewer than two percent of essential medicines are not on patent in most low and middle-income countries. This is probably why Indian companies such as Cipla, Ranbaxy, Hetero, Matrix Laboratories and Strides Pharmaceuticals continue to manufacture and sell into Africa an extensive range of generic ARVs without permission or licenses from the patent holder. To date, none of these companies have faced legal challenges, even though the medicines they are copying are still on patent in the US, the EU and elsewhere.

So if patents are a peripheral part of the access picture, what are the actual barriers to access to high quality medicines? A lack of qualified medical personnel is one obvious factor: Kober and Van Damme (2004), for example, point out that scaling up ARV treatment will not be possible without a substantial increase in numbers of healthcare workers. A lack of infrastructure such as roads and health clinics also hinders access to medicines (Brenneman, 2002; Datar, 2007). This weak infrastructure is responsible for inaccurate demand forecasting, which undermines the ability of producers to supply markets in a timely and competitive manner; the inability of local procurement offices to commit to long-term orders for drugs; and inadequate local technical capacity for logistics, inventory management and transportation (Lalvani et al, 2010).

Related to this, delays during the import process can undermine the quality of pharmaceuticals. Poor storage was identified as a significant cause of degradation both in general (Okeke and Lamikanra, 1995; Nazerali et al. 1996) and specifically during transit (Hogerzeil et al., 1992); a problem often made worse by delays at customs (*ibid.*). Wondemagegnehu (1999) also found that degradation was a significant problem in Myanmar and Vietnam, while many good quality drugs were mislabelled. These issues will be discussed in more detail in the final instalment of this series of working papers.

Discussion

From the foregoing several clear funding lessons emerge for the production of medicines to improve the treatment of chronic diseases in lower-income countries.

1. Despite a major political campaign to promote them, compulsory licenses have not been used except for a few isolated cases. Governments of middle-income countries -- not unreasonably -- fear that their use would jeopardise foreign direct investment and thereby act as a brake on wider economic development. Where they have been used, such as Canada's Access to Medicines Regime, they have failed, apparently because of the cost and complexity of implementing the licenses. Governments of lower-income countries would therefore be ill-advised to rely on compulsory licenses as a mechanism for controlling the treatment of chronic diseases.

2. Voluntary licenses, in which innovator companies grant a license to generics companies in lower-income countries to manufacture copies of their product, have been more widely taken up. Because the innovator directly transfers technology in these instances, and has a reputational stake in the quality of the manufacturing process, these licenses have resulted in a high degree of quality assurance for the resulting generic ARVs. However, the fact that many other granted licenses have not resulted in medicines actually being manufactured suggests that the costs of upgrading manufacturing facilities and developing supply chains might outweigh the benefits for many smaller generic manufacturers.

   Demand is likely to be far higher for chronic disease medications, so volumes will be far greater. This could lead to greater potential for mutual profit in developing countries, making these voluntary licenses more viable. Voluntary licenses may become a more realistic business proposition, which would allow cheap, high quality medicines to be widely distributed in lower-income countries.

3. While differential pricing has been criticised for being too sporadic and arbitrary to make a genuine difference to access in lower-income countries, there are indications this may be changing. Since it enacted its policy of differential pricing for all therapeutic classes, GSK's sales volumes have increased significantly in emerging markets. This strategy also has the advantage that the innovator has a strong reputational incentive to maintain the quality of the medicines it sells into such markets, which may counter some of the regulatory and legal shortcomings which have allowed potentially substandard drugs to penetrate the supply chain.

   Differential pricing, however, depends on companies being able to segment the market. This means that governments of middle-income and rich countries must respect intellectual property and resist the urge to re-import from markets where drug prices are cheaper, or issue compulsory licenses.

4. A defining feature of the response to HIV/AIDS has been the promotion and implementation of a mass treatment campaign based on generic Fixed Dose Combination drugs, many of which have not undergone proper clinical evaluation by a stringent regulatory agency (despite featuring on the WHO's Prequalification list). Furthermore, many are manufactured without the consent of the license holder, and are marketed without the seal of approval of regulators. Although scattered studies show some generic ARVs are well tolerated amongst healthy patients, there are also studies that raise concerns about the quality of some of the ARVs in circulation in lower-income countries.

   Given that so many patients in lower-income countries will require medications for chronic disease, it is essential the medicine supply is of the highest quality. If substandard medicines are widely distributed, the increase in clinical failure and death will have an enormous human and economic cost. It would be foolhardy for governments to rely on un-tested generic copies in their chronic disease treatment programmes.

5. The parlous state of health infrastructure in many lower-income countries is the biggest barrier to access to quality ARVs, and this is also likely to be the case for chronic disease therapies, many of which require close monitoring, follow-up and hospitalisation to be effective. In order to make the best use of scarce resources, scaling up health infrastructure should therefore be prioritised over tax-funded subsidies to local pharmaceutical companies.

Annotated bibliography

1. Attaran, A. 2004. "How Do Patents And Economic Policies Affect Access To Essential Medicines In Developing Countries?" ***Health Affairs*** **23(3): 155–166.**

This paper studies the relationship between patents and access to essential medicines. It found that in sixty-five low- and middle-income countries, where four billion people live, patenting is rare for the 319 products on the World Health Organization's Model List of Essential Medicines. At the time this work was undertaken only seventeen essential medicines were patentable, although usually not actually patented. The overall patent incidence was only 1.4 percent, and this was concentrated in the larger markets. According to the author, these data show that patents are an infrequent determinant of access to essential medicines, while the economic data leave no doubt that the failure of large numbers of potential patients to receive beneficial therapies is largely a consequence of other policy variables.

The study has been criticized on the grounds that a major criterion for a medicine making it onto the WHO EML is that it be cheap. This necessarily precludes most drugs that are still on patent, so the EML has a heavy generic bias. It may therefore be worth conducting a study to determine the patent incidence of all on-patent medicines in low and middle-income countries – or some subset of all on-patent medicines determined by disease incidence.

2. Barton, John H. 2004. "TRIPS and the Global Pharmaceutical Market," ***Health Affairs*** **23(3): 146–154.**

This 2004 paper reviews the international controversy over patents and access to drugs in developing countries and explores the implications of the 1995 Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, the 2001 Doha Declaration, and the 2003 agreement preceding the Cancun meeting. It notes that one of the outcomes of these controversies was the emergence of differential pricing for patented therapies, allowing producers to vary pricing according to a market's ability to pay. However, this depends on preventing the re-importation of drugs form cheaper markets back to markets such as the United States, which provide the profits necessary to underpin innovation. This will bring political problems for pharmaceutical companies in the US, because patients will not tolerate expensive medications being available more cheaply in other countries.

3. Bird, R; Cahoynn, D. 2008. "The Impact of Compulsory Licensing on Foreign Direct Investment: A Collective Bargaining Approach," ***American Business Law Journal*** **45(2): 283–330.**

Amongst the arguments against compulsory licences for medicines is that fact that it send out a hostile message to potential foreign investors, particularly those with products whose profitability depend on the respect of patents, trademarks and copyright. The consequent loss of Foreign Direct Investment to the economy could far outweigh the narrow, short-term benefits of issuing a compulsory license. The authors argue this risk can be mitigated if developing countries act collectively in issuing compulsory licenses, in order to "equalise the bargaining power of MNCs". There is no discussion of the potential impact of strategies on future pharmaceutical innovation.

4. Byakika-Tusiime, J ***et al.*** **2008. "Steady State Bioequivalence of Generic and Innovator Formulations of Stavudine, Lamivudine, and Nevirapine in HIV-Infected Ugandan Adults,"** ***PLoS ONE*** **3(12): e3981.**

Generic medicines form the backbone of the global response to HIV/AIDS, and constitute the majority of drugs on the WHO's Pre-Qualification list. The Global Fund and UNITAID also mainly procure generic ARVs. With so many patients relying on these medicines, it is vital they are exactly bioequivalent to the originator drugs, to minimise the risk of clinical failure and emerging drug resistance. Bearing this in mind, this study looks at the bioequivalence of a common triple dose combination ARV being taken by a sample of 18 HIV-infected Ugandan adults. The generic formulation studied did not meet the strict bioequivalence requirement set down by the FDA, although the researchers claim it would produce a "similar therapeutic response". The researchers conclude that local drug regulatory authorities need to test all imported ARVs to ensure they reach the required quality standards.

The researchers do reveal the manufacturer or origin of the studied ARVs. It is not clear whether they are certified generics, tested for bioequivalence by a regulatory authority (as is the case with all generics approved for use in the EU/USA), or simple copies. The drug in question, Triomordine, is not available for sale within the USA. Seeing as the WHO's pre-qualification programme and the Global Fund's "Option C" promotes the use of untested copies, it is likely that these Ugandan patients have been taking what is essentially an experimental copy drug. This is confirmed by the study's conclusions with regards to the inexact bioequivalence.

5. Chien, Colleen V. 2007. "HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare?" ***PLoS ONE*** **2(3): e278.**

This study examines the contours of the ARV market in Africa following the promotion of generic medicines by the WHO and other authorities. It discovers that most 1st line therapies in use in Africa are copy versions mainly supplied by generic manufacturers at a lower cost than branded equivalents. 2nd line therapies are mainly supplied by branded companies, with generic competitors generally unable to undercut them on price. One third of the market studied consists of "Fixed-dose combination" drugs, most of which are produced by generics companies.

The study concludes that generic and innovator companies both play important roles in the African ARV market. Generic companies supply the majority of first line and fixed dose drugs at a cheaper price. Meanwhile, 2nd line therapies are mainly provided by innovator companies, who tend not to enforce patent rights in Africa, and encourage generic competition by frequently entering into voluntary licensing agreements with generic companies. The study also warns that even taking into account the significant price reductions that have occurred in the ARV market, taxpayers will face an increasingly heavy financial burden if the target of universal access to ARVs is to be met.

6. Chokshi, DA. 2006. "Improving Access to Medicines in Poor Countries: The Role of Universities," ***PLoS Medicine*** **3(6): e136.**

This essay argues that universities should adopt

licensing policies for their innovations that facilitate access by developing countries. This would involve the adoption of "equitable access licensing," allowing any manufacturer in poor countries to legally produce medicines. This implies that pharmaceutical companies that buy the intellectual rights to the university's innovation would have to forego any profit to be made in developing countries. The paper also proposes that universities devote more resources to researching "neglected" diseases. Although the paper attempts to respond to several hypothetical objections it misses the most obvious: most pharmaceutical companies rarely patent drugs in the poorest countries, so it is difficult to see how these licenses would alter the status quo.

7. Seoane-Vazquez, Enrique; Rodriguez-Monguio, Rosa. 2007. "Negotiating antiretroviral drug prices: the experience of the Andean countries," ***Health Policy and Planning*** **22(2):63–72.;**

This study analyses the effect of the Andean countries' June 2003 negotiation of antiretroviral drug (ARV) prices. It found that while the negotiations achieved price reductions for high quality ARVs, many of the Andean countries involved experienced difficulties during the negotiation process. Additionally, prices eventually paid by health ministries where higher than that agreed in the negotiation. This is largely because the negotiations did not include any legally binding contractual clauses. However, the study does acknowledge that the price of ARVs is only a one determinant of access, with factors such as weak infrastructure playing a role. The paper also concedes that multinational companies are important partners for assuring drug quality, but countries should harmonise and centralise their procurement procedures in order to gain advantage during negotiations.

8. Shadlen, Kenneth C. 2007. "The political economy of AIDS treatment: Intellectual property and the transformation of generic supply," ***International Studies Quarterly*** **51(3): 559–581.**

This article examines political relationships between suppliers of medicines, government and patient interest groups in the debate about access to AIDS drugs. It notes that governments of low-income countries cannot simply abrogate intellectual property rights and automatically expect to have a supply of high quality generic medicines, but must be in a position to access foreign supplies.

The paper concludes that the worst-affected countries can only maintain sustainable supplies of generics if they bolster their local medicines production capacity, combined with access to foreign supply from countries like India.

9. Sonderholm, J. 2009. "Paying a high price for low costs: why there should be no legal constraints on the profits that can be made on drugs for tropical diseases," ***Journal of Medical Ethics*** **35: 315–319.**

This paper adopts a legal-ethical lens to examine the welfarist case for removing patent rights for drugs for tropical diseases. It rejects all the arguments for such a move, and argues for complete free pricing on such drugs.

10. Cohen-Kohler , JC; Forman, L; Lipkus N. 2008. "Addressing legal and political barriers to global pharmaceutical access: Options for remedying the impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the imposition of TRIPS-plus standards," ***Health Economics, Policy and Law*** **3: 229–256.**

This paper focuses on the major legal and political constraints preventing implementation of coordinated global policy solutions – particularly, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) and bilateral and regional free trade agreements for patented medicines such as HIV/AIDS drugs. It concludes that greater use of TRIPS flexibilities, advancement of human rights, and an ethical framework for essential medicines distribution are fundamental for improving access to pharmaceuticals globally. However, it also suggests that the introduction of 'TRIPS-plus' arrangements may hinder access to medicines in developing countries to the degree that it restricts the use of other political and trade mechanisms such as

regional bilateral trade agreements which could help ensure that public health imperatives are not superseded by commercial interests.

11. Danzon, P; Wang, Y; Wang, L. 2003. "The impact of drug price regulation on the launch of delay of new drugs: evidence from 25 major markets in the 1990s," *Health Economics* 14(3): 269–292.

This paper analyses the impact of price regulations and controls on the launch of new medicines. If a country artificially decreases the price of a product, then the risk of "spill over" via parallel trade to more lucrative markets may cause a delay in launch. The paper examines delays to launches of 85 New Chemical in 25 major markets, including 14 EU countries between 1994 and 1998. According to the models employed by the authors, only 55% of the possible launches occurred, with the most occurring in the US. The authors conclude that lower prices and smaller markets delay the launch of new drugs, and thereby inhibit access to innovative medicines. Seeing as price depressors such as price controls, government-mandated comparative effectiveness reviews and compulsory licenses are becoming more common in emerging markets, we can expect this to have an even greater impact on the registration of new medicines. This is of particular relevance to chronic diseases, where the bulk of pharmaceutical innovation is currently taking place.

12. Danzon, Patricia M; Towse, Adrian. 2003. "Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents," *International Journal of Health Care Finance and Economics* 3(3): 183–205.

This paper reviews the economic case for patents and the potential for differential pricing to increase affordability of on-patent drugs in developing countries while preserving incentives for innovation. The paper concludes that the risks to innovation posed by compulsory licensing are very high, while originator companies could expand access by strengthening market segmentation and selling at considerably lower prices in poor countries. This strategy, however, is dependent on high income countries respecting intellectual property and not re-importing from cheaper countries. There is some evidence that this does work in the real world, as a major British pharmaceutical company has recently reported large sales increases in emerging markets since adopting the strategy.

13. Ferro do Lago, Regina; do Rosário Costa, Nilson. 2009. "Antiretroviral manufacturers and the challenge of universal access to drugs through the Brazilian National STD/AIDS Program," *Cadernos de Saúde Pública* 25(10).

This study and literature review analyses the Brazilian National AIDS program, which centres around threatening compulsory licenses and promoting local generic manufacture. Domestically produced drugs are certified as copies by the local regulator ANVISA, while imported generic efavirenz from Ranbaxy laboratories has been approved by the World Health Organization for bioequivalence and bioavailability. However, it should be noted that the WHO pre-qualification programme is not a regulatory body, and drugs it approves have not undergone the same stringent bioequivalence tests as required, for example, by the FDA. The WHO pre-qualification programme also issues a disclaimer on the safety of its approved drugs.

14. Ford, N *et al.* 2007. "Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand," *AIDS* 21: S21-S29.

This paper discusses three factors critical to the success of efforts in Brazil and Thailand to achieve universal access to antiretroviral therapy – legislation for free access to treatment; public sector capacity to manufacture medicines; and strong civil society action to support government initiatives to improve access. The paper focuses on the use of TRIPS flexibilities, such as compulsory licenses and local manufacture, in achieving universal access to AIDS therapies. The study, written by members of Medecins Sans Frontieres anti-IP 'access to medicines' campaign, has several omissions. In particular, the paper does not attempt to quantify the longer term harm done to Thai and Brazilian patients by

promoting potentially substandard, locally-manufactured copy drugs. Second, it does not examine whether the use of TRIPS flexibilities has actually improved health outcomes, instead assuming that 'inputs' to the health system in the form of cheaper medicines are an end in themselves, rather than a means of achieving high quality healthcare. It would be useful to compare Thailand and Brazil with South Africa, which had in the past opted for a more patient-centric AIDS treatment model, rather than the 'public health' model represented by Thailand and Brazil.

15. Friedman, Michael A; Besten, Henk den; Attaran, Amir. 2003. "Out-licensing: a practical approach for improvement of access to medicines in poor countries," ***Lancet*** **361(9354): 341–344.**

This paper proposes that the best way to overcome the difference between owners of intellectual property and patients is for innovator companies to promote "out-licensing" of their products to competing generic companies. This would allow generic companies to compete on price in developing countries, while allowing the owner of the patent to ensure the manufacturing process meets the required quality standards. Legal provisions would have to be made to ensure the generic licensee does not compete in high income markets where the majority of profits are made. Many companies now engage in out-licensing for therapies including ARVS and drugs for MDR-TB.

16. Dos Reis Serra, Cristina Helena ***et al.*** **2008. "Bioequivalence and pharmacokinetics of two zidovudine formulations in healthy Brazilian volunteers: An open-label, randomized, single-dose, two-way crossover study,"** ***Clinical Therapeutics*** **30(5): 902–908.**

The aim of this study was to compare the bioavailability and pharmacokinetic properties of 2 capsule formulations of zidovudine 100 mg in healthy Brazilian volunteers.

Twenty-four healthy volunteers were enrolled and completed the study. No statistically significant differences were found between the test and reference formulations of zidovudine 100-mg capsules.

17. Bennett, DE. 2008. "The requirement for surveillance of HIV drug resistance within antiretroviral rollout in the developing world." ***Current Opinion in Infectious Diseases*** **19:607–614.**

This paper describes measures being taken in 2005 to survey drug resistance to ARVs in developing countries. While the paper concedes that weak healthcare systems will not permit the high levels of monitoring and viral load testing currently afforded to patients in high-income countries, it points to literature claiming that ART programmes based on the WHO's treatment protocol "show effectiveness equal to that seen in clinical cohorts in the US and Europe". According to the authors, unnecessary drug resistance could emerge from poor prescribing; lack of free ART; lack of support for adherence; lack of appropriate regimens for children and supply chain failures. There is no mention of drug quality. The paper concludes that drug resistance surveillance should be more widely integrated into ART programmes.

18. Narang, Vishal S. 2004. "Bioequivalence evaluation of two marketed brands of stavudine 40 mg capsules in healthy human South African volunteers," ***Pharmacological Research*** **50(5): 511–516**

This study compares a generic version ARV drug Stavudine manufactured by Cipla for bioequivalence with the originator drug. The study subjects were 24 adult male Caucasian South Africans. The study concluded that the generic version is entirely bioequivalent and therefore interchangeable with the originator.

19. Monif, T ***et al.*** **2007. "Comparative bioavailability/bioequivalence of two different stavudine 40 mg capsule formulations: a randomized, 2-way, crossover study in healthy volunteers under fasting condition,"** ***International Journal of Clinical Pharmacology and Therapeutics*** **45(8): 469–474.**

This study compared the bioequivalence of stavudine 40 mg capsules manufactured by a major Indian generics company with that of the originator. The study

concluded the drugs were bioequivalent and could be used interchangeably in medical practice.

20. Garren, KW *et al.* 2010. "Bioavailability of generic ritonavir and lopinavir/ritonavir tablet products in a dog model," *Journal of Pharmaceutical Sciences* 99(2): 626–31.

This study explored the bioavailability in dogs and chemical potency of generic ritonavir and lopinavir/ritonavir tablet products manufactured by various pharmaceutical companies.

According to the abstract, "the chemical potency of the generic products was not indicative of the plasma levels of ritonavir or lopinavir that were achieved. These results reinforce the need for human bioequivalence testing of generic products containing ritonavir or lopinavir/ritonavir to assure that efficacy in patients is not compromised prior to these products being made available to patients. Procurement policies of funding agencies should require such quality assurance processes."

21. Chachad, Siddarth *et al.* 2009. "Bioequivalence study of two fixed dose combination tablet formulations of lopinavir and ritonavir in healthy volunteers," *Arzneimittel-Forschung* 59(5): E263-E26.

The study was designed to compare the rate and extent of absorption of two fixed dose combination tablet formulations of lopinavir and ritonavir.

The study concluded it can be concluded that the evaluated formulations were bioequivalent in terms of rate and extent of absorption. The safety profiles of both the test and reference formulations were comparable.

22. Monif, T. 2007. A single-dose, randomized, open-label, two-period crossover bioequivalence study of a fixed-dose pediatric combination of lamivudine 40-mg, nevirapine 70-mg, and stavudine 10-mg tablet for oral suspension with individual liquid formulations in healthy adult male volunteers," *Clinical therapeutics* 29(12): 2677–2684.

This study examined the bioequivalence of a generic fixed-dose combination pediatric formulation of lamivudine, nevirapine, and stavudine in a cohort of fasting, healthy Indian men. The study concluded that the FDC was bioequivalent to the individual liquid formulations.

23. Tarinas, A *et al.* 2007. "Bioequivalence study of two nevirapine tablet formulations in human-immunodeficiency-virus-infected patients," *Farmacia Hospitalaria* 31(3): 165–8.

This study examined the bioequivalence of two different nevirapine tablet formulations (nevirapine tablets 200 mg, Novatec, as the test formulation vs. viramune tablets 200 mg, Boehringer Ingelheim, as the reference formulation). The study concluded that "the formulations were bioequivalent in the extent and in the rate of absorption."

24. Chompootaweep, S; Poonsrisawat, J; Xumseang, P. 2006. "Evaluation of the bioequivalence of zidovudine 100 mg capsules in healthy Thai male volunteers," *Journal of the Medical Association of Thailand* 89(3):S79–85

This another bioequivalence study, this time for two oral formulations of zidovudine were evaluated; Antivir (Government Pharmaceutical Organization (GPO), Thailand) as the test formulation and Retrovir (Glaxo-SmithKline, USA), as the reference formulation. The study demonstrated the bioequivalence of the test drug (Antivir) and the reference drug (Retrovir).

25. Ferreira, FGF *et al.* 2010. "Prevalence of primary drug resistance-associated mutations among HIV type 1 vertically Infected children in Belo Horizonte, Brazil," *AIDS Research and Human* Retroviruses 26(2): 229–232.

This study discovered that amongst a cohort of treatment-naïve HIV+ Brazilian children there are high rates of primary ARV resistance. Mutations were detected in four out of 41 (9.8%) children. Based on this finding, the study recommends that testing for drug resistance should be introduced for all newly diagnosed children. The study also cites literature showing resistance rates to be between 3.6% and 19% in Brazil.

26. Gupta, Amita *et al.* 2010. "One-, two-, and three-class resistance among HIV-infected patients on antiretroviral therapy in private care clinics: Mumbai, India," *AIDS Research and Human Retroviruses* 26(1): 25–31.

This study was conducted in order to gain better knowledge of the care outcomes provided by the private sector in India, which is preferred by many patients due to its more flexible and personalised services. The study detected very high rates of drug resistance. The authors argue their results underline the need for greater viral load and resistance monitoring, and use of optimal ART combinations. The study did not disclose whether those patients with resistance had been receiving generic or brand name medicines.

27. Shekelle, P *et al.* 2007. "Antiretroviral (ARV) drug resistance in the developing world," EPC Evidence Reports. Rockville, MD: Agency for Healthcare research and Quality.

This literature is an attempt to determine the scale of resistance to ARVs in the developing world. Although the literature revealed rates of drug resistance to be somewhat lower in these regions than Europe and the US, this is probably because universal ARV treatment began many years earlier in these regions, allowing more time for resistance to develop. The fact that resistance amongst treatment naïve individuals is already at 5.5% in Africa and 5.7% in SE Asia is alarming, seeing as ARV treatment has not been readily available nearly as long. While the study does not entertain this hypothesis, it does recommend that more research takes place into the determinants of drug resistance, particularly adherence to treatment regimens. The However, the study makes specific reference to drug quality and bioequivalence of generics, which is surely of major relevance considering the important role they play in officially-sanctioned treatment protocols.

28. Apisarnthanarak, A *et al.* 2008. "Antiretroviral drug resistance among antiretroviral-naïve persons with recent HIV infection in Thailand," *HIV Medicine* 9(5): 322–5.

This is an investigation into ARV drug resistance among treatment naïve, newly infected people between 2003 and 2006 in Thailand. This timeframe coincides with the establishment of the National Access to ARV Programme, based on the use of the locally manufactured triple combination copy drug, GPO-vir. Annual drug resistance increased from 0 to 5.2%, a rise described as 'alarming' by the authors.

29. Pillay, V *et al.* 2008. "HIV type 1 subtype C drug resistance among pediatric and adult South African patients failing antiretroviral therapy," *AIDS Research and Human Retroviruses* 24(11):1449–54

The emergence of HIV drug resistance is a major obstacle to effective antiretroviral (ARV) treatments. This study examined the drug resistance profiles among South African patients virologically failing ARV therapies between 2000 and 2003, prior to the introduction of a national treatment program. The results concluded that HIV-1 drug resistance develops in South African subtype C-infected patients failing ARV therapy with mutations comparable to those found among patients infected with subtype B viruses.

30. Gottlieb, GS *et al.* 2009. "Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resouce-limited West Africa," *Clinical Infectious Diseases* 48(4): 476–83.

This research discovered "remarkably high levels of genotypic mutations" amongst HIV-2 infected patients in West Africa, consistent with multiclass drug resistance.

31. Nouhin, J *et al.* 2009. "Low prevalence of drug resistance transmitted virus in HIV Type 1-infected ARV-naive patients in Cambodia," *AIDS Research and Human Retroviruses* 25(5): 543–5.

This study found a low prevalence (1.49%) prevalence of transmitted drug-resistant strains in treatment –naïve patients in a cohort of Cambodian patients. This is encouraging, seeing as ARV drugs had been introduced in Cambodia six years prior to the study.

32. Halliburton, M. 2009. "Drug resistance, patent resistance: Indian pharmaceuticals and the impact of a new patent regime," *Global Public Health* 4(6): 515–27.

This article argues that India's 2005WTO TRIPs agreement will raise the price of second and third line therapies beyond the reach of poor patients, condemning them to premature deaths when resistance to first-line therapies sets in. It recommends exploiting flexibilities in the TRIPs agreement, including issuing compulsory licenses.

33. Huang , KHG *et al.* 2009. "Prevalence of HIV type-1 drug-associated mutations in pre-therapy patients in the Free State, South Africa," *Antiviral Therapy* 14: 975–984.

This study found a "reassuringly low" prevalence of pre-therapy drug resistance in the patients studied in the Free State, many of whom had been taking nevirapine. South Africa has been notable for favouring its own treatment protocol over that of the WHO, which is more public-health oriented.

34. Johnston, A. 2010. "Challenges of therapeutic substitution of drugs for economic reasons: focus on CVD prevention," *Current Medical Research and Opinion* 26(4): 871–8.

This paper outlines some of the problems associated with interchanging brand-name drugs with generic equivalents. Although drugs are required to demonstrate generic equivalence, this does not always mean the drug is safe. The study cites numerous examples where generic substitution has been harmful. It also notes that results obtained in clinical practice may differ substantially from those of randomised clinical trials, a factor which clinicians should bear in mind when deciding whether to use a generic substitute.

35. Kesselheim, AS *et al.* 2008. "Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis," *Journal of the American Medical Association* 300(21): 2514–26.

Many physicians and policy makers advocate the use of generic equivalent drugs on the patent expiry of brand-name originator, in order to reduce costs. This study is an attempt to evaluate the clinical differences of generic and brand-name drugs for CVD, in order to gauge their safety and efficacy. The review examined 47 studies, and concluded that nearly all of the studies showed that nearly all the generic drugs studied were similar in clinical outcomes. All the drugs tested had been certified as bioequivalent by the Federal Drugs Authority. However, the studies had several limitations. The majority of studies identified were bioequivalence studies, "which included small populations and were powered to assess differences in pharmacokinetic parameters rather than clinical outcomes."

Notes

1. http://www.livemint.com/2007/08/19235926/Combination-drugs-set-to-lose.html, "The Menace of Combo Drugs." India: Deccan Herald. Available online at www.deccanherald.com/Content/Apr32008/editpage2008040260701.asp; "40 fixed-dose-combination drugs may be off chemists' shelves." India: Business Line. Available online at http://www.thehindubusinessline.com/2007/09/04/stories/2007090451011100.htm
2. "GSK sales jump in emerging markets", *Financial Times*, 4th February 2010, available at http://www.ft.com/cms/s/0/d104345c-1184–11df-9195–00144feab49a.html
3. Attaran, Amir, Why Canada's Access to Medicines Regime Can Never Succeed (February 12, 2010). Available at SSRN: http://ssrn.com/abstract=1552091
4. Bate, R. (2008), "Local pharmaceutical production in developing countries", Campaign for Fighting Diseases, available at http://www.fightingdiseases.org/pdf/local_drug_production.pdf
5. World Health Organization, Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality, Prequalification Programme, World Health Organization, Geneva, all editions since 2002 and through February 1, 2008.
6. Jeremiah Norris, "Critics Ignore Progress on AIDS," *Business Day* (South Africa), September 11, 2006, available at www.businessday.co.za/articles/opinion.aspx?ID=BD4A269210.
7. "New HIV guideline urge phase-out of major HIV drug", *Reuters*, 30 November 2009, available at http://www.reuters.com/article/idUSTRE5AT00K20091130