



Policy Options for Promoting the Use of Generic Medicines in Low- and Middle-income Countries

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Abbreviations

ARV	Antiretroviral
CMS	Central Medical Supplies Public Corporation
EGA	European Generics Association
EML	Essential medicines list
ERP	External reference pricing
EU	European Union
FDA	Food and Drug Administration (United States)
FTA	Free trade agreement
GNI	Gross national income
GMP	Good manufacturing practices
HAI	Health Action International
HMO	Health maintenance organisation
INN	International non-proprietary name
IMF	International Monetary Fund
IP	Intellectual property
IRP	Internal reference pricing
LDCs	Least-developed countries
LMICs	Low- and middle-income country/countries
MNC	Multinational company
MRA	Medicines regulatory authority
MRP	Maximum retail price
NDA	New drug application
NHS	National Health Service (UK)
OECD	Organisation for Economic Co-operation and Development
OECS	Organisation of Eastern Caribbean States
OPS	Organización Panamericana de Salud
PPRI	Pharmaceutical pricing and reimbursement information
R&D	Research and development
TRIPS	Trade-Related Aspects of Intellectual Property Rights
US	United States
WHO	World Health Organization
WTO	World Trade Organization

Executive summary

The use of generic medicines has been steadily increasing internationally as a result of economic pressure on pharmaceutical budgets and the expiry of patents on widely used medicines, particularly in the United States and Europe. In these high-income areas, use of generic medicines has been generally supported by a series of policies promoting their utilisation and these policies have been subject to monitoring and evaluation. It is far less clear which policies should be enacted by low- and middle-income countries interested in lowering their health care costs by increasing generic medicines' utilisation.

Although the development of appropriate pro-generic medicines policies in low- and middle-income countries is both complex and challenging, an evidence base of research results on pro-generic medicine policy design, implementation and outcomes can provide the basis for recommendations.

This review seeks to help policy-makers prioritise pro-generic medicine policy actions through:

- providing an introduction to policies that can be used to address enhancing uptake of generic medicines;
- reviewing existing literature on generic medicines policies with an emphasis on low- and middle-income countries, particularly as the literature relates to research on the impact of such policies; and
- identifying key enabling conditions that need to be introduced before pro-generic medicines policies can be effectively implemented and enforced.

The review of existing literature shows that there is a wide range of policies that are used to promote the uptake of generic medicines. These policies can be divided into "supply-" and "demand-" side policies. Supply-side measures relate to medicine research and development, manufacture, regulation/market authorisation/quality assurance, competition, intellectual property rights and pricing. For the most part, policies related to manufacturing, regulation, market authorisation, quality assurance, competition and intellectual property rights can be activated both before and after the originator product obtains market approval. Supply-side policies include "reference" pricing, price controls and regulatory actions to decrease the time delay for market authorisation of generic medicines.

Demand-side measures are directed to the reimbursement, prescribing, dispensing, selling and purchasing of medicines. They are directed at those who prescribe, dispense and sell medicines, and patients or caregivers who may ask for medicines. This includes policies on prescribing medicines by the International Non-proprietary Name, implementing feedback to prescribers on generic prescribing, generic substitution by dispensers, and educational interventions to promote knowledge about generic medicines and trust in their quality.

However, in low- and middle-income countries, there is a general lack of research on the impact of policies to promote generic uptake. The vast majority of low- and middle-income country studies are descriptive and/or cross-sectional and do not demonstrate the results of policy changes on the uptake of generic medicines. Indeed, the few relatively rigorous evaluation studies of policy changes on generic medicines use in low- and middle-income

countries primarily relate only to the impact of international trade and intellectual property policies on the consumption and price of generic medicines.

Three over-arching “enabling conditions” must be introduced before a low- and middle-income country can effectively implement and enforce any one of a number of pro-generic medicines policies.

1. The first requirement is a mechanism sufficient to provide certainty and confidence that generic medicines are of assured quality, which involves having an effective regulatory system. The national medicines regulatory authority should play a very active role through communicating information about the scientific basis for the granting of market authorisation for generic products (e.g., whether a biowaver was granted or a bioequivalence study was undertaken, identity of the reference product) and about the quality of generic products, plus imposing sanctions on any violation of promotion which is not scientifically grounded.
2. A reasonably robust market supply of generic medicines is required to ensure sufficient competition for downward pressure on prices of quality-assured medicines. The government should understand the barriers faced by generic producers when securing a viable local distribution system for their product. At the same time, the role of the medicines regulatory authority is critical in ensure timely entry of generic medicines into the market through lowering market authorisation costs for generic medicines, proving support for bioequivalence testing, and efficiently handling application for market authorisation to reduce any delays.
3. The characteristics of the healthcare system in many low- and middle-income countries suggest the importance of demand-side policies as medicines are largely financed out of pocket and selection of products purchased are made directly by consumers or patients without a prescriber as an intermediary. Hence, incentives that focus on market mechanisms are vital. Experience from high-income countries suggests that aligning different users and consumers of generics are necessary when selecting policy options. These include prescribing by generic name, generic substitution, financial incentives for pharmacy and medicine outlet personnel to sell low price generic medicines, and continued education of consumers about generic medicines.

Efforts at developing a more robust monitoring and evaluation initiative in-country is important largely part because it appears to be consistently missing from the pro-generic repertoire of many countries. This is not a trivial goal; programme evaluation is complex and requires substantial resources from a variety of areas, including human and financial resources, capacity development, institutional capacity and political will.

1. Introduction

"WHO not only supports generic products. We aggressively promote them, whether through guidelines for conducting bioequivalence studies or through the prequalification programme. Generic products serve public health in multiple ways. In terms of improving access to medicines, price and quality go hand in hand. Generic products are considerably less expensive than originator products, and competition among generic manufacturers reduces prices even further. Generics serve the logic of the pocket. An affordable price encourages good patient compliance, which improves treatment outcome and also protects against the emergence of drug resistance."

Dr Margaret Chan,
Director General,
World Health Organization,
28 February, 2011

Sustainable Development Goal 3 and prior to this, Target 8e of the Millennium Development Goals, acknowledge that the availability and affordability of medicines is not adequate in many countries. For many low- and middle-income countries (LMICs), a key challenge for policy-makers is to increase access to quality-assured medicines by increasing their availability and affordability. Increasing the use of quality-assured generic medicines is therefore a key strategy for improving the affordability of medicines (United Nations Gap Report, 2010; WHO, 2001). The use of generic medicines has been steadily increasing internationally because they are generally lower priced than originators and an increased number of generic versions of commonly used medicines are becoming available as patents expire. In high-income countries, the generic medicines issue has been highlighted through the enactment of high profile legislation in the United States (US) [See Section 3.1.1.2] and through several reviews of European Union (EU) and Member State pharmaceutical legislation, which have aimed primarily at containing rising health-care costs. This has resulted in a range of pro-generic medicines policies that have been widely debated and various policies have been evaluated. Each country and region has a different health and industrial policy context, and the development of appropriate pro-generic medicines policies is both complex and challenging. Such policies are likely to be different for each country.

There are many barriers to the increased uptake of generic medicines that need to be addressed by pro-generic medicines policies. Variations in price and availability have a great impact on the affordability of medicines, particularly for the poor and disadvantaged who mostly pay out-of-pocket in LMICs. Increasing the uptake of generic medicines is not a simple task, neither from the perspective of the generic medicines manufacturers, nor from that of the health system itself. Amongst other strategies, health systems require incentives to ensure that generic medicines are of assured quality, and for health care professionals and consumers to prescribe, dispense and use generic medicines. Further, people who dispense and/or sell medicines play a vital role in informing consumers about the price of generic medicines of assured quality (King and Kanavos, 2000).

Policy-makers must understand what generic medicines are and the various policy options for increasing their uptake. Given the policy paths and barriers to increased uptake of

generics, multiple as well as coordinated policies are needed in order to make medicines more affordable.

1.1 Aim of this review

The review seeks to:

- provide a brief introduction to policies that can be used to address enhancing the uptake of generic medicines in the pharmaceutical sector;
- review existing literature on generic medicines policies with an emphasis on LMICs, particularly as the literature relates to research on interventions and outcomes designed to look at the impact of such policies; and
- identify any necessary prerequisites for generics policies in LMICs and useful complementary policies, in order to help policy-makers prioritise policy actions.

1.2 Definitions

1.2.1 Generic medicine

Differences in the requirements for market authorisation of generic medicines between countries, especially differences related to the basis for demonstrating therapeutic equivalence and the fact that they can be sold under either a brand (i.e., proprietary name or trade name) or the name of the active ingredients (International Non-proprietary Name, INN), have contributed to a variety of definitions of what is a “generic medicine”. These differences have also caused different understanding of what is a generic medicine. Some of these definitions are overlapping even though different terms are used. This continues to cause confusion in the debate over generic medicines and makes comparison of research studies and countries difficult (Homedes and Ugalde, 2005).

Appendix 1 illustrates the variety of definitions and concepts used in the literature. This review uses the WHO definition from 2006 which defines a “generic” medicine as “Pharmaceutically equivalent or pharmaceutically alternative product[s] ... Multisource pharmaceutical products that are therapeutically equivalent are interchangeable” (WHO, 2006a). It is significant that there is no mention in this definition of whether or not the “originator” molecule is, or was, under patent protection.

There may be several forms of the same medicine on the market at any one time. Generic medicines can include products sold under the INN (“unbranded” generics) or under a brand name by a manufacturer that is not the originator and not under licence from the originator (typically called “branded” generics). Branded generics are actively marketed and comprise the majority of generic medicines in many LMICs. Where originator medicines are sold under a brand name by a third party under licence from the originator, these are called “licensed generics”. “Authorised” generics are prescription medicines whose marketing approval derives from the originator manufacturer’s new drug application (NDA) itself, yet are marketed and sold as generic versions of the originator (Federal Trade Commission, 2011).

It has been suggested that this type of “licensed” and/or “authorised” generic medicine is an effort on the part of the originator company to protect the market share of the originator medicine. The tactic is to raise the overall price, thereby mitigating the loss of sales to generic producers. Often, in countries that allow for unbranded generic medicine sales, a price gradient exists from highest to lowest price (i.e., originator/authorised generic – branded generic – unbranded INN generic).¹

1.2.2 Bioequivalence and biowaiver

The requirements to obtain market authorisation of a multi-source pharmaceutical product, depends on the regulatory framework applied by the medicines regulatory authority (MRA) of each country. In many, but not all countries, medicines are considered to be “therapeutic equivalents” and thus suitable for generic substitution if, amongst other factors, they are “pharmaceutical equivalents”² and/or “bioequivalent”.³

For instance, in the US and the EU, proof of therapeutic equivalence with the single-source (originator) product may be required for the market authorisation of a multi-source product (FDA, 2008; EMEA, 2010). Determination of “equivalence” takes place for different dosage forms (immediate release oral solids, sustained release oral solids, different types of injectables and topicals). The national regulatory authority may issue a “biowaiver” to exempt a requirement for bioequivalence testing. Evidence is still required for equivalence, but it may only need to be pre-existing evidence, such as in vivo (clinical trial) or in vitro (dissolution test) evidence, or merely assurance of ingredients.

In some countries bioequivalence evidence for every product is not considered necessary, but only evidence to prove *pharmaceutical equivalence*. Many MRAs in Latin America do not require bioequivalence evidence but a proof of pharmaceutical equivalence. Therefore, some countries in Latin America (such as Argentina, Brazil and Mexico) distinguish those multi-source products with proof of therapeutic equivalence tests as true “generics” and those with just pharmaceutical equivalence as “copy or similar medicines” (Homedes and Ugalde, 2005; Sundar, MR, 2011).

In 2006, the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO 2006a) provided recommendations for a biowaiver of bioequivalence testing of essential medicines. The WHO provides national regulatory authorities with sufficient background information on the various active pharmaceutical ingredients (APIs) for oral administration on the WHO Model Essential Medicines List (EML) to enable them to make

¹ The primary emphasis of this report is on “small molecules” and not “biosimilars”. There is still some lack of clarity about definitions of biosimilars, but the US Food and Drug Administration’s definition asserts that biosimilars are: “...highly similar to the reference product they were compared to, but have allowable differences because they are made from living organisms.” See www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm

² Products that contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route (WHO, 2006b).

³ Bioequivalence is defined by the World Health Organization as follows: “Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve (AUC)) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.” (WHO, 2006b). Note that products are considered **pharmaceutical alternatives** if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules).

an informed decision as to whether generic formulations should be subjected to *in vivo* bioequivalence studies or whether a “biowaiver” can be applied. The term biowaiver is applied to a regulatory approval process when the dossier (application) is approved based on evidence of equivalence other than through *in vivo* equivalence testing. The WHO has proposed that many APIs on the Model EML, can be considered for a biowaiver procedure, eliminating the need for *in vivo* bioequivalence testing (World Health Organization, 2006b).

The evaluation of bioequivalence data often presents a major challenge (technical and financial) for regulatory authorities in LMICs. To the extent that there are any local manufacturers, not all of them can carry out bioequivalence studies. Therefore, access to a contract research organisation is critical since these studies may require (1) access to the originator product; (2) the capacity to carry out studies in healthy humans that compare the proposed generic product with the originator, including; (3) measurement of plasma concentrations of substances using a reliable, sensitive and specific assay (Hill and Johnson, 2004).

1.2.3 Low- and middle-income countries (LMICs)

For the purpose of this review, countries have been classified according to the World Bank (2010) classification system (<http://data.worldbank.org/about/country-classifications>). It divides countries according to 2009 gross national income (GNI) per capita (calculated using the World Bank Atlas method):

- low-income, \$995 or less (e.g., Afghanistan, Malawi, Haiti);
- lower-middle-income, \$996 - \$3,945 (e.g., Pakistan, Zambia, Bolivia);
- upper-middle-income, \$3,946 - \$12,195 (e.g., Thailand, Jordan, Brazil).

All other countries, according to the World Bank scheme, are considered “developed” or high- income countries (GNI per capita \$12,196 or more). The focus of this review is on LMICs.

Note: Sometimes the abbreviation LMICs is used for the single classification of lower-middle-income countries. This is not the case in this review.

Aggregating LMICs does not mean that their social, economic, political and health characteristics and contexts are all the same. On the contrary, each LMIC is unique and their characteristics will certainly have effects on the implementation of pro-generic medicines policies. Moreover, their internal health disparities cannot be ignored. However, for the purpose of this review, the term LMIC is used to separate them from countries that are characterised a) by more resources; b) in various cases, a longer tradition of promoting and evaluating generic medicines policies; and c) organisational structures that facilitate the implementation of certain generic policies (for instance, largely financing medicines through publicly-funded healthcare systems).

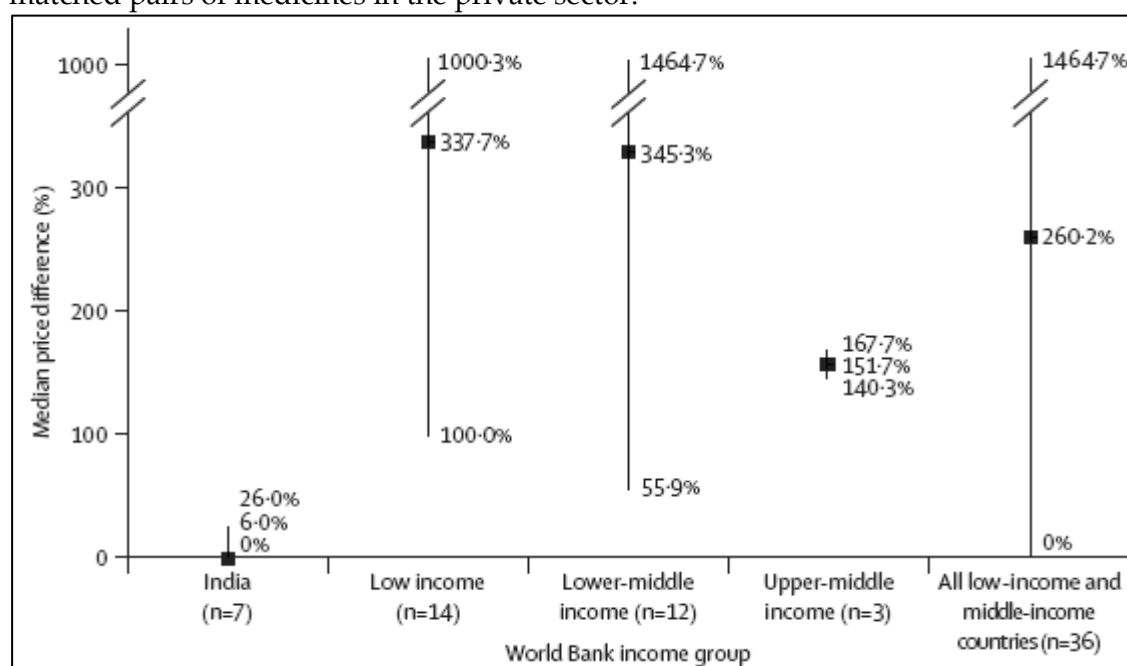
1.3 The potential of generic medicines to improve access to essential medicines

The fact that some LMICs have better availability and lower medicine prices than others shows that access to quality-assured, affordable essential medicines can be improved

through stronger partnerships amongst governments, pharmaceutical companies and civil society. The WHO concept of essential medicines, developed over 30 years ago, and its associated Model EML, assists countries to select safe and effective medicines that are relevant to their populations' needs. Many medicines on the Model EML are produced as 'generic' versions of medicines originally made by the so-called "originator" company (i.e., a manufacturer that was first on the relevant market with the particular medicine and that conducted research and development (R&D) that lead to the product). Typically, the originator company gives the medicine a unique name as a 'brand' to identify it in the minds of the providers and consumers.

In the last decade, studies on medicine prices in LMICs have revealed high prices for originator medicines in the large majority of settings, often 2 to 5 times higher than lowest-priced generic products (Cameron et al., 2009). Figure 1 shows the median price difference between originator brands and lowest-priced generics for matched pairs of medicines in the private sector by country income group.

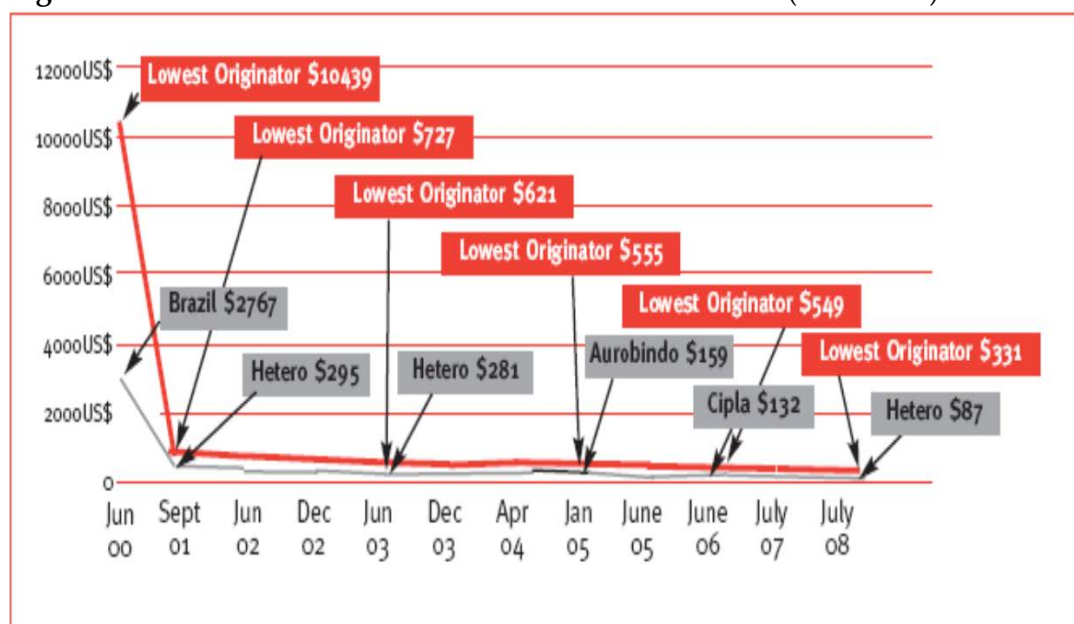
Figure 1: Median price difference between originator brands and lowest-priced generics for matched pairs of medicines in the private sector.



Source: A Cameron, M Ewen, D Ross-Degnan, D Ball, R Laing. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet* 2009; 373: 240–49.

Figure 2, below, presents the well-documented example of the fall in annual cost of the first-line antiretrovirals, stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), from 2000 to 2008 in the presence of generic competition (Doctors without Borders, 2008).

Figure 2: Decrease in annual cost of first-line antiretrovirals (2000–2008).



Source: Médecins Sans Frontières, 2008, *Untangling the Web*, 8th edition.

For many countries, there is potential to achieve large savings if generic products are used, rather than originator brands. Table 1 shows the total potential savings (in US dollars) and savings by individual medicines (as a percentage) if lowest-priced generics were used in a selection of countries (Cameron et al., 2012).

Table 1: Potential savings of using generics in selected countries.

Country (n=number of medicines)	Total potential cost savings if switch to generic version (2008 USD)	Average percentage savings across individual medicines
China, public hospitals (n=4)	\$369,889,300	65.1%
Colombia (n=9)	\$3,229,092	88.7%
Ecuador (n=12)	\$3,066,407	63.2%
Indonesia (n=9)	\$6,405,597	84.2%
Jordan (n=11)	\$887,262	55.9%
Kuwait (n=6)	\$64,261	9.3%
Lebanon (n=8)	\$4,397,432	67.5%
Malaysia, private hospital and retail sectors (n=10)	\$7,419,942	67.2%

Source: Cameron A, Mantel-Teeuwisse AK, Leufkens HGM and Laing RL. (2012) Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved? *Value in Health* 15 (5): 664-673.

1.4 Research and development of new medicines as part of the medicine “life cycle”

Price differentials between the originator product and generic products often persist long after the originator has lost its patent protection. These higher prices for originator products have been justified on the basis of high R&D costs for the product. Generic medicines do not need to include R&D costs and thus provide the opportunity for major savings in health-care expenditure. However, even generic medicine companies are profit-driven and need to provide an assured quality medicine that yields a return on investment.

Each medicine has a ‘life cycle’. This extends from discovery and development to patenting and market authorisation (i.e., registration by an MRA). Patent holders themselves may produce a “authorised generic” version before patent expiry (e.g., as discussed in Section 1.2.1). After patent expiration, branded and INN generic versions may be produced by third parties.

Key components of the R&D of new medicines are stages of clinical trials that must be carried out before its commercialisation. The duration of these trials will vary in length. Estimates by the pharmaceutical industry suggest that about 8 to 12 years are needed for a new molecule, not previously developed, to pass through the clinical trials and receive approval for marketing. The task of developing the laboratory and clinical evidence on safety and efficacy of the new medicine in humans is usually undertaken by the originator company, although much of the early research work may be funded by government structures such as science councils, or that early stage trials are conducted by one company, but then sold or licensed to a manufacturer who completes the product registration and commercialisation steps. Nonetheless, the task of reviewing all this evidence and giving final market approval is organised by the MRA. Sometimes the MRA may place restrictions on the sale of the medicine, and sometimes require further so-called ‘pharmacovigilance’ activities (including additional activities, called “Phase IV”). The responsibility of the MRA does not stop when it gives market approval; it continues through pharmacovigilance until the product is no longer on the market. During the clinical phase and until market approval, the originator company continues to spend money for R&D. Thus, all these activities carried out by the originator company will cause expenses until the time the product is marketed and sold.

Usually, the originator company, although not always, applies for intellectual property (IP) protection (generally in the form of one or more patent applications) for the product. Patent applications are submitted at, or more usually before, the start of clinical development. Review of the patent application is organised by the national IP Office. This is usually a completely separate administrative body from the MRA.

Irrespective of whether the originator product is patent protected or not, the originator company will seek to recover the claimed cost of R&D and obtain profits as soon as possible upon market approval and before generics can become “second movers”. If the originator product is protected by an issued patent, this allows the company to set the price at a level to maximise profits as soon as possible, although this price will be eroded once the originator product loses patent protection and essentially shares the market with generic versions. Their profits are also impacted by competition from sales of other medicines (for instance,

one of similar therapeutic profile that would be a therapeutic competitor). The originator will often develop its own version to compete with generic versions.

The originator company can also try to maintain market exclusivity using other means. Specifically, under certain free-trade agreements (FTAs), the data used to gain market authorisation for the originator will not be made available to a generic manufacturer for a certain period of time, ranging up to 10 years or more. Thus, the generic manufacturer either needs to produce the clinical trial data itself (which is very expensive and unethical) or wait until this period of exclusivity expires and make use of the clinical trial data of the originator which demonstrates safety and efficacy. The period where data for market authorisation is not provided to the generic company is called a “data exclusivity” period. Such exclusivity periods also exist within countries (i.e., the US) and may be extended to signatories of these FTAs.

Many countries do not recognise such a concept. Even if an originator product is not patent protected, this data exclusivity effectively acts as a patent. Moreover, in some countries, such as the United States, the MRA is required to consider the patent status of medicine such that, if a patent on the originator exists, marketing approval will not be granted to a generic until the patent has expired or is found to be invalid in a court of law. This so-called “patent linkage” is an additional, IP-driven policy and can delay entry of generic versions of the originator product. See Section 3 for more information.

1.5 Facilitating entry of generic medicines on the market (see also Section 3)

The date of entry of a generic version of an originator product depends on national policies. There is much variation in this regard. For example, provisions can be adopted that allow the early application by a generic manufacturer for a licence to develop a generic version of an originator product still under patent (“Bolar” provision). The time before patent expiry would be used to develop the generic product and permit speedy market entry once the patent has expired.

Another example is the granting of market exclusivity rights for the first manufacturer of a generic product that enters the market after the expiry of the patent of the originator product. This would be designed to attract manufacturers to speed up their processes in order to receive this limited market exclusivity.

If the originator product is patent protected, producers of generic versions must normally wait until the patent expires or is declared invalid before they can enter the market. However, there are strategies to allow market entry of generics where a patent exists. Compulsory licensing of patents has been used in situations where countries argue that an originator product was essential for public health but not affordable (e.g., in the case of efavirenz, a key antiretroviral for the treatment of HIV patients in Brazil) [Beall and Kuhn, 2012].

Other strategies to promote market entry of generic medicines are IP regulations that make it more difficult for the originator company to either obtain IP protection in the first place, or extend IP protection because it is seen as a threat to access. It should be noted that patent

linkage, as described above, is not required in many countries. The MRA may authorise multiple versions of the originator medicine and leave the originator company to seek redress through the courts for any damages that they allegedly suffer.

Countries usually strive to provide incentives for innovation of new medicines (not the topic of this review) and balance those with incentives for access to affordable medicines. In promoting affordable, quality-assured medicines, policy-makers have many choices as to which stakeholders to impact by pro-generic medicines policies. Some policies will depend on whether there is a patent on the originator, but it is important to note that many policies work regardless of whether the originator product is patented or not.

1.6 Healthcare/pharmaceutical policies relevant to generic medicines

Policies to improve access to medicines can be divided into so-called “supply-side” and “demand-side” policies (King and Kanavos, 2002). Supply-side policies are primarily directed towards specific stakeholders in the healthcare system that are responsible for medicine regulation/market authorisation/quality assurance, competition amongst manufacturers, IP rights and pricing. These policies can be initiated both before and after the originator product gains market approval and/or the expiry of the patent on the originator.

Generally, demand-side policies include reimbursement, prescribing, dispensing and purchasing by consumers and patients and are directed at stakeholders such as healthcare professionals prescribing medicines, people selling or dispensing medicines and patients/consumers. This review uses these two policy designations as its organising principle. People may differ as to whether a given policy is either supply- or demand-side.

1.6.1 Supply-side policies

Table 2: Supply-side policy domains.

Supply-side policy domains	Section of review
Medicine regulation/market authorisation/quality assurance	3.1.1
Trade and IP policy	3.1.2
Generic price competition policy	3.1.3
Pricing and purchasing policies	3.1.4

Table 2 lists the various supply-side policy domains and the relevant sections in this review where they are discussed.

Supply-side policies relate to the following:

- speed with which a generic product is reviewed by the MRA;
- incentives for generic manufacturers to file an application for market authorisation;
- quality of the generic product;
- ability of the originator to obtain IP protection in the first place;
- ability of the originator to extend IP protection and to protect itself from claims of invalidity;

- ability to obtain a medicine if the patent owner does not want to make it available;
- level of competition amongst manufacturers; and
- price(s) of the generic product(s).

1.6.2 Demand-side policies

Table 3: Demand-side policy domains.

Demand-side policy domains	Section of review
Reimbursement policies	3.2.1
Prescribing policies	3.2.2
Dispensing policies	3.2.3
Policies impacting consumers/patients	3.2.4

Table 3 lists demand-side policy domains and the relevant sections in this review where they are discussed. These measures usually relate to doctors, people who dispense and/or sell medicines and patients who consume the medicines. These policies are generally free of the kind of IP rights issues described above.

Demand-side policies relate to the following:

- medicine reimbursement;
- prescribing of generic by doctors and other healthcare providers;
- dispensing and/or selling of generics by pharmacists and others;
- information about the medicine that is given to patients and others;
- ability of consumers to understand the difference between the originator and generic versions;
- confidence of prescribers, dispensers and consumers in the quality of generic medicines; and
- overall consumption pattern of generics in the healthcare system.

1.7 Contents of this review

Section 2 describes the methodology used in the literature review. Section 3 discusses the findings of the literature review by looking at a series of generic medicine policy domains (e.g., quality, price, reimbursement, prescribing) and published research, if any, on the impact of the policy dimension on the uptake of generics. (Uptake is defined in this review as a change in volume/consumption or price.) Section 4 discusses the findings from the literature review with a focus on LMICs, underlines the current limitations of assessing the positive and negative effects of changes in policies, and highlights areas for further research. Section 5 presents recommendations on prioritising pro-generic medicines policy implementation. Section 6 presents the conclusions.

1.8 Who is the target audience for this review?

Primary audiences are policy-makers, decision-makers and policy advisors, particularly in LMICs. The report is also directed to all other stakeholders of the pharmaceutical sector, such as:

- health policy analysts;
- health insurers, public and private;
- pharmaceutical industry and wholesalers;
- international organisations (e.g., donors, think tanks);
- associations or representatives of pharmacies or people who dispense (which we includes also as selling) medicines;
- health professionals and their associations;
- consumer and patient groups; and
- media

2. Methodology

2.1 Data collection

A narrative review of literature published in English, French, Spanish and Portuguese between January 2000 and March 2010 was carried out with the principal objective to identify policy options to promote the use of generic medicines in LMICs. The following search engines were used: MEDLINE, EMBASE, Thomson Reuters (formerly ISI) Web of Science, EconLit, International Network of Rational Use of Drugs (INRUD), PAIS International, Cumulative Index to Nursing and Allied Health Literature (CINAHL), POPLINE (One Source), Scientific Electronic Library Online (ScieLo), the Latin American Literature on Health Sciences (LILACS) and the Drug Policy Review material collected by the Cochrane Collaboration.

The first search used the keywords “generic” or “generics” in the title and/or abstract. For PUBMED, MeSH terms were used, and major subject headings were used for CINAHL, EMBASE, CSA/PAIS, and POPLINE. The search strategies were meant to capture both high-income countries, as defined in Section 1.2.3 (e.g., US, European countries, Canada, Japan, New Zealand and Australia) and LMICs. For more details on the search strategies, see Appendix 2. Although the focus was on LMICs, the decision was made to include literature on high-income countries because our working assumption was that the LMICs-related literature would be sparse. The focus on high-income countries was to summarise existing knowledge for each of the policy domains.

In a second search, “generic” and “generics” was replaced by “multisource”, “interchangeable” or “interchangeability” alone or in combination with “policy” or “policies” to check for completeness. The results were compared with those from the first search. The second search contained the same references that appeared in the first search⁴.

To search for grey literature the following websites were reviewed: Organisation for Economic Co-operation and Development (OECD), World Bank, World Health Organization (WHOLIS), Pan American Health Organization (PAHO)⁵ and European and US generic medicine trade associations. If searching was possible on the websites, the following terms were used: generic medicines, legislation and type of study. In addition, MRA and other government pharmaceutical websites were used as the primary sources for obtaining national medicine policies and other legislation relating to generics.

The literature review carried out for this review was complemented by the previous descriptive review of the literature carried out by Nguyen et al. (2008). Their search terms matched the ones listed above, but their time period was 1990 to 2007 and they only looked at English language literature.

A secondary objective of the literature review was to identify interventional studies analysing the effect of the implementation of policies promoting the uptake of generic

⁴ Almost all of the abstracts in this smaller subset included the word “generic” in addition to these other search terms. Intuitively, it is difficult to see how any paper that relates to policies for generic medicines would not include the term generic.

⁵ A recently published document by PAHO (2010) on generic medicines in the Americas was one of the key documents identified in the grey literature.

medicines. The uptake of generics can be measured in various ways: (1) as a function of volume of market share of generics; or (2) as a function of price such as savings through larger procurement or prescription of generic medicines instead of originator medicines. This specific subset of research-based articles for LMICs was extracted from the review based on the inclusion criteria listed in Table 4.

Table 4: Inclusion criteria for publications on policy impact.

Criteria	Explanation
Study objective	To study the impact of a policy or a set of policies to promote the use of generic medicines. All policies that fall into the following policy domains were considered: competition, consumer education, dispensing, marketing authorisation and labelling, prescribing, price regulations, reimbursement, trade related/IP.
Study design	Interrupted time series analysis and/or repeated measures studies and/or controlled or uncontrolled before and after studies.
Study sites	LMICs (as defined by the World Bank, or if not included, by IMF definitions) Public and/or private health care institutions and/or pharmaceutical retail sector
Study outcome	Volume and/or price change, costs (expenditure) in combination with volume and price change
Data collection	Primary or secondary data processed and analysed by the authors of the study
Study period	2000 to 2012

2.2 Data analysis

The original search in all the databases were combined in an EndNote® library and duplicates removed⁶. The remaining 4,993 references were used for a second screen where all references were removed that did not include the words “generic” or “generics” in the title and/or abstract (Appendix 2). This resulted in a total of 679 references.

Two teams of independent researchers reviewed each of the 679 titles independently. If the publication was unrelated to generic medicines (i.e., a study about “generic” administrative policies or “generic” factors related to water purification) or merely evaluated the use of medicines (unrelated to policies), they were excluded. In addition, all references that did not have an abstract were excluded. Cases of disagreement were resolved individually by detailed discussion on the justification for an exclusion. This second screening resulted in a total of 439 references which were transferred to RefWorks® (www.refworks.com).

For these 439 publications, the abstract was used to classify the publication into “low- and middle-income” and “developed/high-income” countries depending on the World Bank classification (World Bank, 2010). For each of these categories, the reference was classified into one of the following policy domains: competition, consumer/patient, dispensing,

⁶ EndNote® only removes duplicates if the references show the identical citation, including spacing and punctuation marks. Duplicates not identified by EndNote® were identified by searching on the primary author. True duplicates were then manually removed.

regulation (in marketing authorisation and labelling), prescribing, price controls, reimbursement, and trade related aspects/IP rights. Some references covered more than one of these domains, which were classified as “others”. As mentioned in the introduction, these policy domains were adapted from the literature about generics policies (e.g., King and Kanavos, 2002; Tobar, 2008). If the publication was not found to be relevant to one of the domains it was excluded.

For each of the references, the full text was retrieved. Out of 686 publications on generic medicines, 315 were identified that focused on generic medicines policies (236 related to high-income countries and the rest were on policies in LMICs). From the full texts, information on the following criteria was obtained: country, LMICs (yes or no), study type (original, review, others), objective(s) of the study, principal findings, and comments. The reference was excluded if the methodology was not clearly described for original studies or reviews. Publications that were not an original study or a literature review were only included if they presented new aspects and the origin of the data presented was appropriately referenced. Personal opinion or discussion papers were excluded.

References included in this review were selected according to their relevance describing generic medicines policy options. The principal focus was on literature from LMICs. All original studies and reviews from LMICs identified by the search were included except those in which there was a repetition of the findings in other references or where they were outdated. For instance, where a new policy was implemented in a country changing existing generic policies, preference was given to the more recent literature. In total, 79 descriptive peer-reviewed studies for narrative review and 10 interventional studies analysing the effect of the implementation of policies promoting the uptake of generics in LMICs were included.

It is important to note that this review is not focused on a comprehensive review of the literature from high-income countries. Studies and reviews from high-income countries were only included if they best summarised research findings and particular policy evaluations on each of the policy domains.

3. Results

Descriptions of pro-generic medicines policy options and their impact

This section of the review presents information on various generic medicine policies (supply-side and demand-side) with a focus on their use in LMICs, and findings from interventional studies on the impact of such policies on generic medicine uptake.

We provide a brief descriptive overview of the background and contextual issues related to a particular policy domain for LMICs and, if relevant, for high-income countries. Then we provide a table giving the objective of each domain, a list of the policy options for each domain, and a brief description of each policy.

We then provide specific country examples of these policies where information was available. Not every policy option listed in the tables is described in the text. This is due to several factors: a) the policy option is reasonably explained within the table itself; b) we could not find examples in the literature which described the option in sufficient detail; c) we could not find examples that documented the impact of the policies on generic medicines use. Further, measures described in this section are interrelated (e.g., market authorisation, the subject of Section 3.11) and can be influenced by IP provisions found in Section 3.12, such as the so-called *Bolar* provision.

Studies are highlighted in shaded boxes when they document a policy effect on uptake and/or the price of generic medicines.

3.1 Supply side policies

3.1.1 Medicine regulation, market authorisation and quality assurance

MRAs generally have jurisdiction over pre-marketing assessment and evaluation of the quality, safety and efficacy of a medicine, including compliance of manufacturing sites and processes with good manufacturing practice (GMP) standards, assessment and inspection of all components of the pharmaceutical supply chain, maintenance of a register of available products, as well as post-marketing surveillance activities, including random sampling of registered medicines for quality control and pharmacovigilance (Hill and Johnson, 2004). Other pharmaceutical legislative actions with respect to regulation include differential market authorisation fees (allowing generic producers to benefit from preferential administrative costs in the hope of attracting more generic competition), labelling and a transparent marketing approval process that is documented (see Table 5). National legislation impacts the timing of entry of generic medicines to the market, the process required to gain marketing authorisation, as well as the conditions to withdraw a product from the market.

With the provision of information about the quality of medicines, including generic medicines, MRAs can play an active role in promoting the uptake of generics by increasing

the trust of consumers, patients and healthcare professionals in the quality of the medicines on the market. As described in the country examples below, some MRAs have the authority to identify promotion practices in which manufacturers make false claims about the quality of their products, and can bring action against those who violate regulations.

Table 5 describes the policy options to promote the uptake of generic medicines via regulatory requirements promulgated by national MRAs concerning marketing authorisation and post-marketing surveillance.

Table 5: Policy options to promote the uptake of generics via market authorisation and regulatory requirements.

Objective of the policy	Policy	Definition and brief description of policy options
Reducing the time of market authorisation for generics	Shortening the review time of applications for market authorisation	These policies are intended to encourage market authorisation of generics through shorter data exclusivity periods (where they exist), and/or shorter generic market approval times, which would attract generic manufactures to apply for market authorisation. These measures could include strengthening the administrative processes for granting market authorisation for generic medicines, increasing market authorisation fees for originator medicines, which could be used to improve administrative processes of granting market authorisation for generic medicines.
	<i>Bolar</i> provision	This is the early use (i.e., an exemption from patent infringement) by a generic manufacturer of a patented product in order to develop a generic version of an originator product. The time before patent expiry would be used to develop the generic product and permit speedy market entry once the patent has expired.
Encouraging generic manufacturers to apply for market authorisation	Reducing market authorisation fees	This policy allows generic producers to benefit from preferential administrative costs in the hope of attracting more generic competition.
	Grant exclusivity period to the generic medicine which first enters the market	A market exclusivity right for the first manufacturer of a generic product that enters the market after the expiry of the patent of the originator product would create incentives for generic manufacturers to receive the market exclusivity. Deciding on the exclusivity period is important as there is a trade-off between granting exclusivity and increasing competition.
Reducing	Labelling of generic	Requiring that all product labels and packages

information asymmetry	medicines	include the INN, and that it is clearly visible, enables users to identify products that contain the same active ingredient.
Ensuring the quality of generic products	Monitoring of good manufacturing practice (GMP)	National or international monitoring scheme to ensure GMP that would aim at streamlining market approval processes and ensure adherence to regulation nationally and internationally. The pre-qualification programme of the World Health Organization is an international effort to ensure GMP of products.
	Publication of inspection reports and lists of approved generic equivalents (i.e., US FDA Orange Book)	More transparency in the market authorisation and quality assurance is thought to increase the trust of health professionals and consumers in generic medicines.
	Post-market surveillance	Monitoring quality of medicines after granting market authorisation is aimed at detecting substandard products, whether originator or generic.
	Sanctions for false quality claims	MRA puts sanctions on those who promote false quality claims (for instance, that the originator product is of superior quality). This is intended to prevent others from using undue promotion and provide consumers with trustworthy information.
	Surveys of health providers, medicines dispensers and sellers and consumers	Regular analysis of the perception of generic medicine quality is intended to support governments to design and implement policies to increase quality of generic medicines and their perception.
	Therapeutic equivalence	Defining for which medicines demonstration of bioequivalence is required in order to obtain market authorisation is important. Proof of therapeutic equivalence would increase trust in the effectiveness of generic medicines.

3.1.1.1 Low- and middle-income countries

Examples of regulatory actions related to market authorisation and regulation to promote the uptake of generic medicines in LMICs are described.

Reducing the time of market authorisation

a) Shorter market approval times for generic medicines

Regulatory measures are in place in a number of LMICs to encourage market authorisation of generics through shorter approval times for generics. For instance, in Brazil, generic market authorisation is required to occur in six to eight months, compared to eight to 14 months for originator products. In Colombia, approval times are three months (generics) versus six months for originators (Homedes and Ugalde, 2005). Argentina, Brazil, Chile and Venezuela also have lower market authorisation fees for generics. Furthermore, some countries have organised a regional cooperation capacity for medicines regulatory authorities. This is the case in the Caribbean (see Text Box 1).

b) The early application by a generic manufacturer for a licence to develop a generic version of an originator product still under patent

The so-called “Bolar” provision (named after the corresponding US legislation) is the early use (i.e., an exemption from patent infringement) by a generic manufacturer of a patented product in order to develop a generic version of an originator product still under patent. (This is permitted by Trade-Related Aspects of Intellectual Property Rights [TRIPS] Agreement Article 30, TRIPS 1994.) In Mexico, legal reforms allow generic manufacturers to seek market authorisation for a medicine under patent three years prior to the expiration of the patent in order to conduct the necessary studies, tests and experimental production. Even though the market authorisation is only granted once the patent expires, the objective is to shorten the time required for the roll-out of production of the generic product (Moise and Docteur, 2007). In Argentina, in the case of a product or process protected by patent, any third party may use the invention prior to its patent expiration in order to obtain the information required for the approval of a product or process by the MRA.

Ensuring quality of generic medicines

a) Publication of inspections reports

The programme for the rational use of medicines in Delhi started in 1994 to increase trust in the quality of generic medicines. Health facilities draw medicine samples and have them tested centrally. Between July 2000 and July 2002, only 20 out of 3529 samples were found to be of sub-standard quality. The wide dissemination of these results helped to increase confidence in generics as evidenced by a decline in concerns expressed about generic quality (Chaudhury et al., 2005).

b) Demonstration of therapeutic equivalence as a requirement for market authorisation

In Latin America, the regulatory regimes for generic medicines are varied (Gonzalez et al., 2008). Brazil and Mexico had schemes oriented towards a demonstration of therapeutic equivalence and this restricts generic substitution⁷ to products allowed in lists of authorised competing medicines, prescribed by their INN names and with distinctive labels (Gonzalez et al., 2008). In Mexico, from 2010 all registered medicines (except originator products) need to demonstrate therapeutic equivalence (Gonzalez-Pier and Barraza-Llorens, 2011). Panama and Venezuela are in the process of designing and implementing a similar process. Other

⁷ In general, generic substitution is a process whereby dispensers of medicines can override the prescription of a doctor and dispense generics even when the doctor has specifically written a prescription for a branded product. It is to be distinguished from “INN prescribing” when a doctor prescribes a medicine using the generic name of its active ingredient.

countries (Chile, Ecuador and Peru) do not have requirements for bioequivalence (Gonzalez-Pier and Barraza-Llorens, 2011).

3.1.1.2 High-income countries

USA example

Here we have used the US Food and Drug Administration (FDA) as an example of a regulatory authority in a high-income country playing an active role in promoting generic penetration, as soon as a patent expires, by reducing the time for market authorisation of generics.

The generic medicines landscape in the US is shaped by Public Law 98-147 of 1984 (referred to hereafter as the Hatch-Waxman Act), which attempts to balance the interests of the generic and originator companies. The principal methods for facilitating faster market access for generics are the ability of a manufacturer to submit an Abbreviated New Drug Application (ANDA) demonstrating bioequivalence without the need to replicate original clinical tests, the application of the Bolar provision mentioned above, and a 180-day market exclusivity right for the first manufacturer (Nightingale and Morrison, 1987; Mrazek and Frank, 2004).

Research suggests that the policies in the US promoting the use of generic medicines has reduced the delay between patent expiry and generic product entry to market from more than three years to less than three months for high revenue medicines. Based on countable units (tablets or capsules), uptake of generic medicines have increased from 19% of the total US pharmaceutical market by volume in 1984, to 56% in 2005 (US Congressional Budget Office, 1998; Generic Pharmaceutical Association, 2005) to over 80% in 2011 (Kaplan, Wirtz and Stephens, 2013).

Two other factors unrelated to market authorisation seem to be key to successful generic penetration in the US:

- i) the pressure by Medicaid and private health insurers wanting to contain costs through prescribing and dispensing only generics; and
- ii) state laws requiring generic substitution. However, although significant generic market coverage by volume has been achieved in the US, despite having more than half of the market volume in generic medicines, the market share by value was slightly more than 10% (Generic Pharmaceutical Association, 2005).

The FDA actively promotes the quality of generics with, for example, the widely distributed “Myths and Facts about Generics” article (FDA, 1999). In a wider sense, the FDA has also brought action against manufacturing companies misrepresenting a patented product’s benefits, as was seen with the US\$430 million fine against the producer of Neurontin® (gabapentin) [FDA, 2004]. Furthermore, scientific publications have also been active in combating instances of malpractice by manufacturers of originator products that misrepresented the benefits of their products over generics. In what was known as the “Levothyroxine (Synthroid®) scandal”, the producer of Synthroid® suppressed the publication of data proving the equivalence of generic products, so that Synthroid® would

continue to be deemed therapeutically superior. Once it was evident that data had been purposefully withheld, the *Journal of the American Medical Association* published the article exactly as it would have appeared several years earlier had the researchers been allowed to make their findings known in order to highlight the manufacturer's unethical behaviour (Rennie, 1997; Dong et al., 1997).

The “balance” aimed for in the Hatch-Waxman legislation can be undermined by settlements between originator and generic companies. Originator companies can delay generic competition by agreeing to pay a generic competitor to hold its competing product off the market for a certain period of time (called “pay for delay”). The US Federal Trade Commission has viewed these settlements as anti-competitive, arguing they deprive consumers of lower-cost medicines that might otherwise be available much sooner (US Federal Trade Commission, 2009). Significantly, in the US courts have determined that even though a generic producer who is first to market in the US has a six month “window” of market exclusivity, this does not preclude competition from a generic version developed by the originator company (US Federal Trade Commission, 2009). This practice has generated increasing controversy, with generic companies contending that such “authorised” generics undermine the goals of the Hatch-Waxman Act, and originator companies defending them as pro-competitive and consistent with the Act.⁴

On June 7, 2013, the US Supreme Court decided that the lower courts can hear suits against pharmaceutical patent holders who pay generic manufacturers not to produce a generic version of an originator until after the patent term expires. The US Supreme Court has thus held that these pay-for-delay settlements are not automatically anti-competitive but they will receive greater federal scrutiny (See www.nytimes.com/2013/06/18/business/supreme-court-says-drug-makers-can-be-sued-over-pay-for-delay-deals.html?_r=0).

Europe example

Amongst the supply-side measures of European countries, some have introduced an abridged (fast track) medicine marketing application process and Bolar-type provisions. Regulations on the marketing authorisation of the EU Member States have been harmonised, but national common practice and case law application still lead to differences across countries (Garattini and Tediosi, 2000). It is difficult to assess the impact of these single measures on generic uptake. Some European countries have significant generic medicine market share but this might be attributed to a range of measures.

The European Commission has also looked at pay-for-delay patent settlements. A monitoring exercise was launched in the light of the findings of a competition inquiry into the pharmaceutical sector (European Commission, Competition Directorate-General, 2009). The sector inquiry highlighted the risk that certain types of patent settlements may have

⁴ There are other ways in which generics can be delayed. One company (Actavis) devised a plan to effectively remove its twice-daily Alzheimer's disease treatment from the market just prior to the availability of a generic alternative, thereby forcing patients who take this drug either to discontinue taking it or switch to the newer once-a-day Actavis version, which has exclusive sales rights until 2029. The unique nature of this patient population—Alzheimer's patients with moderate-to-severe dementia—makes it likely that a switch from the twice-daily medicine to the once-daily version would be a permanent one for practical purposes, as providers, patients, and families would be reluctant to switch back to twice-a-day therapy even if they believed that it represented a better value. http://aspe.hhs.gov/sp/reports/2015/GenericMarket/ib_GenericMarket.pdf

negative effects on European consumers by depriving them of a broader choice of medicines at lower prices and indicated that the Commission could monitor such patent settlements. In June 2013, the European Commission (EC) fined Danish pharmaceutical company Lundbeck as well as eight other generic manufacturers for delaying market entry of the generic versions of Lundbeck's antidepressant citalopram (Ngo, 2013).

Text Box 1: Regional cooperation in the Eastern Caribbean

The Organisation of Eastern Caribbean States (OECS) is comprised of Antigua and Barbuda, Dominica, Grenada, Montserrat, St. Kitts and Nevis, St. Lucia, St. Vincent, the Grenadines, the British Virgin Islands and Anguilla. This organisation is an interesting case study of regional cooperation amongst countries with relatively small populations and economies that therefore have limited individual regulatory capacities and small markets to serve. (See OECS Secretariat, 2008.)

Several aspects of generic medicines policies have been considered jointly by the governments involved:

- The Caribbean Regional Drug Testing Laboratory in Jamaica undertakes product testing analysis for Caribbean countries on government requests and for a fee for the private sector.
- The same quality assurance standards are enforced: 1) the standards of the country of origin; and 2) either the British Pharmacopeia or the US Pharmacopeia standard.
- The label of every unit must contain the expiry date of the product. Manufacturers can be asked to provide certificates of analyses on microbiological and pharmacological tests or bioequivalence data within a month of request by the Pharmaceutical Procurement Service (Burnett, 2003).

3.1.1.3 Pre-qualification for regulating the quality of generic medicines

In LMICs, the challenge of implementing generic policies is partly attributed to the constraints in demonstrating medicine quality. A key issue is the presence of substandard products on the market (WHO, 1997a). In a study undertaken more than a decade ago in Nigeria and Thailand, 36.5% of sample medicines were below pharmacopoeial standards. This was mainly attributed to poor manufacturing practices (Shakoor et al., 1997). The WHO Prequalification Programme, set up in 2001, is a service to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria, tuberculosis and reproductive health. The WHO list of prequalified medicines is a tool for both national and international agencies and organisations involved in bulk purchasing of medicines. Prequalification entails the assessment of the quality standards, technical competence and financial viability of a supplier, so that countries purchasing from a pre-approved supplier can rely on the quality and reliability of this supply, as well as containing costs of administration since the market authorisation processes do not need to be duplicated (Burnett, 2003).

In the early 2000s purchasing via prequalified systems in LMICs remained infrequent even though this system was proven to deliver quality antiretroviral (ARV) medicines to countries with limited monitoring systems in place (Kumarasamy, 2004; Wainberg, 2005).

The situation has changed dramatically. The Global Fund to Fight AIDS, Tuberculosis and Malaria has a strict quality assurance policy and maintains lists for ARV, tuberculosis and malaria products that are either prequalified by the WHO Prequalification Programme and/or approved or authorised for use by a stringent MRA (such as the US, EU or Japan) and/or are reviewed by an expert review panel that does a quality risk/benefit assessment of a product not yet qualified by the WHO (Global Fund, 2010).

3.1.2 Trade and intellectual property policy

There is a large amount of literature devoted to IP, trade and medicines written from the point of view of the US, EU and middle-income-emerging markets, such as India and Brazil. (A review of this literature is beyond the scope of this report.) This is part of the much larger debate about IP rights and access to medicines, encompassing economic, scientific and public health issues.

Primarily, international framework agreements, such as the TRIPS Agreement, determine the way that pharmaceutical products are protected by patent law for countries that are members of the World Trade Organization (WTO). The 2005 date of TRIPS compliance applies to most LMICs that are WTO members. This includes critical large-scale generic manufacturing countries, such as India, Brazil and China.

Table 6 presents policy options related to trade and IP that have been described in the literature identified for this report.

Table 6: Policy options related to trade and intellectual property which aim to balance patent protection with increasing generic medicines uptake.

Policy objective	Policy	Definition and brief description of policy options
Protection against undue monopoly created by use of patent	Pre-grant opposition	Providing third parties the ability to interfere if there is justified reason that a patent should not be granted (e.g., for patents that do not represent new and useful innovations).
	Definition of what are patentable products	Narrowing the definition of what medicines can be patented by disallowing the practice of evergreening (patent coverage for “new uses” of existing, already patented substances).
Protection against undue barriers to entry of generic medicines into the market	Transparency of patent information	Making sure information on patent expiry is transparent and available to generic manufacturers.

Measures to ensure medicine affordability for the public	Compulsory licensing	Permission granted to produce the patented product by a third party without consent of the patent owner, under certain circumstances (TRIPS Article 31). ⁸
	Voluntary licensing	Permission granted by the patent owner to third party in order to produce a patented product.
	<i>Bolar</i> provisions	See also description in Table 5.
	Parallel importation	Providing for a principle of “exhaustion” of patent rights upon the first sale by the patent owner can allow broad parallel importation so that a government can procure quality, affordable patented medicines from other countries within the area where exhaustion of rights is deemed to occur after first sale.

3.1.2.1 Impact of free trade agreements on access to generics medicines in LMICs

Manufacturing, using, selling, importing and offering to sell copies of patented medicines in most LMICs without permission from the patent owner is legally no longer allowed, but is allowed in the 49 least-developed countries (LDCs). The WHO Model EML can be used as a policy tool designed to help governments decide how to spend limited government budgets. Most medicines on the WHO Model EML are off-patent (Attaran, 2004), so strong patent protection only has an impact on access to new and future medicines that appear on national EMLs. However, a recent shift in the model list now provides for more high-cost on-patent medicines as essential. It remains to be seen how governments will afford them.

Countries, such as Brazil, India, Thailand and China, are in a challenging situation with regards to generic medicines. They have the capacity to manufacture medicines and manufacturers often have ties to pharmaceutical companies in the US and EU. Thus, these companies wish to have strong in-country IP protection. At the same time, these countries still experience income inequalities; however, they are viewed as emerging economies with a rich middle class and elites representing lucrative markets, so are excluded from differential prices offered to LDCs. National policies need to provide for TRIPS flexibilities that would enhance, not bar, promotion of generic medicines use. For instance, in 2008 the Philippines signed amendments to their laws, which included IP provisions, such as compulsory licensing, a Bolar provision, and the permitting of parallel importation (Republic of Philippine Act No. 5902, 2008).

⁸ There are additional mechanisms, not detailed here, involving technology transfer agreements as a means to regulate price. The Meningitis Vaccine Project (<http://www.meningvax.org/developing-conjugate-vaccine.php>) created a structure whereby a vaccine manufacturer accepted technology transfer was willing to make a conjugate vaccine with a stipulated final product with a stipulated price ceiling.

Trade agreements amongst LMICs are rare. Trade agreements between high-income countries and LMICs do, however, play an important role on national generic policies in LMICs and may act as barriers to entry of generic medicines. That is, the bilateral trade agreement between a high-income country and an LMIC may impact access in the LMIC. The US and EU have entered into a series of free trade agreements (FTAs) with several LMICs. The EU has, or is presently negotiating, agreements with trading blocs, like Central America, MERCOSUR, the Andean Community and with countries, such as India, Thailand, South Korea, Canada, Ukraine and Moldova. These bilateral agreements often contain “TRIPS-plus” measures. There are two kinds of these measures:

- Areas that are already covered by a WTO agreement like TRIPS and are simply strengthened (e.g., by reducing the burden on patent applicants, such as expanding the scope of patentability, lowering patent eligibility standards and reducing fees).
- New areas of coverage beyond the original scope of the WTO and TRIPS. These latter TRIPS-plus measures include limits on the use of compulsory licences, data exclusivity, patent linkage, patent term extensions for delayed patent approval/marketing authorisation and additional IP enforcement mechanisms. Several of these are discussed below and impact both high-income countries and LMICs.

Data exclusivity

Data exclusivity refers to a practice whereby, for a fixed period of time, MRAs do not allow the market authorisation files of the originator to be used to authorise marketing of a therapeutically equivalent generic version of that medicine. It is important to understand that data exclusivity is unrelated to patents. In countries where there is no patent for a given medicine and data exclusivity is granted, this will provide a “patent-like” monopoly for a set period (e.g., 10 years in the EU). During the data exclusivity period, if another company wants to seek marketing authorisation for a similar version of a medicine or a vaccine, it has to generate and submit its own test data. The barrier is that the associated cost and time delays act as a strong disincentive to price-lowering competition. Further, there may be ethical barriers to redoing clinical trials.

The US Hatch-Waxman Act contains data exclusivity provisions, as do some bilateral and regional FTAs that have been negotiated, or are being negotiated, by the US with both high-income countries and LMICs (e.g., Singapore FTA, Thailand FTA, Chile FTA, Morocco FTA, Korea FTA) [Timmermans, 2005]. With regard to the India-Japan FTA, Japan was pressing for data exclusivity (DNA India, 2010). Like the FTA with Japan, India was also negotiating FTAs with the EU, which is pressing for data exclusivity (Moszynski, 2010). As of the time this report was written, this FTA has still not been concluded and data exclusivity is one stumbling-block. The EU is negotiating data exclusivity as part of all FTAs with trading blocks like Central America, MERCOSUR, the Andean Community, and with countries such as India, Thailand, South Korea, Canada, Ukraine and Moldova.

In many countries, pharmaceutical companies may not have considered the market sufficiently valuable to justify the expense and administrative cost of securing patents. In that case, the introduction of data exclusivity laws may bring into exclusivity medicines that would otherwise be open to generic competition.

Patent linkage

In some bilateral trade agreements, there are 'linkages' between patents and medicine regulations that can hinder generic uptake in LMICs. For instance, certain bilateral FTAs with the US stipulate that a country's MRA may not approve a generic medicine for marketing while the brand name medicine (originator) is under patent (Correa, 2006; Jorge, 2007). This means that the approval process (which may take some months) must take place after the patent has expired, so there will be a time period where the originator medicine will continue to maintain market exclusivity post-patent expiry, which can negatively affect the access to generic medicines.

This patent linkage is not universally applied and many countries do not mandate it. However, certain countries have already created forms of patent linkage schemes (e.g., Hungary) that impose a requirement on generic companies to make a statement about the patent status as part of a regulatory dossier submission, and will not approve a generics submission without it. Slovakia requires that market authorisation given to a generic medicine will be suspended until patent expiry (EGA Report, 2008). This becomes a barrier to generic market entry. This is a practice that has been strongly rejected by the EU and is prohibited in the EU through Directive 01/83/EC. In 2012, the European Commission issued an opinion calling on Italy to remove its patent "linkage" provisions (Taylor 2012).

Patent term extensions

A patent term extension can be granted when various delays (e.g., in the patent application approval process) reduces the amount of time that a patent owner can effectively enforce a patented product once the product has received marketing authorisation. The US and the EU have negotiated FTAs that contain patent term extensions when a delay in the granting of a patent exceeds a certain amount of time (four to five years). Moreover, these agreements grant extensions to "compensate" for "unreasonable delay" in the granting of regulatory marketing approval.

Patent term extension provisions have been included in US and EU FTAs with various LMICs. One can expect that patent term extension provisions will be relied on by various foreign pharmaceutical industries to lengthen the effective life of the patents on their products. Patent extensions to "compensate" for delays in patent registration and/or market authorisation may likely delay the market entry of generics and hence competition.

There are some evidence-based interventional studies on the impact of IP on access to, and uptake of, generic medicines in LMICs. (See below) These relate primarily to the FTAs mentioned above between the US and EU and one other country (bilateral) as opposed to multilateral agreements. Bilateral agreements seem quicker to conclude and pertain to subject areas where there is no consensus amongst WTO Members.

Ford et al. (2007) used a time series analysis of antiretroviral (ARV) prices before and after key policy implementation in Brazil and Thailand to create case studies of ARV prices in these countries. The Brazilian experience shows that negotiations with pharmaceutical companies alone have largely failed to secure optimal prices. By relying on this strategy, Brazil ended up paying up to four times more for second-line, patent-protected ARV medicines as compared with prices available internationally where patents did not exist or were not enforced (Ford et al., 2007). As most LMICs do not currently have adequate pharmaceutical manufacturing capacity, compulsory licences have important international repercussions.

Beall et al. (2015) constructed a case-study database of compulsory licensing activity for ARVs and compared compulsory licence prices to those in the World Health Organization's (WHO's) Global Price Reporting Mechanism and the Global Fund's Price and Quality Reporting Tool. Thirty compulsory licence cases were analysed with 673 comparable procurements from WHO and Global Fund data. They found that compulsory licence prices exceeded the median international procurement prices in 19 of the 30 case studies, often with a price gap of more than 25%. They concluded that "compulsory licensing often delivered suboptimal value when compared to the alternative of international procurement, especially when used by low-income countries to manufacture medicines locally."

Akaleephan et al. (2009) attempted to quantify the impact of the US-Thailand FTA on medicines access. According to a simulation model, IP provisions of this FTA were estimated to delay the uptake of generics and increase medicine expense by extending market exclusivity, with the cumulative potential expense projected to be \$US6.2-63.5 million for the first year to \$US 806- 5,215.8 million in the tenth year.

These findings coincide with a study by Kessomboom et al. (2010) who created an econometric scenario model of the impact of the US-Thailand FTA on Thailand's pharmaceutical market and medicines access under various assumptions of enhanced market exclusivity for different originator's active ingredients. Prices were expected to increase due to the delay in generic entry. It is relevant to note that negotiations on this FTA have been suspended since 2006.

A 2009 study by IFARMA also used an econometric scenario model to estimate the impact of the proposed EU-Andean FTA on access to medicines in Colombia. The study found that introduction of the two measures on data exclusivity and patent term extensions would lead to an increase of US\$756 million in Colombia's total pharmaceutical expenditure (at present value, PV) in 2025, and at the same time, a decrease in consumption of 10%. See also IFARMA (2010) using identical methods to look at the impact of the proposed EU-Andean Trade Agreement on access to medicines in Peru.

Supakankunti et al. (2001) looked at the actual impact of TRIPS on Thailand's pharmaceutical sector. They analysed data on foreign direct investment, total medicine supply, gross national income per capita, total medicine value, and price before and after 1992. The price of originator medicines did not change due to the imposition of TRIPS. However, there were few data available for generic medicines.

Overly aggressive IP enforcement: a threat to generic competition

Far-reaching IP enforcement potentially ‘chills’ generic competition because it creates a high level of legal uncertainty for generic competitors. Moreover, enforcement can also obstruct the import, transit or export of legitimate generic medicines. For example, customs authorities in the Netherlands have seized a substantial number of consignments of generic medicines from India in transit through the Netherlands. In October 2008 at Schiphol airport (the Netherlands), a consignment of clopidogrel from India destined for Colombia was seized on the ground of infringement of one or more patents alleged to be valid and enforceable in the Netherlands and owned or licensed by Sanofi-Aventis. In another example, in November 2008 at Schiphol airport, a consignment of abacavir from India, purchased on behalf of UNITAID and destined for Nigeria, was seized on the ground of infringement of one or more patents alleged to be valid and enforceable in the Netherlands and owned or licensed by Glaxo. In effect, the ‘fiction’ is that generic medicines actually manufactured in India and in transit to third countries were treated as if they had been manufactured in the Netherlands. Generic companies may face expensive and time-consuming litigation, be less able to challenge frivolous patents and may see their medicines wrongfully seized. Scaled-up enforcement provisions can therefore expand the monopoly power of IPR holders, undermining the balance between IP protection and public health.

3.1.3 Generic competition policy

The generic medicines industry can compete with the originator industry provided that the generic industry is assured of having a high share of the pharmaceutical market and if price differentials are maintained between originator and generic medicines. In countries lacking a competitive market, an increased volume demand for generic medicines is often created through public sector procurement by donor funds, price negotiations by intermediaries and differential pricing policies (Waning et al. 2009; Pan America Health Organization, 2005). Competition has been examined by analysing the behaviour of brand and generic products after expiration of a patent, but there is little research into the patterns of competition amongst generic firms themselves after an originator’s patent expires (Kanavos et al., 2008).

This topic is the subject of a separate review in this series (Promoting competition in the pharmaceutical market, WHO/HAI, 2011).

Table 7 lists policy options described in the literature which aim to increase generic competition.

Table 7: Policy options related to competition and generic medicines.

Objective of the policy	Policy	Definition and brief description of policy options
Increase competition of generic products on the market	Increasing the number of generic product entries	Ensuring a sufficient number of generic alternatives from different manufacturers.
	Therapeutic substitute products as a strategy to increase therapeutic competition	Different active pharmaceutical ingredients but with similar therapeutic effect may help lower prices.
	Price information transparency	Through standardised price comparison, purchasers are able to identify the lowest price per unit for the same quality product. Apart from increasing competition, the rationale is to decrease information asymmetry.
	Collectively managing IP: patent pools	Makers of generics join patent pools to receive licences to a package of IP needed to make the medicines. This creates “downstream” competition.

3.1.3.1 Low- and middle-income countries

It has been argued that in many LMICs, whether or not a generic product succeeds on the market depends less on the number or timing of generic competition *per se* than on the external influence of politics, perceptions, and multinational companies (MNC) on the number of generic competitors. For example, during the years that followed the 1972 Pakistani legislation prohibiting the manufacture, prescription and sale of medicines under a brand, patent or proprietary name, the leading MNCs increased their dominance in the overall market and prices did not fall as expected. In light of these consequences, in 1976 Pakistan discarded these mandatory requirements (Quraeshi, Luqmani and Malhotra, 1983). This created doubt regarding the quality and efficacy of generic medicines that has continued with a continuing hesitancy regarding prescribing generic products and their lack of substitution by pharmacists (Jamshed et al, 2009).

In LMICs, few policies on competition have been documented, especially in the private sector. South Africa introduced a Competition Act which was used effectively by the Treatment Action Campaign as leverage in a campaign for MNCs to issue voluntary licences for a number of ARVs (Treatment Action Campaign, 2002). Additionally, competition amongst licensed generic manufacturers of an on-patent medicine can reduce prices. It is noteworthy that competition is a cross-cutting theme and has been mentioned in relation to other policy domains.

The following policies that impact generic competition were identified from the literature review.

Price information to increase competition

Price competition is likely to require a high level of price information transparency. When the proportion of generics increases, the price difference between originator and generic also increases (Lexchin, 2003). However, pricing information is not shared by manufacturers and wholesalers, and patients do not always know the real or lowest possible retail price of their medication. This so-called information asymmetry is a key factor in maintaining high prices of many medicines.

In the last decade multiple efforts have been made to increase medicines price transparency. For example, Brazil, Colombia and Peru publish retail (patient) prices in on-line databases/price observatories (“banco de precios”) [Ministerio de Protección Social, Republica Colombia, 2010; Ministerio de Salud Peru, 2010].

In Mexico the state-funded consumer organisation publishes prices of a selection of medicines (originator and some generic products) in their monthly electronic consumer information (Mexico Federal Consumer Agency, 2010). Importantly, this information to consumers is by INN and commercial/trade name to enable consumers to compare prices for the same pharmaceutical ingredient. At the international level, the Global Price Reporting Mechanism makes public procurement prices of HIV, tuberculosis and malaria medicines publically available (WHO, 2010a).

Creating a patent pool to increase ‘downstream’ generic competition

A patent pool is a mechanism for the collective management of IPR by creating groups of IPR related to a particular technology (e.g., ARVs) and making them available to generic producers in order to increase ‘downstream’ competition and thus, in principle, lower prices. Recent patent pools have been created to facilitate more systematic transfer of technology and competition (downstream) and/or to promote innovation (upstream). The impact on promoting the market entry of generic medicines of the Medicines Patent Pool (MPP; see ‘t Hoen et al., 2011) has been evaluated. The MPP has just released a five-year study of results that can help inform future discussions and deliberations in the access movement. According to this analysis, the organisation’s licences have saved the international community US\$79 million through lower prices of ARVs, equivalent to one-year of treatment for 625,000 people. In the coming years, it is expected to generate total savings of between USD\$1.18 and 1.4 billion (<http://www.medicinespatentpool.org/progress-and-achievements-report/>).

Creating a patent pool at the national level requires a considerable pharmaceutical market size.

3.1.3.3 High-income countries

Interest in promoting the uptake of generic medicines seems less intense in countries, such as France, Italy and Spain where prices are already regulated (de Joncheere et al., 2002). However, the increasing need to contain prices has encouraged or even pushed high-income countries, such as the European countries, to further exploit the potential of generic policies. This includes encouraging generic competition. (Vogler et al. 2011). Further, a decade ago,

several European countries did not have a sufficient number of generics on the market, so they introduced specific pro-generic policies (Habl et al., 2008). In the following sections, some policy options, particularly with regard to promoting generic competition, are summarised, which have been documented in high-income countries. While in European countries, prices, at least for reimbursed medicines, are regulated (see section 3.1.4.2). With regard to generic medicines competition, various policy elements have been introduced.

Providing a sufficient number of generic alternatives

This first policy option (Table 7) is based on the fact that having a sufficient number of generic medicines on the market is an important prerequisite for generic competition, including price competition. There is extensive good quality evidence from OECD countries, and some evidence from LMICs, that competition can reduce prices for essential medicines. One source of evidence is the large body of studies evaluating the effect of laws that countries have adopted to encourage generic medicine entry and generic competition after patent expiry. There are many studies of the effects of generic competition on prices and market shares of generics in the US following adoption of the Hatch-Waxman Act in 1984 and also studies in Canada, some EU countries, and Australia (WHO/HAI, 2011a).

It is certainly connected to the patent situation and IPRs (see section 3.1.2), but also might involve incentives to the market authorisation holders of generic products to quickly enter to the market (see section 3.1.1). The EU adopted regulations to promote the uptake of generics in 2004 which adopted some similar features as used in the US. See US Congressional Budget Office, (1998) for a summary of research of the effects of generic competition on prices in the US, and Mrazek and Frank (2004) for an EU summary.

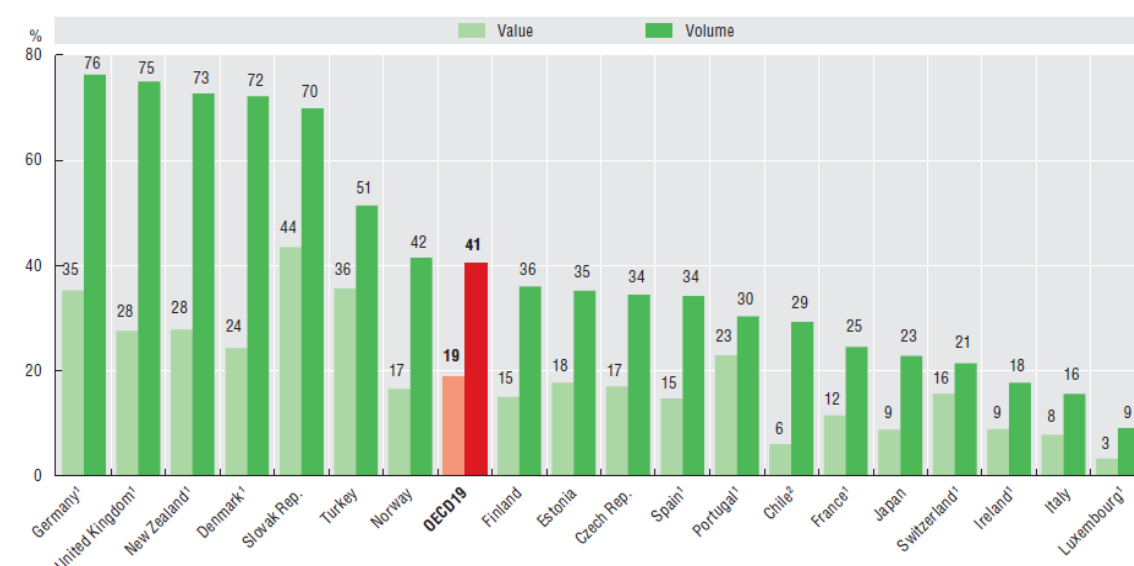
In the 2009 Pharmaceutical Sector Inquiry report (European Commission Competition Directorate-General 2009), the European Commission looked into the issue of a possible distortion of the pharmaceutical sector following instances of delayed market entry of generic medicines, as compared to what might be expected. The European Pharmaceutical Sector Inquiry showed that in 17 EU Member States, generics enter the market at an average price slightly under 80% of the originator's price. After three years, the prices of both the originator and the generics dropped on average to about 75% and 55%, respectively, of the originator's price at generic entry (European Commission, Competition Directorate-General 2009). One study found that for the US market, generic medicines are on average about 85% lower in price than the pre-entry brand-name medicine price (Federal Trade Commission, 2010).

Leopold et al. (2010) studied 30 European countries and confirmed the problem of the lack of generic medicines in small markets. Availability of generics was especially low in the Baltic States, as well as in the Czech Republic, Slovenia, Hungary Bulgaria, Romania and Iceland.

In case of the countries with a smaller population size, the pharmaceutical market might not be attractive enough for the pharmaceutical industry, which can result in availability problems with generic medicines (HMA 2007) and mirrors the situation in many LMICs.

Figure 3 (below) shows the wide variation in the share of generic medicines in the total pharmaceutical market (by volume and value) for various European countries as of 2011.

Figure 3: Generic medicine share (volume and value) for selected European countries (2011).



1. Reimbursed pharmaceutical market.

2. Community pharmacy market.

Source: OECD Health Statistics 2013, <http://dx.doi.org/10.1787/health-data-en>.

Source: OECD Health Statistics 2013, <http://dx.doi.org/10.1787/health-data-en>

Therapeutic substitute medicines as a strategy to increase competition

Even for medicines still on-patent, competitive pressure from close therapeutic substitutes (me-too medicines) can place downward pressure on prices (WHO/HAI 2011a). Various organisations, such as hospitals, social health insurance agencies, ministries of health, health maintenance organisations (HMOs), and pharmacy benefit management companies can negotiate lower prices through competition for formulary listing amongst suppliers of medicines within narrow therapeutic classes of medicines (e.g., beta blockers, statins, selective serotonin reuptake inhibitors) [WHO/HAI 2011a]. This policy has been used in the US, in the internal reference price systems of countries such as Norway, Australia, and New Zealand. See also Section 3.1.4, and in some health insurance systems in LMICs (e.g., Indonesia's social health insurance system for civil servants, called ASKES). Germany is another country with such an approach, clustering even therapeutically similar originator products in its reference price groups (Habl et al, 2008).

3.1.4 Pricing, purchasing and manufacturing policies

A key feature of the generic medicines market in some countries is that the initial investment by the first generic company on the market is rewarded by market exclusivity (Mrazek and Mossialos, 2004, Kanavos et al., 2008). Yet, when originators lose patent protection (and, thus, lose market monopoly), there may not be price competition with generic competitors that enter the market, despite generic prices being lower than the originator price. There is evidence to suggest that originator medicine prices are relatively independent of generic competition, so that these prices may increase rather than decrease post-patent expiry. This is a phenomenon known as the 'generics paradox' which predicts that a higher penetration by generics would not necessarily lead to a reduction in originator prices (Kanavos et al, 2008).

Price controls of various kinds are used by government agencies to ensure that prices are kept at a level deemed affordable and lower than would be set by originator companies acting on their own (Stigler, 1998). There are different policies and methods for regulating medicines prices that have effects on the uptake of generic medicines. Such policies may address different price types, such as price control at the ex-factory price level, regulation of medicine prices in the supply chain (regulation of distribution margins) and taxes and duties, which also impacts the final price of a medicine.

Table 8: Policy options to regulate generic medicine prices and public purchasing.

Objective of the policy	Policy	Definition and brief description of policy options
Price regulation	Setting generic medicines prices relative to prices of originator products	The price of generic medicines is set in relation to originator products (e.g., no more than 60% of original price).
	Internal reference pricing (IRP)	A method to compare prices of pharmaceuticals in a country with the price of identical pharmaceuticals (ATC 5 level) or similar products (ATC 4 level), or even with therapeutically equivalent treatment (not necessarily a pharmaceutical) in a country. Often performed in the course of a reference price system (Vogler et al., 2006).
	Originator price control	Setting originator product prices, which could have some effect on generic prices through various mechanisms (e.g., external reference pricing, value-based pricing) as generic prices are often set in relation to these originator product prices (see below).
	External reference pricing (ERP)	The practice of comparing medicine prices across countries. There are various methods applied and different comparator country “baskets” [WHO/HAI review on ERP (2011c), WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies (2013)]
	Cost-plus pricing	The cost-plus pricing procedure takes the production cost, R&D cost and other costs, such as promotional expenses, into account when setting the price of a medicine. Although this is not common in Europe anymore, some LMICs still use this mechanism.
Regulating profits	Regulating mark-ups in the supply chain	The government defines the mark-up (usually a percentage) which can be added at various stages of the pharmaceutical distribution chain (e.g., for distributors, wholesalers, retailers) to cover costs (e.g., retail pharmacies are permitted a maximum mark-up of 20%

		on the wholesale selling price). In order to regulate mark-ups, governments require information not only about prices, but also price components and the cost of providing services by those in the supply chain. The United Kingdom's government has used this in the past, but has replaced it with value-based pricing.
Indirect price controls	Government subsidies	Subsidies could include reducing input costs for local factors of production, such as duties, tariffs and taxes.
Decrease information asymmetries	Publication of generic medicine prices (on packages or posters in dispensaries or other public places)	With more price transparency, the consumer can make more informed decision about price and offered products.
Purchasing options	Open tender	Distributors and suppliers submit their bid to the potential buyer. The buyer compares the price and specifications of the product and selects the offer which provides the best value for the price offered. Advantages are increased price transparency and the certainty of demand for the supplier once the buyer decides which supplier is awarded the tender.
	Restricted tender	In restricted tenders, only suppliers which are authorised prior to the tender can participate. This may help to eliminate the problem of suppliers submitting bids for cheap products that are not authorised by the local MRS (Ali, 2010), or are of poor quality.
	Pooled procurement	Joint purchasing of medicines to achieve economies of scale (e.g., across various countries within a region, various agencies within a country, or large global organisations).
	Tender systems for purchasing ambulatory care medicines	Procedure in which the purchaser invites marketing authorisation holders of generic products to submit offers for a specific active ingredient.
Manufacturing	Joint manufacturing	Small countries form regional cooperative and regulatory ventures for the manufacture of generics in an attempt to achieve economies of scale.

3.1.4.1 Low- and middle-income countries

Some countries lack price controls. For example, Thailand does not have a national medicines pricing policy (Sooksriwong et al., 2009) but does employ some policies to indirectly control medicine prices and expenditures in the public sector (e.g., a national EML and a National Health Insurance Scheme). However, there is currently no policy to regulate medicine prices in the public or private sectors, whether it is a procurement or selling price. In Thailand, different prices for the same generic medicine are found (Sooksriwong et al., 2009). Originator medicines are priced well above international benchmark prices.

a) Internal reference pricing

Internal reference pricing is a method to compare prices of medicines in a country with the price of identical medicines, similar products, or even with therapeutic equivalent treatments (not necessarily a pharmaceutical) in that country.

Rothberg et al. (2004) measured the impact of a South African internal reference pricing programme covering items for which appropriate generic equivalents were available. The programme had an immediate effect by lowering the rate of inflation of medicine prices as a result of switching from originator or branded products to generic medicines, or switching from higher-priced to lower-priced generic equivalents. There were substantial savings for insurance programmes.

Text Box 2. South Africa pricing policies (Gray, 2009)

A number of medicine pricing policies have been attempted, with more or less success. Manufacturer price control measures are in place, amongst them a single exit price (SEP) which is the only price at which the manufacturers can sell the medicine to any entity other than the state. A single, flat distribution or dispensing fee was intended to control costs in the medicine distribution chain; however, setting the dispensing fee was challenging. A value-added tax on medicines is in place. The use of various strategies for bulk purchase tenders is limited to the public sector, and no regional procurement initiatives have yet been attempted. Although TRIPS flexibilities such as the means to issue compulsory licences and allow parallel importation are in place, these have not been used. On the demand-side, co-payments are routinely used in the private sector which encourage generic medicines uptake. However, there is some evidence that the impact of the savings from generic medicines was reduced due to the fact that doctors tend to prescribe newly launched, high-priced medicines instead of generic medicines. Gray further notes that “The extent to which the various pricing interventions have exerted downward pressure on medicines prices (and/or on medicines expenditure) in South Africa’s private sector is challenging to depict.”

b) Regulating originator product prices and its impact on generics

In Mexico, price regulation applies to patented medicines via an external reference pricing mechanism. Originator products that have lost their patent protection (after October 2004) are excluded from governmental price controls, as are all existing generic products as it has been argued that the prospect of price competition eliminates the rationale for price regulation (Moise and Docteur, 2007). The Mexican price control system is very weak as a price control mechanism for patented products as it remains largely voluntary. The fact that

most, if not all, manufacturers choose to participate suggests that the system is one that is perceived by manufacturers as being ineffective (Moise and Docteur, 2007).

In June 2008, the Philippines signed its current medicine price control policy (i.e., the setting of a maximum retail price for a list of medicines which falls under this policy (Universally Accessible Cheaper and Quality Medicine Act of 2008). It would appear that branded, on-patent medicines of MNCs were the main target of the Philippine price control laws (Oplas, 2009). This price control may make branded medicines become more affordable to poor people. This, in itself, is not a bad thing. However, it can be argued that MNCs will be unintentionally helping a portion of the niche market of local (and generic) producers and if local generic producers cannot cope with further drastic price reductions, then they will be forced to either stop marketing some products, lose market share or maybe close up. The Philippines global market share is only about 0.5% or less of the total MNCs revenues on average. MNCs therefore can afford to endure temporary profit reductions from selling some of their price-controlled medicines at lower prices. Such losses can be recouped from revenues elsewhere, especially in more wealthy countries.

c) Other price controls

India has a long tradition of regulating both the quality and price of medicines. There is a Central Drugs Standard Control Organization (CDSCO) headed by the Drugs Controller General of India (DCGI) with deputy medicines controllers in the various regions. In addition, the larger states have individual medicines control offices headed by respective state medicine controllers. Medicine prices are controlled for selected medicines by the National Pharmaceutical Pricing Authority (NPPA) under the Ministry of Chemicals and Fertilizers.

Until 2012, India's price control was based on a maximum retail price (MRP or sales price) (Tripathi et al., 2005) determined using a cost-plus formula, where the retail price is calculated as the cost of production (e.g., materials, packaging) plus post-manufacturing costs including trade margins and the manufacturer's margin (Kotwani and Levison, 2007; WHO and HAI, 2011b).

In November 2012, India approved a new medicine pricing policy designed to increase the number of essential medicines under price control (WHO, 2012). The legislation is designed to curtail prices of costly brands sold by domestic and international manufacturers. Under the new policy (which is essentially an internal reference pricing system), the ceiling price of a particular medicine would be calculated by taking the average of the prices of all the brands that have more than 1% market share. Of the new medicines that will come under the new pricing policy, 348 (including medicines for cancer and HIV) are defined as essential.

In China, hospitals can have a monopoly both on purchasing medicines and on supplying medical services. This means that hospitals, whose finances are heavily reliant on the sale of medicines, have no incentive to reduce their prices. Instead, hospitals simply pass on the price cuts to their suppliers (manufacturers and distributors), which are being faced with increasing financial difficulties. To alleviate the burden of medical expenses on society and ensure the implementation of the medical insurance scheme, the retail prices of

pharmaceutical products qualified for the programme and included in the National Basic Medical Insurance Scheme Drug Catalogue are regulated. The pricing mechanism is based on three considerations when setting the maximum retail price: i) production cost; ii) a wholesaler price spread set by the government; and iii) the prices of comparable products on the market. Interestingly, it has been argued that there are not enough human and technical resources to verify the production costs reported by the manufacturers; therefore, prices are set at the level wanted by manufacturers (Tang et al., 2006). This would indicate a weakness in the way it is implemented, rather than the design.

A study of the Sudanese National Medicines and Poisons Board's medicine pricing mechanism was conducted in 2008. With respect to the Board's ability to control prices of imported medicines, the study found that, of those medicines whose prices were approved by the NMPB and over 10 times an international reference price, over 70% were generics. The authors of this study concluded that the "... current pricing system is of limited benefit in controlling medicine prices in Sudan" (Ali and Yahia, 2012).

d) Government subsidies

There is sparse literature on the use of government subsidies to generic manufacturers in LMICs. In upper-income countries, government subsidies to local manufacturers are not uncommon. Between 2010 and 2012, Taiwan's Ministry of Economic Affairs granted US\$7.6 billion in subsidies to six local pharmaceutical companies that produce generic medicines. This, in turn, spawned investment totalling NT\$430 million in the industry (Yi-jing, 2011).

Purchasing

a) Public procurement of generic medicines

Some countries have introduced sealed-bid, or even open-bid, competitive tendering to supply specific generic medicines to the public sector through insurance or reimbursement systems. These proposals represent an opportunity to encourage the promotion of generic medicines and price generics closer to the marginal cost of production—a process that could be subsequently applied to originator patented medicines in a therapeutic class with many competitors. The winner of the tender may, or may not, be the company with the generic version, although it usually is.

Unfortunately, papers in peer-reviewed journals about medicine tenders in LMICs are rare, and papers about tendering of generic medicines are almost non-existent.

Milanovic et al. (2004) described the experience of purchasing medicines by the largest hospital in Serbia via general tendering. This was an aggregate tender for various commodities (including medicines) of about €3 million. The whole tender procedure (including other goods) took three months and was described as "resource-consuming, laborious, and risky".

Ford et al. (2008) described a brief history of the various South African ARV tenders. The first ARV tender, concluded in 2004, locked the government into a three-year agreement with manufacturers. Prices were, as with other medicine tenders, set for the entire period,

scheduled for pre-determined price escalations at various time points, or linked to international exchange rate fluctuations.

However, the South African ARV tender for the period 1 January, 2011, to 31 December, 2012, saw ARV medicines at, or around, the best available prices. For example, the prices of tenofovir and efavirenz, two key ARVs, which, together, will account for almost half of the total expenditure on ARV medicines, have been reduced considerably. Tenofovir will cost an average of 65% less than before while the average price of procured efavirenz will be reduced by 64% (Treatment Action Campaign, 2010). The most recent 2015-2018 tender supplying the South African Government is primarily for triple therapy fixed-dose combination treatments (see <http://www.prnewswire.com/news-releases/south-african-national-department-of-health-selects-mylan-as-a-leading-supplier-for-20152018-antiretroviral-tender-300014545.html>).

Various potentially onerous clauses in the 2004 South Africa tender made future tenders very restrictive (Ford et al., 2007). As an example, bidders had to submit two copies of the actual patent and a copy of any licence agreement with the patent holder, along with the bid document, once at the request for proposal/bid and again at the bid closing date. It therefore was not clear whether a generic manufacturer, which held neither patent nor agreement with the patent holder, would be able to enter the bidding process, even if that generic production was compliant with IP law.

In the public sector in West Bengal in India, procurement of essential medicines (which are primarily generics) is done centrally through an open tender system. Procurement prices are therefore uniform from one public health facility to another although the availability of many essential medicines in the public sector is very poor (Tripathi et al., 2005). The authors speculated that one reason for this is that, for these medicines, there were difficulties in finding enough suppliers to actually participate in the Central Medical Stores open tender bidding.

In Sudan, since 1992, the Central Medical Supplies Public Corporation (CMS) supplies medicines to public health facilities solely against cash payment (Ali, 2010). A survey of staff at the CMS (Ali, 2010) revealed that many of them believed purchasing non-registered medicines (i.e., not authorised in Sudan), using international open-tenders, improves affordability by getting the cheapest medicines from the global market. However, in its international open tender of 2008, more than 70% of medicines that won the tender were not registered in Sudan and, therefore, could not be used within the country.

Tendering may also cause difficulties in planning production for generic manufacturers because they will not know which tenders will be awarded ahead of time. However, in most cases, manufacturers are able to adjust their numbers accordingly as shown in the vaccine market where tendering is common practice. Such concerns would be minimised if the tender process involves an open tender for generics below a government set price (Faunce, 2006). For tendering contracts to function properly, enforceable penalty clauses for failure to deliver, or other contract defaults, are crucial. The simplest such clause would specify that a defaulting contractor should reimburse the government for the extra cost of obtaining supplies from elsewhere.

b) Pooled procurement

Some countries standardise demand according to an EML and conduct pooled procurement to benefit from economies of scale. This, in principle, avoids the costs of sustaining local production facilities that may not be viable in any case. Such pooled procurement is done in the Organisation of Eastern Caribbean States and the Gulf Cooperation Council (Burnett, 2003). However, the evidence as to whether such pooled procurement is effective in increasing generic penetration is unclear. But if the end result is that lower prices are being offered by an originator, the health system still benefits.

c) Joint manufacturing

One proposed method to address the lack of generic competition in LMICs is to form regional cooperative ventures for the manufacture of generics in an attempt to achieve sufficient volumes (Lanjouw, 2004). However, this may not be economically feasible as the cost of goods produced may still be higher than what is available by international tender from the likes of Indian generic producers (Kaplan and Laing, 2005).

In China, the number of local generic competitors had a negative effect on local product prices (Wang, 2006). At the same time, joint manufacturing requires the harmonisation of MRA regulation which is not always feasible.

3.1.4.2 High-income countries

Price regulations

Most high-income countries have some form of price regulation. Prices are usually regulated for reimbursed medicines (i.e., coverage of the costs by a third party payer; usually the reimbursement package covers the majority of the population). With regard to Europe, according to the Pharmaceutical Pricing and Reimbursement Information (PPRI)¹⁰, if the government deems a medicine (originator or generic) is reimbursable, then all EU Member States must have, in principle, some type of direct price control. There are only a few exceptions: Malta, which has no state price control on medicines in the private sector (but public procurement in the public sector), as well as Denmark and Germany. The latter two countries are officially understood as the two “free pricing” countries in Europe; however, Germany started to introduce some price regulations for high-priced medicines from 2011/2012 and both Germany and Denmark have been applying regulatory approaches in reimbursement procedures, targeting the reimbursement prices of medicines (Carone, 2012). (See

http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf)

¹⁰ PPRI was originally a research project funded by the European Commission, Health and Consumer Protection Directorate-General (DG SANCO) and the Austrian Federal Ministry of Health, Family and Youth (BMGFJ). The EU co-funded project started in April 2005 and ended in October 2007. Today, PPRI continues as a sustainable, Member State-borne initiative to exchange information and share experiences amongst pricing and reimbursement authorities. The objective of the PPRI project was to establish a network of national authorities for pharmaceutical pricing and reimbursement and to improve information and knowledge on the pharmaceutical systems in the Member States of the enlarged EU. We refer the reader to the PPRI report (Vogler et al., 2008) and the national PPRI/PHIS Pharma Profiles about the pharmaceutical systems in the European countries (available at <http://whocc.goeg.at/Publications/CountryReports>). The information provided here is based on the PPRI report, but updated by the PPRI project leader, GÖG/ÖBIG, in the course of the so-called PHIS (Pharmaceutical Health Information System) project (e.g. in the PHIS database [GÖG/ÖBIG, 2011b] and, as part of their work, as the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Data is updated as of December 2012.

In Belgium, the Czech Republic, Cyprus, Greece, Latvia, and Luxembourg, all medicines are price controlled, whether reimbursable or not. In Bulgaria, the Netherlands, Portugal and Romania, the distinction criterion for price control is not reimbursement, but rather prescription status; thus, prices of prescription-only generics are controlled (GÖG/ÖBIG 2011b, Vogler et al., 2006; Vogler et al., 2008, Vogler et al., 2011). As explained in the introduction of this section, there are different policies and methods to implement price regulations. Some policies are more appropriate and thus tend to be applied to new, on-patent medicines (e.g., external reference pricing [see below] and value-based pricing, which involves setting prices in relation to the perceived value to the payer and/or to society). Other policies (e.g., internal reference pricing) tend to be more specific to generics. Since generics prices might be linked to those of originator medicines, the pricing policies and the prices of those medicines also impact generics prices.

a) Setting prices relative to originator products (“generic price link”)

Several European countries set the price of a generic at a specific percentage lower than the originator product. This policy of generic price link is applied in the following EU Member States:

- generics priced up to 20% lower than the originator: Czech Republic, Greece, Ireland, Italy, and Luxembourg;
- generics priced 20% to 50% lower than the originator: Belgium, Cyprus (for locally produced medicines), Hungary, Poland, and Portugal;
- generics priced at least 50% lower than the originator in France.

Several countries have more specific types of pricing rules. For example, Estonia, Spain, Lithuania and Austria provide mechanisms for reducing the prices of the second and further generics. In Austria, this policy also aims to reduce the prices of originator medicines after generic medicines have come to the market. For more information, see the Text Box 3 below, extracted directly from a PPRI report (Vogler et al., 2008).

A study analysed the differences in prices of originator and generic medicines in 16 European countries and found higher price differences in countries (Denmark, Finland, Sweden) that applied no generic price link policy, but had competition, compared to the countries with a generic price policy (Vogler, 2012a). In spite of some limitations (e.g., small basket of medicines analysed, possible impact of other policies), these results might be a basis to critically discuss and review the generic price link policy.

Chen et al. (2008) examined the effects of Taiwan's generic price link policies (such as: prices for bioequivalent generics should not exceed 80% of prices for their corresponding branded medicines and a medicine that is being registered for the first time should not be priced higher than the lowest amongst prices of existing generics in the same group). For each medicine class, they investigated changes in daily expense, consumption volume, and total expenditures from a pre-action period to a corresponding post-action period. Daily expenses in medicines were reduced. However, in response to this policy change, hospitals in Taiwan tended to greatly expand the volume of medicines prescribed for their regular patients. Consequently, the total expenditures for the three classes of medicines grew substantially

after the action. This weakened the capability of the price adjustment action to control total pharmaceutical expenditure.

b) External price referencing

External reference pricing (ERP) compares medicine prices across countries (see Table 8). In 2012, using ERP as a basis for setting medicines prices was applied in 24 of the 27 EU Member States. Germany started to implement ERP for a few medicines in 2012. Only Sweden, the UK and Denmark do not apply it (Vogler et al., 2008, Vogler et al., 2011, GÖG/ÖBIG, 2011b, updated information by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies). In most of the EU countries, ERP is undertaken for reimbursable medicines, since these prices are usually price controlled, and is particularly applied to new, on-patent medicines. The methodology applied for ERP differs between the countries (Leopold et al., 2012).

EPR, or at least the way in which countries apply EPR, has been subject to some criticism. The most frequently mentioned concerns are that referencing is usually done to official list prices and not to actual lower prices, discounts and rebates are kept confidential, so true prices are not known, and that ERP does not consider the willingness and ability of countries to pay (OECD, 2008; Vogler, Zimmermann et al., 2012; Carone et al., 2012).

A full discussion on the limitations and possible advantages and benefits of EPR is not included in this review, but is the subject of another WHO/HAI review in this series (WHO/HAI, 2011c). It is mentioned here because it is a major pricing policy for originator medicines and may have an impact on the price of generics. Use of ERP for pricing generic medicines may reduce the effect of competition on lowering prices of generics.

Text Box 3. Medicine pricing “rules” in Austria

Specific pricing rules apply for generics that are to be included in the reimbursement list. The first follow-on product is considered as economically efficient if the price is at least 48% below the price of the now off-patent original brand. Furthermore, economic efficiency is assumed if the second and each subsequent “follower” offer a sufficiently large price difference to the previous included generic. The price of the originator has to be reduced by at least 30% within three months of the inclusion of the first generic follower in the positive list, in order to ensure the economic efficiency of the original product. This means that the price of the first follower has to be 25.7% below the price of the discounted original product. This percentage was 20% in 2004 and 22.9% in 2005.

Estonia applies a similar pricing mechanism for reimbursable pharmaceuticals. If a generic first applies for reimbursement, the same pricing procedure is used as for the original product. In case that a new original product is added to the reimbursement list, which already includes one or more generic alternatives, the original product has to be cheaper than the previously added generic. If the original product is first in the positive list, the generic product has to be at least 30% cheaper than the original. The next pharmaceutical to join the list has to be 10% cheaper than the valid reference price and the next two pharmaceuticals must be priced 5% below the reference price. All subsequently added pharmaceuticals must be cheaper than the previously added generic or below the reference price.

c) Internal reference pricing

Internal reference pricing (IRP) comprises an analysis of the prices of identical or therapeutically similar pharmaceuticals within a country. IRP is not only applied as a procedure to set prices, but also, even more often, for reimbursement purposes. Often, it is designed in the form of a “reference price system”, in which groups of identical or similar medicines are clustered, and a maximum reimbursement amount (so-called reference price) to be covered by the third party payer is fixed. These reference groups usually include off-patent products, but may also include other medicines considered as alternatives (e.g., parallel-imported medicines (see Habl et al. 2008)). If a patient wants a medicine whose price is above the reference price, s/he will bear the difference between the reference price and the full retail price, in addition to possible co-payments (e.g., percentage co-payment of the reference price).

Several European countries implement internal reference pricing and a reference price system in various forms (Kanavos et al., 2008; Habl et al., 2008). In 2012, 20 of the then 27 EU Member States (all but Austria, Cyprus, Malta, Ireland, Luxemburg, Sweden and the UK) applied a reference price system (Vogler, 2012b; Carone, 2012, updated information by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies).

There are different approaches on how to design a reference price system, which has an impact on generics prices and generics uptake. Major elements of a reference price system are the design of the reference groups and the methodology for setting the reference price.

While the reference price system generally accounts for savings due to price reductions, both by generic manufacturers and originator manufacturers (Pavcnik, 2002; Aaserud et al., 2007), the creation in Germany of four reference categories containing on-patent active ingredients (e.g., statins) at the beginning of 2005, led to a saving of 340 million Euro in 2005 and 2006 (Schröder et al. 2006). In 2006, the possibility to exempt medicines with a pharmacy retail price of 30% below the reference price from co-payment was introduced and proved to be a major incentive for generic manufacturers to decrease prices (Habl et al., 2008).

Kalo et al. (2007) studied therapeutic reference pricing in Hungary, where the reference price is based on therapeutic classes and includes on-patent originator brands. Therapeutic reference pricing was expected to reduce the expenditure on statins by switching therapy to cheaper, presumably generic, alternatives, but it was not successful. Prices decreased for generic statins, as expected, but the average unit price of statins did not decrease. This is because the price of patented statins did not change.

Portugal used to set the reference price at the price of the highest-priced generics of the reference group (Habl et al., 2008, Portela, 2009). Portugal was the only country in the EU with market shares of generics higher in value than in volume, which is an indication of rather high generic prices. In 2010, Portugal changed its reference pricing methodology to set the reference price to the average of the five lowest-priced medicines, and shortly afterwards, the break-even point at which generics shares became lower in value than in

volume was reached (Vogler, Zimmermann et al., 2012). There is still some room for further reductions in price.

Based on an econometric analysis of IMS data in high-income countries (mostly the EU), Kanavos et al. (2008) concluded that although reference pricing leads to a decline in lowest generic prices by up to 47%, regulation in these countries caps the effect of competition through the reference price and generic prices in the presence of a reference pricing show a slower price decline over time than without such pricing control methods.

d) Price information transparency

Information on prices in other countries is an issue particularly for national authorities applying external reference pricing, usually for on-patent products. National authorities usually ask manufacturers to submit price data, but some countries search price databases themselves. Usually, this is done by pricing officers in the Ministry of Health although other approaches are used (for instance, in Austria, a Ministry-owned institution, Gesundheit Österreich, runs the Pharma Price Information (PPI) in order to support the Pricing Committee). A price database (EURIPID) has been established to support EU Member States (www.euripid.eu). It was developed under Council Directive 89/105/EEC (commonly referred to as the “Transparency Directive”), which requires publishing, at least once a year, the medicine prices fixed by European national authorities.⁵

See Section 3.2.4 for price information transparency impacting consumers/patients.

Purchasing

Tendering is an important tool for purchasing pharmaceuticals (whether or not generic), used in most EU Member States. There is much more information about tendering in European countries than in LMICs. Tendering in Europe is particularly used in hospital settings – often in response to European and national procurement regulations (Vogler et al. 2010), but also serves in many countries to purchase pharmaceuticals for a specific public function (e.g., vaccines or for army purposes). Tenders typically include specific objectives and conditions. According to a survey amongst 30 countries, tendering for pharmaceuticals in ambulatory care is used in Belgium, Cyprus, the Czech Republic, Estonia, Germany, Hungary, Ireland, Lithuania, The Netherlands, Romania, Slovenia and Iceland. The authors concluded “While tendering can easily be used for up to 25% of the medicines in a hospital setting, only Cyprus and Iceland use it for a significant volume of medicines in ambulatory care.” (Leopold, et al, 2009).

The most commonly known tendering systems in the out-patient sector are those used by insurance companies in the Netherlands and sickness funds in Germany. Under the Dutch preference price policy, health insurance companies determine one or a limited number of medicine(s) per cluster (medicines with the same active ingredient, dosage form and strength), as preferred, for a fixed period of usually six months. The preferred medicine winning the tender will be reimbursed. In terms of savings, the preference price policy was

⁵ This medicines price database is established based on a call for proposals by the European Commission (http://ec.europa.eu/enterprise/newsroom/cf/itemdetail.cfm?item_id=2572&lang=en).

considered to be very successful. Initial total savings (projected to be €355 million annually) exceeded expectations since the preference policy scheme resulted in fierce price competition amongst generic companies (Kanavos et al., 2009).

Literature on Germany and the Netherlands, and other tendering systems, show that tenders contribute in the short term to significant cost savings. There is little or no research on the long-term implications of such policies, and their impact on doctors, the distribution chain and the generic and research-based pharmaceutical industry (Kanavos et al., 2009; Dylst and Simoens, 2010; Dylst et al., 2013).

It is noteworthy that the European Generics Medicines Association takes a negative view of tendering (Carradinha, 2009), asserting that “... such initiatives do not support long-term competition in the pharmaceutical market or provide access to medicines and may jeopardise the sustainability of the generic medicines industry”. One issue is that, in the short term, tendering drives prices down because it is usually an all or nothing situation. (Not all players can win the tender; only one or a few.). In the longer term, the number of available players in the market is reduced, leading to a decline in competition between companies, which may lead to higher prices.

The South African public sector is increasingly using split tenders (i.e., shifting to multiple awards per medicine instead of a single award to the lowest cost supplier) [Gray, 2014]. The rationale for these “split” tenders is to either maintain capacity of several suppliers and/or avoid dependence on a single supplier for an important medicine. If a country is making a single, large, annual purchase of medicines and the public health prospects of a default are real, then “splitting” a tender makes sense.

Text Box 4. Successful tendering in New Zealand

New Zealand uses cost-effectiveness analysis and internal reference pricing to maintain the national pharmaceutical schedule. Suppliers had two to three months to submit closed bids. The winner is obligated to supply the fluctuating total market demand for three years and to indemnify the government against unexpected disruption of production or supply. In that case, the government could legally approach other suppliers with the winning tenderer paying the difference (Faunce et al., 2006). Evaluation of the bids was staggered, with those offering greatest cost savings processed first. As a result of tendering, the New Zealand generics market rapidly shifted to a “low-price, high-volume” model with increased generic competition expanding to a 25% share of the total pharmaceutical market. Tendering soon became a powerful bargaining tool for the New Zealand government against the pharmaceutical industry. In a small market with little local manufacturing, such as New Zealand (less than 0.1% of global pharmaceutical sales), tendering is an important strategy for ensuring small-volume medicines continue to be available (Faunce et al., 2006).

3.2 Demand-side policies

So-called demand-side policies to promote generic medicines include incentives for doctors, dispensers and/or sellers of medicines, patients and consumers (Simoens, 2010).

3.2.1 Reimbursement policies

Reimbursement policies prioritise medicines with regard to their coverage by public funds. For the large majority of patients in much of the world, medicines are paid out of pocket and are not entitled to any form of reimbursement. In many countries, only a small proportion of the population may have access to medicines that are supplied free of charge.

Table 9 lists the main policy option related to reimbursement.

Table 9: Policy options related to reimbursement to promote generic medicines uptake.

Objective of the policy	Policy	Definition and brief description of policy options
Cost-savings for payers while ensuring access	Co-payments	Shifting the extra costs of providing originator products to consumers, instead of payers, incentivises consumers to switch to more affordable options.

3.2.1.1 Low- and middle-income countries

Few studies on policy options related to reimbursement exist in LMICs and none on reimbursement as an incentive for using generic medicines. This is not surprising given the lack of insurance systems and/or insufficient funds to subsidise medicines for their poor.

3.2.1.2 High-income countries

Reimbursement

With a few exceptions (e.g., higher reimbursement rates for generics in Portugal for some years), no specific reimbursement policies promoting generics are in place in high-income countries. Generics promotion as an element of the pricing and reimbursement systems in high-income countries usually refer to policies, such as internal price referencing and competitive policies (such as auction or tendering systems).

The types of reimbursement policy that are common in high-income countries refer to the out-patient sector (McGuire et al., 2004). Briefly, most European countries have reimbursement lists defining which pharmaceuticals are included (positive lists) or which are excluded (negative lists). As of 2011, positive lists exist in 24 of the 27 EU Member States countries. In general, positive lists contain those pharmaceuticals which are considered as reimbursable. Four countries (Germany, Hungary, Spain, and the UK) have negative lists which explicitly exclude medicines from reimbursement.

Medicines on a positive list are reimbursable (i.e., eligible for reimbursement, but not always 100% reimbursed); however, specific reimbursement rates for different therapeutic classes have been defined. Patients would have to co-pay a percentage rate.

Co-payments

Co-payments are mechanisms where the patient pays a certain fee for their medication, either as a percentage of the product price, as a flat fee, or a deductible. Generics-specific co-payments could be lower percentage co-payments for generics (e.g., as occurs in Portugal), or a lower prescription fee for generics compared to originators (see the example below from a pilot in Austria). Co-payments can be used to differentiate between originator and generic products so the co-payment is equal to the amount of the excess above the maximum reimbursement price (i.e., termed the "reference price" in some countries). See Section 3.1.4.2.

Austvoll-Dahlgren et al. (2009) produced a Cochrane Review of the impact of price capping and co-payments on rational medicine use, although not on generic medicine use, specifically. Overall, there were 13 studies were from the US, five from Canada and one each from Australia, Nepal and Sweden. This review found that cap and co-payment policies (including tiered policies that may specifically target more cost-effective medicines for reduced price) can decrease overall medicine use and decrease third-party medicine spending. But reductions in medicine use were found for both life-sustaining medicines and medicines that are important in treating chronic conditions. Tiered co-payments may also reduce overall medicine use if patients are not willing to substitute other medicines, or if the changes in the tier structure also included increased co-payments for generics. Few evaluations were included in each policy group and the quality of the research was found to be generally low to moderate.

In Germany, patients who had to co-pay did switch to alternatives available at the reference price (Zweifel and Crivelli, 1996).

In a review of 30 studies, few substitutions for generics resulted from plans introducing or increasing generic versus a brand cost-sharing differential. This raises the question of what magnitude of price difference would need to be in place for a differential effect to be seen, and whether and how perceptions of quality influence the patient's price sensitivity (Gibson et al., 2005).

In Australia, in 1990, a Minimum Pricing Policy in which the patient paid the difference between the branded and generic product had little effect on generic uptake. A much larger impact on generic uptake was noted when substitution with patient consent was allowed in 1994 (McManus et al., 2001).

A longitudinal study from Sweden showed that co-payments have a large effect on consumer choices (Andersson et al., 2005). This result has been confirmed by another study in the US where the co-payment was the intervention that had the most impact on consumers switching from an originator to the generic product when compared with an advertisement campaign, member mailing, free generic samples for doctors and financial incentives for doctors (O'Malley et al., 2006).

In a pilot project with a small sickness fund in Austria, during an observation period of one year, one part (€1) of the prescription fee was reimbursed to the insured when a generic was dispensed. This resulted in an increase in generics uptake (from 23% to 40% in the five selected therapeutic classes observed) and in a reduction of €2.47 per prescription, and proved that financial incentives in relation to the co-payment had an impact (Gouya, 2008).

3.2.2 Prescribing policies

There is a range of policy options to encourage health care providers to prescribe generic medicines. They range from permitting, encouraging and making mandatory the use of the INN (generic name) when prescribing medicines to providing financial and non-financial incentives (see Table 10).

Once legislation on generic prescribing is enacted, one of its critical tests is the rate at which doctors prescribe by INN only. A positive perception in terms of quality, efficacy and cost savings is the key driver to increase generic prescription rates (Hellerstein, 1998).

Table 10: Policy options to promote the prescribing of generics.

Objective of the policy	Policy	Definition and brief description of policy options
Promote the prescribing of generic medicines	Regulations to permit or mandate the prescribing of medicines by the INN	Mandatory INN prescribing requires prescriptions to be written using the INN and not a brand name. Exceptions are typically made in certain cases. Permitting voluntary INN prescribing leaves this up to the discretion of the prescriber.
	Clear exemption rules and documentation	Requesting an extra note on the prescription if only the prescribed branded product can be dispensed.
	Training of doctors and other health care providers who prescribe medicines	Training to increase the prescribers' familiarity with using INN only, and how to communicate to patients about the quality of generic medicines
	Financial incentives	Implementing individual prescribing budgets by insurers for the associated or contracted prescribers means that the prescriber has an assigned amount of money so that there is a need to be cost conscious in order to pay for all prescriptions out of the allocated budget.
Decrease information asymmetry	Campaigns directed towards prescribers regarding generic	Increasing the confidence of prescribers in the quality of generic medicines.

	medicines and their quality	
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3.2.2.1 Low- and middle-income countries

Regulatory policies on prescribing by INN

From the viewpoint of the healthcare system in LMICs, there may be an advantage to prescribing by the INN as the prescriber does not need to use time and energy in choosing between different products. Two examples are described here.

Tobar (2008) reviewed policies to promote generic medicine use in Latin American countries. Despite voluntary or mandatory prescribing by INN being part of the law and implemented in Argentina, Ecuador, Peru, Panama and Paraguay, it has not been enforced in all the countries and, therefore, showed little effect on prescribing behaviour in some of the countries.

In Pakistan, during the period in which medicines were required to be manufactured and marketed by the INN, MNCs mounted a campaign to induce doctors to write the manufacturer's name along with the generic name on prescriptions. Doctors, who had expressed concerns about unqualified dispensers and/or sellers of medicines making inappropriate generic substitutions, were responsive to this suggestion. In an early publication, a survey of doctors conducted by a leading manufacturer indicated that about 60% of the prescriptions they had written included a specific company name (Quraeshi et al., 1983).

Other factors influencing implementation of pro-generic prescribing policies in LMICs

Various studies in LMICs evaluated doctors' perceptions of generic medicines. The results identify factors that should be considered when implementing policies to promote the uptake of generic medicines in these countries.

Jamshed et al. (2009) highlighted the many difficulties in creating and successfully implementing a coherent generics medicines policy in Pakistan. Notably, there was a clear preference for originator brands by consumers, doctors and dispensers and/or sellers of medicines "presumably related to the local marketing practices..." and "false intuitions and beliefs regarding quality of generics and deficient know-how about generics...". Another factor is that in a number of LMICs, patients directly purchase prescription-only medicines from pharmacies and medicine outlets (by-passing the writing of a prescription by a doctor) as regulations are not enforced.

Understanding the characteristics associated with the prescribing of generics is relevant when developing effective mechanisms to implement pro-generic policies. A study from Zimbabwe found no difference in the prescribing of generic medicines between dispensing and non-dispensing doctors (Trap, 2002). However, a systematic review of literature on dispensing and non-dispensing prescribers including 21 studies from high-income and

LMICs found that dispensing prescribers were more likely to prescribe originator products (Lim et al., 2009).

An interventional study from South Africa evaluated the effect of a four day training course in 22 clinics (11 intervention and 11 control clinics) to promote the prescribing of generic medicines amongst other aspects (Meyer et al., 2001). The study found a substantial increase in the use of generic medicines three months after the intervention when comparing with one month before the training (a 24% increase in the intervention versus a decrease of 16.7% in the control clinics). This educational intervention in South Africa was labour intensive and its medium-/long-term impact may be expected to be low without any reinforcement.

3.2.2.2 High-income countries

Financial incentives to prescribe generic medicines

In Europe, policy-makers have focussed financial incentives more on doctors' prescribing behaviour than on pharmacies' dispensing practices. (For an early reference, see Garattini and Tediosi, 2000). Previous measures included fund-holding, which was done in Ireland ("Indicative Drug Target Scheme"), combined with a financial initiative (but suspended in 2005⁶), or the use of penalties when exceeding pharmaceutical budgets, like in Germany in the 1990s (Rafferty, 1997; Himmel et al., 1997). However, initial positive results attributed to pharmaceutical budgets did not continue in the longer run. Budgets were exceeded, but no repayment was done, and eventually legislation on the pharmaceutical budgets were changed (Rosian et al., 1998).

Sturm et al. (2009) carried out a systematic review of financial incentives for prescribing on medicine utilisation, health outcomes, health care utilisation, and expenditure. In total 13 studies met their inclusion criteria (10 from the UK, two from Ireland, one from Germany). Five of these studies measured generic medicine use as an outcome and showed that with financial incentives, prescribing of generic medicines increased by a median of 10.6%.

The implementation of physician budgets appears to have boosted the German generic medicines market during the 1990s. Generic prescriptions as a percentage of potential generic prescriptions increased from 60% in 1992 to 75% in 2003 (Busse and Riesberg, 2004). As of December 2012, physician budgets are in place in six of the then 27 EU Member States (Vogler and Schmickl, 2010, updated information of WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies).

Campaigns targeting prescribers

⁶ The Indicative Drug Target Scheme (IDTS) in Ireland has been officially suspended since 2005. The IDTS aimed to encourage general practitioners to prescribe economically by allowing them to invest savings made through more economic prescribing in practice development. The targets set took into account the age and gender of the patients and excluding certain specialist and expensive medicines. The scheme has been voluntary; there have been no sanctions in place for those who fail to meet their target (Elliot and Byrne 2007).

Other solutions include the provision of information to doctors indicating where they can achieve costs savings.

Studies of the impact of cost-savings information provided to doctors in the UK and Spain indicate a greater reduction in volume of prescriptions for originator products than in more complex incentive schemes (Roberts et al., 1997; Rausell et al., 2005).

However, resistance remains, and uptake can be uneven. In New Zealand, 52% of doctors were opposed to generic substitution without their approval in 1992 (Tilyard et al., 1990). Prescription rates for generics are also shown to differ across therapeutic areas, with the highest seen for commonly prescribed medicines such as antimicrobials, cardiovascular-renals and central nervous system medicines (Hellerstein, 1998).

Nearly all US hospitals purchase generically, and this has been fully accepted by the medical staff. Most US hospitals are members of group purchasing organisations that negotiate for a large order and the best price. The organisations have formal advisory bodies to evaluate potential vendors and qualify those that can supply quality products and may enter the bidding. Most hospitals use a formulary system for stocking their pharmacies, with the Veterans Administration and Department of Defense hospitals stocking generics. Their medical staff accept this. This is likely in part to be related to their trust in the quality of the generics through the US FDA market authorisation procedures.

In European hospitals, however, there is less awareness about generics. This is attributable to that fact that originator products are provided to hospitals at large discounts, or even for free, in some European countries where it is not forbidden (Vogler et al., 2010).

Similarly, the trust by doctors in the quality of generics—due to good experiences over time—seems to be a relevant factor that pre-disposes to the prescribing of generics. Another factor is that they are conscious of the limited ability of patients to afford medicine co-payments (Simoens, 2010). A good example of information and motivation for a rational use of medicines are sickness funds representatives (the “délégué(e)s d’Assurance Maladie”) who regularly visit doctors to inform and explain the rationale of guidelines and agreements to them (Lopes et al., 2011).

On the other hand, in countries of the former Soviet Union, perceptions of generics are predominantly negative. Many factors are responsible for this. Poor enforcement of the medicine control system, restrictions on medicine prescribing from the doctor’s point of view, and huge MNC advertisement budgets directed to doctors and consumers are perceived as mainly responsible for the bad image of generics. Moreover, undergraduate and postgraduate medical education uses brand names of some medicines, which creates a precedent early on in education (Balabanova et al., 2012; de Joncheere and Paal, 2003).

Training of prescribers to use INN

With respect to INN prescribing in EU Member States (as of December 2012), such prescribing is voluntary in 18 states and mandatory in five (Greece, Lithuania, Portugal,

Romania and Slovakia). It is not allowed in Austria, Denmark, Greece, Sweden, or the private sector in Cyprus. Lithuania and Slovakia changed from voluntary to mandatory INN prescribing in 2010 and 2011 respectively (Vogler and Schmickl, 2010; Vogler, 2012b).

In the UK, medical students are taught to prescribe by INN in medical schools, and INN prescribing is common practice even for patented medicines. In 2008, 82.6% of all prescription items were prescribed by INN in England (Health and Social Care Information Centre, 2009). Many journals require use of INN names in manuscripts.

Other factors influencing implementation of pro-generic prescribing policies in high-income countries

In Slovenia, 89% of 107 general practitioners interviewed regarded generic medicines as of the same effectiveness as originator medicines (Kersnik et al., 2002). Doctors reported that they would prescribe generic medicines if they were 30% below the price of originator products and if they received academic detailing from unbiased sources as they were pressured by pharmaceutical companies to prescribe certain brands.

A study from Greece found that only around half of the 1,204 doctors surveyed thought that generic medicines are of high or very high quality, safety and effectiveness, and 70.8% reported preferring to prescribe the originator product (Tsianou et al., 2009). The decision to prescribe a generic was related to the doctors' age and their beliefs about the efficacy and effectiveness of generics. At the time the study was conducted, Greece did not have any policies focussing on the demand-side (incentives for doctors, pharmacists or consumers to use generics). Greece has one of the lowest generic penetration rates by volume in Europe.

A retrospective study using social security claims data from South Korea analysed the effect of the policy to separate prescribing from dispensing roles on the use of generics (Lee and Malone, 2003). Contrary to the hypothesis of the authors, the number of claims increased by 13.9% and expenditure nearly doubled due to an increased use of originator products. The authors explained this result as a shift from the retail sector to the insurance sector. Previously consumers paid for medication out-of-pocket, but after the policy change consumption increased because people had to obtain medicines with a prescription via social security institutions which did not have policies in place to promote generic medicines.

3.2.3 Dispensing policies

There are several policies which promote the dispensing (or selling) of generic medicines. Generic substitution is one of the most commonly used policies. One can distinguish four different scenarios: generic substitution is forbidden, allowed, encouraged or mandatory (WHO, 2001).

Within the last three categories, prescriber and patient authorisation may or may not be required. If generic substitution by the dispenser is permitted by law, the dispenser chooses whether to dispense a generic equivalent product or the prescribed product. Besides substitution policies, there are other policies that promote the dispensing or selling of generic medicines as shown in Table 11.

Table 11: Policy options to promote the dispensing of generic medicines.

Objective of the policy	Policy	Definition and brief description of policy options
Increasing the dispensing or selling of generics	Generic substitution	People who dispense or sell medicines are permitted, encouraged or mandated to sell pharmaceutically or therapeutically interchangeable medicines rather than originator products.
	Manipulating mark-ups, margins and/or dispensing fees	Regressive mark-ups can be applied to distributors, wholesalers, and/or retailers. However, most countries who regulate mark-ups apply fixed percentages regardless of whether the product is the originator or a generic.
Decreasing information asymmetry	Educational campaigns	Informing people dispensing and selling medicines about generics, and issues related to quality of these products, may make them more inclined to dispense/sell generics. Training of dispensers on how to communicate these issues with patients and others is important.

3.2.3.1 Low- and middle-income countries

Generic substitution

Amongst the Sub-Saharan countries, policies allowing generic substitution exist in Ghana, Uganda and South Africa. In the latter, the system introduced in 2003 provides for a mandatory offer of generic substitution. In its current form, the South African generic substitution provision compels pharmacists to offer patients a generic substitute for any medicine prescribed, unless the prescriber explicitly states that the medicine should not be substituted or where the price of the generic is higher than that of the originator. The final choice, however, rests with the patient (van der Westhuizen et al., 2010).

Savings of 9.3% over a three-year period could have been made with generic substitution of antidepressants according to research carried out by the School of Pharmacy at the North-West University, South Africa (van der Westhuizen et al., 2010). However, the authors noted that total substitution would be unlikely because in 40% to 60% of cases, prescribers and patients would opt for the originator or brand-name product.

A mandatory generic substitution policy in the public sector exists in Indonesia. This was done in conjunction with an industrial policy of production of "logo generic medicines" led by state-owned manufacturers and with the entry of private manufacturers being encouraged by the government. By the mid-1990s, nearly 200 commonly used essential medicines were available by generic name, supported by 408 dispensers and/or sellers of

medicines that were obliged to provide generics, leading to an overall generic dispensing rate of 15% of prescriptions (WHO, 1997a).

Iran is an example of a country where mandatory substitution policies have been implemented in both the public and the private sector, in combination with the procurement of medicines by the INN or generic name (Nikfar et al., 2005).

In Saudi Arabia, generic substitution by pharmacists is permitted. While the prescriber's approval is not a requirement, patient consent is required. Generally, there is currently no information available to healthcare professionals that documents the therapeutic and bioequivalence between medicines (Alrasheedy et al., 2013). These authors suggest that Saudi Arabia needs a formulary of interchangeable medicines to guide appropriate generic substitution.

In various Latin American countries, the substitution of medicines has been restricted to a certain list of medicines (i.e., those for which therapeutic equivalence is proven) [OPS, 2010]. Therefore, the impact of pro-generic medicines policies on the uptake of generic medicines depends largely on the number of products authorised for substitution. Brazil has a list of products authorised for substitution. By law, these authorised products should be prescribed and marketed with the INN, should not be patent-protected, and must demonstrate therapeutic equivalence with the originator. This official list, available in all pharmacies, guarantees the substitution of only these products.

Other factors influencing the dispensing or sales of generic medicines

A literature review identifying 13 studies on the perceptions of pharmacy personnel or those in other medicine outlets regarding generic medicines showed that they were largely guided by economic considerations, such as the profit margin between generic versus originator products, perceived quality of the generic product, perceived risk of substitution depending on the therapeutic class of the medicine (narrow therapeutic index products less likely to substituted), the customer, and the doctor (good communication with the doctor facilitated substitution). Most of the studies were from the US; only one was from an LMIC (Malaysia) [Chong et al., 2010]. Another literature review (Al-Gedadi and Hassali, 2008a) on the views of people dispensing or selling medicines and generic substitution practices highlighted the importance of understanding the motivation to promote the use of generics.

A study from West Malaysia of 40 community pharmacists found that the main driver for generic substitution was the high profit margin (Babar et al., 2008). However, dispensing of originators was very common, even amongst those treating chronic diseases.

A study from Tanzania analysed the percentage of generic medicines out of 900 products sold by 39 private sector dispensers and/or sellers and 11 private sector medicine stores (Nsimba et al., 2007). Only 14% of the medicines sold were generics (either INN or branded generics). The authors suggested that this was due to the fact that the originator brand products had a higher profit margin, that their names were easier to memorise, and that patients preferred originators.

In Malaysia, a baseline assessment was undertaken in 2007 to describe the perceptions and opinions of community pharmacists about their views on generic substitution (Chong et al., 2010). Of the 219 respondents, a large majority (87%), regardless of region, felt they should be granted substitution rights with some exceptions. Around 80% did not consult the prescriber regarding substitution. At the time of the assessment, generic substitution in the private sector was not regulated in Malaysia (i.e., there was no prohibition on substitution and prescribers were not required to give permission for substitution on prescriptions).

Using certain health services to obtain a prescription was found to promote or discourage the selling or dispensing of generics in Mali, the Philippines and Sierra Leone.

Medicine acquisitions in private and public facilities in three different study sites in Mali were observed where the probability of acquiring a generic medicine following a visit to a public health facility was significantly higher than following a visit to a private provider (Maiga et al., 2003). The study concluded that the private sector could play a key role in influencing consumers' choice of generic use and that the national pharmaceutical policies need to acknowledge this influence by implementing strategies where consumers receive adequate information on the efficacy of generics (Maiga et al., 2003).

In contrast with Mali, a study in the Philippines found that patients using dispensers with links to public sector doctors spent 49.3% more on medicines than those where there was no link, and that by switching to generics, patients could save up to 58% of expenditure (James et al., 2009).

In a comparison between dispensers and doctors in Sierra Leone, dispensers were shown to dispense medicines as generics more often than doctors (59% versus 45%) and make greater use of the EML. The authors argued that this was because they were less influenced by medical representatives and had more experience of working in state facilities where medicines are dispensed and sold predominantly as generics (Palmer and Lisk, 1997).

3.2.3.2 High-income countries

Generic substitution

As of December 2012, out of a total of 29 European countries (the then 27 EU Member States, plus Croatia and Norway), generic substitution is not allowed in seven countries (i.e., Austria, Bulgaria, the private sector in Cyprus, Greece, Ireland, Luxembourg and the UK). It is optional in 16 countries, and is mandatory in five countries (i.e., Denmark, Finland, Germany, the public sector in Malta and Sweden) [data as of August 2012 from Vogler and Schmickl, 2010; Vogler 2012b].

In the UK, the government decided against the introduction of generic substitution, planned for 2010, following a public consultation (Vogler, 2012). It was believed that the comparatively high market share of generics, achieved by strongly encouraging prescribing medicines by the INN, could hardly be further increased. Other factors were also clearly at work. Bulk purchasing of generic medicines by the National Health Service (NHS) and a

high percentage of initial generic prescribing by NHS doctors (most prescriptions for NHS patients in England are now written generically) have created the conditions for this large generic market share (Association of the British Pharmaceutical Industry, 1999).

In general, although there is no evidence of a strict correlation between generic substitution and generic uptake, there are indications about the impact of pro-generics measures, especially generic substitution and INN prescribing. In this respect, enforcement appears to be particularly relevant for generic substitution and INN prescribing. Countries that have introduced these measures in a mandatory way tend to have higher generics uptake than those with indicative generic substitution and/or INN prescribing (Vogler, 2012b).

The importance of enforcement of pro-generics policies is highlighted in Sweden, which introduced a mandatory generic substitution policy in 2002 where pharmacies have to offer patients the cheapest available equivalent product unless substitution is restricted. Sweden was one of the few European countries that achieved savings in pharmaceutical expenditure in recent years. This was attributed by Swedish experts to their generics policies, particularly mandatory generic substitution (Vogler et al., 2008). Analysis of sales volumes showed that the consumption volume of substitutable products increased. Comparable non-substitutable products levelled out or declined (Andersson et al., 2008). The authors conclude that the introduction of the mandatory substitution policy has resulted in an increased consumption of such products, which indicate savings. Interestingly, although the savings were substantial, it was found that the amount of savings, and therefore the success of the policy, largely depended on the pharmacies stocking the cheapest substituted product (Andersson et al., 2005).

A survey of 16 originator companies and seven generic companies in Finland found that after the introduction of generic substitution, producers of originator products showed decreased profit margins (Timonen et al., 2009).

Another study in Finland explored what medicine-related factors influenced people's choice of prescription medicines five years after generic substitution had been introduced. External characteristics of the medicines, such as the colour and shape of the tablet/capsule or the appearance of the package, were not significant characteristics for people but price, familiarity, and availability were important factors in the choice of product (Heikkila et al., 2011).

McManus et al. (2001) in Australia and Hoffmann et al. (2009) in Germany used claims data to show volume changes in the utilisation of generics after policy changes related to generic substitution. McManus (2001) showed that the dispensing of generic fluoxetine and generic ranitidine increased significantly after the introduction of the substitution policy.

Hoffmann et al. (2009) found in Germany that implementing contracts between insurance companies and pharmacies that obligate pharmacies to sell a certain product for which the insurance company received a discount, resulted in an increase in the percentage of prescriptions in which the doctor specified "no substitution". This increase was particularly seen in prescriptions for elderly patients, which may have been related to the elderly taking more medicines (including those for which substitution might cause difficulties) and having

difficulties distinguishing between medicines. This can lead to inadvertent switching or multiple intake. However, there were large differences between regions that could not be explained by the differences in the policy change.

For selected European countries, the reductions in public expenditure on originator products due to generic substitution was 20% to 50% (Simoens and De Coster, 2006). This assessment was done a few years ago; current savings might be expected to be considerably higher since more patents have expired.

In several countries in Europe, generic substitution by pharmacies is combined with mandatory or allowed/encouraged generic prescribing by doctors using the INN and a reference price system (Vogler et al., 2008). Generics substitution or INN prescribing, together with a reference price system, is seen in 21 of 29 European countries (27 EU Member States, plus Croatia/Norway (data as of September 2012 from Vogler, 2012b and information from PPRI network members). In combination, these two tools appear to positively influence each other (Vogler et al., 2008). Only one EU member State (Austria, a country with rather low generic uptake) lacks all three of these policies.

The Netherlands had a system in which the pharmacist was allowed to keep a third of the savings achieved by generic substitution (Simoens and De Coster, 2006). From the mid-1990s until 2004 the generic market share increased from about 20% to 50% in volume. In 2004, this financial incentive was abolished. Generic market share continued to increase. This is attributable to a contractual arrangement between the payers and stakeholders, which included a commitment to generic promotion, as well as the continuation of a well-introduced and accepted policy that no longer appeared to need incentives.

Regressive mark-ups

Fixed percentage mark-ups result in higher profits when higher-priced products are dispensed or sold. Regressive mark-ups (lower percentage mark-ups on higher priced products) are intended to encourage the dispensing and sales of lower priced products. In European countries, regressive mark-ups are more often applied than fixed (linear) mark-ups, to remunerate both wholesalers and pharmacies (Vogler et al., 2008, PHIS database). Dispensing fees are applied in a few EU countries. In European countries, regressive mark-ups have tended to replace fixed mark-up (e.g., Portugal changed to a regressive system in early 2012).

In France, pharmacy remuneration includes an incentive for the dispensing of generics. If a pharmacist dispenses a generic, they receive the same amount of money as if the originator product was dispensed (Lopes et al., 2011). It should be noted that this incentive is supplemented by voluntary generic substitution and contractual agreements between the sickness funds and the pharmacists in which the latter are committed to achieve a defined substitution rate target. From 2005 to 2009, the generics market shares for reimbursed medicines in the out-patient sector in France increased from 15% to 24% in volume and from 8% to 14% in value (Lopes et al., 2011).

In Syria, for example, mark-ups in private pharmacies range from 30% when the pharmacy procurement price is SYP40 or less, to 8% when the procurement price is SYP501 or higher (Cameron et al., 2009).

For more information about regulating mark-ups in the pharmaceutical supply chain, see the WHO/HAI review on this topic: <http://haiweb.org/what-we-do/price-availability-affordability/resources-for-pricing-policies/>

3.2.4 Policies impacting consumers/patients

It has been argued that the decision by consumers/patients on whether to purchase an originator or a generic depends mainly on two factors: price and the perceived quality of the products (Rizzo and Zeckhauser, 2008). The patient makes an evaluation of whether the savings made by choosing a generic outweighs any perceived difference in quality between the originator and generic. Rizzo and Zeckhauser (2008) have argued that perceived quality has two relevant dimensions: a) safety and efficacy; and b) the “importance” of the medical condition. For instance, a consumer might choose a generic medicine for treating a headache, considering it of less importance than a life-threatening infection for which the consumer prefers an originator product (Rizzo and Zeckhauser, 2008).

Few measures exist in LMICs to encourage patients to request generics or to penalise them for not doing so. For one thing, medicines are most often paid out of pocket by the consumer when purchased in the private sector. This is aggravated by the fact that even if a patient's knowledge of generics is good, this does not necessarily translate into action. Table 12 presents policy options have been described to promote uptake of generic medicines by consumers/patients. As seen from a high-income country perspective, the situation is rather different with co-payments and the reference price system being used as policy levers in countries with high reimbursement coverage.

Table 12: Policy options to promote the uptake of generic medicines by consumers/patients.

Objective of the policy	Policy	Definition and brief description of policy options
Increasing consumption of generic medicines	Communication of health care providers to consumers/patients about generic medicines	A main source of information about generic medicines for consumers is health care providers. Communication from health care providers to consumers can increase awareness and information about generic medicines.
	Public education campaigns	Campaigns to inform and create awareness of the relative cost benefit of generic medicines compared to originator products for an equally high safety, quality and efficacy profile. The MRA can play an important role in these campaigns.

	Limitation or banning of free samples of all products	Free samples aim to create brand loyalty by consumers. Free samples of originator products discourages generic medicines uptake.*
	Prohibition of direct-to-consumer advertising of prescription-only products	Promoting products creates brand loyalty by consumers. Advertising originator products discourages generic medicines uptake.
	Price information accessible to consumers	Price information enables consumers to compare prices of therapeutically equivalent products and promotes informed decisions.

* We could identify no literature describing this policy option implemented in a specific country context related to promoting the uptake of generic medicines.

3.2.4.1 Low- and middle-income countries

Labelling of generic products (see also the section on regulation and market authorisation)

In Brazil, where generic penetration was 30% market share by value in 1997, generics are identified by a yellow stripe and a capital “G” on the package (de Joncheere et al., 2002). Only products with this identification can be substituted for the reference medicine. Eighty-six percent of respondents surveyed (n=3,182) knew that generics cost less, and the vast majority deemed the quality of generics to be equal to that of the originator (Bertoldi et al., 2005). A little over half of the respondents (57%) were aware of the packaging required for generics and 48% misclassified an originator product as a generic, indicating that although theoretical knowledge may be good, in practice recognition is low (Bertoldi et al., 2005).

Hence, it is difficult to assess the impact of generic campaigns on patients as they may use them unknowingly, and patients seldom ask for generics proactively.

Factors influencing consumer behaviour change with regard to generics

Changing consumer attitudes requires a combination of strategies, including legislation and regulations, price controls, information and communication strategies, and advocacy (Chetley et al., 2007).

A study in South Africa analysed the perception of generic medicines held by 73 consumers in two different regions of the country, and found that consumers defined quality as the effect that the medicines had on their symptoms (Patel et al., 2010). Consumer choice of care and treatment was mainly influenced by cost, choice, and receipt of individualised attention (Patel et al., 2010). The doctor’s recommendation of a generic medicine was regarded as more important than the dispenser’s recommendation. Interestingly, the study found that not wanting to use generic medicines supplied in the public sector had more to do with them being thought of as second-class than in actually experiencing inferior quality (Patel et al., 2010).

A survey of 396 consumers in one region in Malaysia found that 32% believed that generic products caused more side effects and 64% knew that generic products are less expensive than originator products. This suggests knowledge gaps about generic medicines which likely affect consumer preference for originator products (Al-Gedadi et al., 2008b).

Some other studies from LMICs do not focus on generics *per se* but help to shed light on consumer perception of medicines. Various studies show that price is often used to judge quality (Holloway et al., 2002) and product that are free-of-charge are viewed suspiciously (Loennroth et al., 2001). See also Text Box 5.

School children can be effective change agents in improving community medicine use. (ICIUM, 2004). One piece of research for this is the school-based peer-led project carried out in Chisinau, Moldova, in 2003–2004, called “Involving students in the unnecessary use of antibiotics in common cold and flu” (ICIUM, 2004). The school education programme included the training of trainers, after which school students were trained in six workshops with their classmates. There were two parents’ meetings, creation of a booklet, a vignette video, two newsletters, a poster and a poster contest. The programme emphasised general knowledge about medicines, such as INN, generic and brand names, how to ask questions about medicines in the pharmacy, and other important issues on appropriate medicine use.

3.2.4.2 High-income countries

Promotion campaigns to encourage generic medicines use

Promotion campaigns have been undertaken in many European countries such as Belgium, Italy, Portugal, Spain and the UK (Simoens and De Coster 2006), but rigorous formal evaluations of the impact of these campaigns could not be identified.

The role of an MRA in providing information of generic medicines has been discussed in the section on marketing authorisation and regulation.

In the US, a controlled trial on the impact of consumer education on the consumption of low-cost generic medicines concluded that the receipt of regular mailed information about cost-saving generic versions of the medicines can increase the rate of generic substitution amongst consumers (Sedjo et al., 2009). However, the study did not provide information about the cost of the intervention.

Reductions in co-payments and out-of-pocket payments

For patients and consumers in high-income countries where pharmaceutical costs are often at least partially covered, the actual co-payment and out-of-pocket payments play a major role.

Communication by health care providers about generic medicines

According to some studies, the root cause of patient dissatisfaction when switched to generics is closely related (Spearman, $r=0.81$) to the communication they received about the change to a generic product (Dowell et al., 1995). Interviews suggest that the 20% of patients who reported that they were "very unhappy" with their generic medication did so primarily because of the nature of the communication they received rather than the change itself (Dowell et al., 1995). Fifty-three percent of patients did not have a physician or pharmacist talk to them about generics. But of the 47% where the discussion was held, 91% used the generic (versus a baseline of 65% if no such talk had occurred) [Dowell et al., 1995].

Studies in Spain indicate that patient education is successful in increasing patients' acceptance of generic medicines and their satisfaction with the medicines (Valles et al., 2002). Following a 40-second verbal explanation to patients about generics by a pharmacist, 71% accepted generics. Of the minority who declined, reasons cited were: 1) patients wanted to consult with their doctor; 2) the generic would not have the same effect; 3) a cheaper product was necessarily of worse quality; and 4) patients would only accept a generic if they saved money (Casado Buendia, 2002). All of these reasons, except the last, can be tackled through improved communication and education.

"Adopters" of generics were more likely than those not taking generics ("non-adopters") to use medical experts (doctors and pharmacists), as well as other information sources (friends, relatives, salespeople, store reputation, magazines and newspapers) [Gaither et al., 2001]. Overall, assurance by the doctor or the pharmacist and cost savings were the major inducers to switching to generics. However, very few health care professionals initiate this conversation. It is also regrettable that many consumer organisations have no position on generics and that political leadership on this issue seems to be lacking (Gaither et al., 2001). On the other hand, pharmaceutical companies (in the US and Europe) routinely sponsor patient groups (European Federation of Pharmaceutical Industries and Associations, 2012).

Factors influencing consumer behaviour change with regard to generic medicines

a) Beliefs

Consumer perceptions of generic medicines have been studied in high-income countries and point out some perceptual disconnects amongst consumers. A survey of 1,047 adults commercially insured by a large pharmaceutical benefit manager in the US found that only 30% believed that branded medicines are more effective than generic medicines. However, 63% of them preferred to take originator medicines. This is similar to findings from a survey of around 800 patients recruited from general practitioners in three regions in Germany, which found that 37% were sceptical about generics precisely because they were cheaper than originators (Himmel et al., 2005). In a US survey in Georgia, over 60% of respondents indicated that generics are as safe and effective as brand medicines, and are equivalent in quality, but only 24% actually asked their physician or pharmacist for generics when receiving a prescription (Carroll et al., 1989 in Gaither et al., 2001).

b) Severity of illness

In the US, patients are generally positively inclined to generics (40% to 60% positive opinions across studies spanning the 1970s to 2000) (Gaither et al., 2001). Variations between individuals are attributed to factors such as age, socioeconomic grouping and ethnicity, and

factors such as the type and severity of illness and whether the patient has consulted with a health-care professional (Gaither et al., 2001).

c) Presentation of generic medicines in comparison to the originator product

In many high-income countries, acceptance of generic medicines by patients is problematic. In New Zealand in 1990, 56% of doctors in a survey reported problems associated with the use of generics. Out of these problems, 88% were due to patient confusion over the size, shape and taste of the product (Tilyard et al., 1990) affecting patient perceptions about generics. However, patient awareness has improved in many countries as patent-protected and marketed medicines often have a unique shape or colour (Garattini and Tediosi, 2000).

Text Box 5. Price as a Proxy for Quality/Price as a Modifier of Clinical Response (Waber et al., 2008)

The human psyche seems to equate price with quality, which is a big barrier to greater use of generics. In an interesting study, Waber et al. (2008) looked to see if the therapeutic efficacy of medicines is affected by commercial features, such as lower prices. Because such features influence patients' expectations, they may play an unrecognised therapeutic role by influencing the efficacy of therapies, especially in conditions associated with strong placebo responses. They studied the impact of price on analgesic response to placebo pills. They recruited 82 healthy paid volunteers and informed them about a (purported) new opioid analgesic approved by the US FDA. It was described as similar to codeine with faster onset time, but was actually a placebo. After randomisation, half of the participants were informed that the medicine had a regular price of \$2.50 per tablet and half were notified that the price had been discounted to \$0.10 per tablet. No reason for the discount was given. All participants received identical placebo tablets. Voltages were applied to induce pain.

For all voltages tested, pain reduction was greater for the regular-priced tablet ($P < 0.001$). These results are consistent with described phenomena of commercial variables affecting quality expectations and expectations influencing therapeutic efficacy. Placebo responses to price have implications for generics. They may explain the popularity of high-priced medical therapies (e.g., COX2 inhibitors) over low-priced, widely available alternatives (e.g., over-the-counter non-steroidal anti-inflammatory medicines), and why patients who switch from originators may report that the generic equivalent is less effective.

4. Discussion:

Key messages for policy-makers in low- and middle-income countries

A wide range of policies are used in high-income countries and LMICs to promote the uptake of generic medicines. Some policies seem to be specific to high-income countries, primarily those with strong publicly-funded insurance systems, where public payers have the possibility to target prescribers and dispensers with appropriate measures. Such policies are rarely used in LMICs.

High-income country-specific solutions and policies may well serve as a model of good practice for LMICs, but we strongly emphasise that these should not be copied without considering the complexities of the local context (Vogler et al., 2008). Indeed, even in Europe, there is great diversity in pharmaceutical policies (Simoens, 2008).

Many health systems in LMICs have technical, financial and political constraints, which result in less effective health policies (such as those promoting the use of generics). These well-known structural and functional challenges include deficiencies in human resource skill mixes and poor physical and managerial infrastructure, leading to failure to strengthen policy planning, weak implementation mechanisms and lack of evaluation (Ranson et al., 2010; Kumaranayake, 1998; Hongoro and Kumaranayake, 2000). In these countries, the demand side of health systems is important, but often neglected, in terms of policy and evaluations (Ensor and Cooper, 2004).

Barriers for effective implementation of generic medicines policies exist beyond LMICs. There are many specific factors in European countries that impede pro-generic policies, such as greater IP protection and market exclusivity for originators than in the US, price linkage between generics and originators in some countries, and a lack of demand-side measures which discourages doctors, pharmacists and patients to use generic medicines (Kanavos et al., 2008).

As a result, we strongly highlight the issues of ineffective implementation and the lack of enforceability—problems that are not restricted to LMICs. These problems can be addressed using a variety of approaches directed to all levels of the health system (e.g., INN prescribing, generic substitution, regulatory measures, [financial] incentives, sanctions, information provision, and monitoring systems).

The following sections summarise what we consider the key “lessons learned” from this review of pro-generic medicines policies. We particularly emphasise lessons for LMICs. People may differ with our choice of policies and into which category the policy belongs. As the poor in LMICs frequently use informal private providers, it is important to bring the informal sector into an overall public policy net (Mills et al., 2002). The role of patients in providing an advocacy platform, especially in countries in which patients pay their own way cannot be overemphasised. Many of these same conclusions have been reached before by others looking at interventions regarding the rational use of medicines (Le Grand and Hogerzeil, 2001) and medicines registration programs (Ratanawijitrasin et al., 2002a; 2002b).

Research is limited on the effect of various policies to increase use of generic medicines in LMICs. Nonetheless, countries are presently incorporating pro-generic medicines policies into their national medicines policy and legislation, making their evaluation even more important in order to implement appropriate adjustments if necessary to improve their effectiveness.

4.1 Supply-side pro-generics policy options

Regulatory and intellectual property provisions

National regulatory authorities with relatively strong enforcement and market authorisation procedures would tend to counteract aggressive use by companies of evergreening their products (i.e., switching patient demands by launching second-generation products with little or no added therapeutic value). Patent authorities that lack confidence to avoid weak or invalid patents, particularly second-generation patents, which may form part of a “patent thicket”, can unwittingly block the entry of generic medicines.

Some of the elements of a Hatch-Waxman-type legislation (see Section 3.1) may be relevant for LMICs. Generally, the more complex the competitive marketplace, the greater is the need to balance the interests/needs of the originator and generic industries. Emerging markets (such as South Africa, India, Thailand, and Eastern Europe) should fully understand the advantages and disadvantages of Hatch-Waxman type legislation to their own needs.

A further lesson is that more nuanced regulatory policies may be used to encourage the uptake of generics. For instance, linking market authorisation requirements (e.g., language on product labels) to those of larger neighbouring countries might save some investment costs for generic manufacturers. Examples of countries that have done so are Malta (linked to UK) and Luxembourg (linked to Belgium).

A critical lesson is that the TRIPS Agreement can have important influences on generic medicines availability, both positive and negative. TRIPS encourages flexibilities, such as pre-grant patent oppositions, compulsory licensing, Bolar provisions and the limiting of what is considered patentable (Musungu et al., 2004, Musungu and Oh, 2006). Under the Doha Agreement and Article 30 of TRIPS, governments can provide limited exceptions to the rights conferred to a patent owner. Compulsory licensing can lower price of medicines, but it is important for policy-makers to understand that this price reduction would not necessarily be substantial if this does not result in generic competition (Hassan et al., 2010). In other words, issuance of a compulsory licence by a government may not necessarily result in immediate supply by a third-party company (Hassan et al., 2010). A non-exclusive compulsory licence (WTO: TRIPS Article 31[d]) would allow several third-party companies to make the same medicine. Strengthening IP protection in LMICs without mechanisms to foster generic medicines uptake may actually reduce accessibility of medicines without necessarily improving incentives to innovate. Hence, strengthening IP protection should entail strategies to promote generic medicines uptake to increase access to medicines.

LMICs should follow the lead of EU Member States that do not allow patent linkage with regard to marketing authorisation. The European Commission has made it clear that this is at the discretion of the courts and that the authorities should disregard the patent situation of the originator while dealing with the marketing application of a generic medicine (European Commission Competition Directorate-General, 2009). However, some LMICs have already created forms of patent linkage schemes (e.g., Mexico), which impose a requirement on generics companies to make a statement about the patent status as part of a regulatory dossier submission and will not grant marketing approval without it. Slovakia suspends market authorisation given to a generic product until patent expiry (EGA Report, 2008). This becomes a barrier to generic market entry.

TRIPS requirements go into effect for all WTO members by 2016. Whether patents will be applied for and granted in many LMICs is an open question, but for major emerging markets (Brazil, Thailand, India and China), patent linkage may be an issue unless this linkage is eliminated by legislation. Linkage requirements have been negotiated in many FTAs. But they do not have to be a foregone conclusion.

With respect to the existence of “me-too” patents designed to extend patent monopoly, they almost certainly will be applied for and for major emerging markets (Brazil, Thailand, India and China) this may be an issue unless stricter patentability rules are created and enforced to prevent such evergreening.

Competition policies and price regulation

With regard to competition policies, having a sufficiently broad range of quality-assured generics on the market is an important prerequisite for implementing other generics policies (such as internal reference pricing) as each of these policies would be translated and supported by generic competition. See Section 5.1.2.

Overall, there is a complex interaction between industrial policy and public health policy, not covered in this report, which can act as a barrier to generic policies. One such seemingly paradoxical example is the protection of a domestic pharmaceutical industry through methods such as tariffs on imported goods (Olcay and Laing, 2005), and restrictive quotas, which could lead to continuing operation of inefficient, poor quality domestic pharmaceutical production (Bate 2008), and/or domestic products with prices higher than international reference prices. This could be counterproductive to the promotion of quality assured generic medicines of affordable prices.

Various medicine price databases, such as the Price and Quality Reporting Tool of the Global Fund (<http://www.theglobalfund.org/en/pqr/>) and the WHO/HAI database (<http://haiweb.org/what-we-do/price-availability-affordability/price-availability-data/>) generate greater price transparency in various LMICs although these efforts remain insufficient.

Price controls may not be applied to all medicines, but may be focused on specific groups, such as essential medicines, medicines in the public sector, or medicines that are reimbursed.

Internal reference pricing might be most suitable for generics with a range of identical or similar medicines being available, and external price referencing might be chosen for patent-protected medicines with no competitors on the market. However, it is important to note that internal reference pricing at a level of the least-expensive medicine may inhibit the economic viability of generic producers and ultimately product availability.

Patients and doctors should be sensitised to the relative prices of competing medicines. This will theoretically allow them to evaluate price against the benefits of different therapies. The truly well-informed patient (with the caveat that this reality is difficult to achieve) can pay extra for medicine sold above the reference price if they believe the potential benefit is worth it (National Institute for Health Care Reform, 2012).

In countries with health insurance systems, generic producers may have little incentive to reduce their prices to below an originally set reference price level, as this may trigger further downward adjustment by health insurance companies. For example, Germany introduced internal reference pricing in 1989, changing from a system in which patients paid a flat prescription fee to one in which insurers paid the same maximum reimbursement for all generic equivalent medicines and patients paid the difference between the reimbursement price and the manufacturer's price. The companies reduced their prices by 10% to 25%, leaving it up to the patients to continue to pay an even larger amount for generics. The decline in prices was most pronounced for brand name products and for branded products that faced a larger number of generic competitors (Pavcnik, 2002; see also wider review of evidence on the impact of internal reference pricing in Aaserud et al., 2007).

It has been argued that cost-plus pricing has the disadvantage of difficult-to-verify production costs reported by the manufacturer and that it can only be effectively used for locally manufactured products. Accordingly, a country that heavily relies on imported medicines would not be able to effectively implement a cost-plus pricing policy. Cost-plus approaches were once widespread in Europe, but are being replaced by other criteria, such as internal and/or external reference pricing, and, more recently, cost-effectiveness criteria that theoretically provide sounder alternatives for setting prices (Espin and Rovira, 2007).

In Thailand, Sooksriwong et al. (2009) suggested that a price regulation system should be implemented at every level of the medicine supply chain, from manufacturers to hospitals/medicine stores to patients. Such statements are easy to make, but the development of a price control system is often a long and difficult political process.

Various governmental subsidies for medicine manufacturers may not increase their availability and may actually decrease the amount of medicines that can be bought with available resources, as manufacturers can respond by increasing their prices and profits accordingly (Folland et al., 2001). By reducing the need for (local generic) manufacturers to compete with regional or global suppliers, such subsidies can also have the self-defeating result of dis-incentivising local producers to become competitive on the international market. Prices of generic medicines do not necessarily have to be regulated upstream by price controls and subsidies as this may create distortions in the market. In principle, generics prices could be brought down by reducing input costs for local factors of production, such as duties, tariffs and taxes and by promoting competition between producers.

It is vital to monitor the impact of such policies as they may not have the intended effect, as was the case in Peru. In 2007, medicines in Peru were exempt from paying import taxes, but this had no effect on wholesale prices or consumer prices (Meza Cornejo, 2010).

Pooled procurement and tendering

One lesson from the ARV situation is that a possible barrier to pooled procurement is a lack of regulatory and procurement capacity at the country level. With respect to pooled procurement of ARVs, generics were almost always lower priced than differentially priced originator ARVs, except where little generic competition existed and this was primarily in the protease inhibitor markets (Waning et al., 2009).

Given competition in the generics market, tenders are a useful policy option that aim to lower prices for generics. One policy option that has been used is a restricted tender system (in contrast to open tenders) for purchasing from well-known pre-qualified suppliers whose products have been previously authorised and with whom the procurement authority has had satisfactory results. However, the disadvantage of restricted tendering is that repeat tendering rounds may increase the likelihood of market concentration if the same suppliers win contracts, so that competitors let their product market authorisations expire. If tendering is for a single bidder to win 100% of the market, it only takes one company to trigger intense price competition amongst incumbent firms, if achieving the lowest price is the single most important criterion in this “single winner takes all” scenario. Very low prices and winning of the tender is preferable to staying out of the market provided this does not have any impact on quality or the continuity of supply resulting in risk to patients (Kanavos et al., 2009).

Tenders might be set up in a way that several manufacturers are selected for supplying the medicine at the same price. This might, in principle, prevent excessive concentration and its negative effects on future prices (Bumpas and Betsch, 2009). However, this policy may have unintended consequences downstream. For instance, stocking multiple manufacturers of the same medicine could be administratively cumbersome for pharmacies (Competition Bureau, Canada, 2007). A further lesson here is that the time period for which tenders are awarded could be limited to encourage more diversity in the market.

Other criteria besides price can be included in a request for tender, such as quality of the product, quality of the delivery system (e.g., appropriate coating of tablets for ease of swallowing) and security of supply. The tendering system could be structured to ensure patients and their doctors retain adequate choice of subsidised treatments.

4.2 Demand-side pro-generics policy options

Demand-side policies are neglected but critical

The fact remains that in many LMICs, much of the population does not have health insurance, so interventions relating to financial incentives/disincentives to purchase generic medicines (e.g., co-payments) would have to be provided through other mechanisms.

Governments and others should have a genuine interest in keeping expenditure in pharmaceuticals low and, hence, put in place strategies to increase demand of lower-priced quality-assured generic medicines. Lacking universal health coverage, promoting the use of low-priced medicines should be one of the top priorities of governments in LMICs.

Publication of medicines prices to increase transparency

Greater price transparency decreases information asymmetry. Health care professionals and consumers/patients often do not have sufficient information to make an informed decision about medicines prices. As well, patient price information may not be published in a way that is easily accessed by people.

It is unfortunate that many LMIC authorities have insufficient information to make pricing decisions. In high-income countries, although price transparency appears not to be a problem with regard to generic medicines in the context of internal reference pricing, it is still a problem when prices are needed from other countries for originators (e.g., for external reference pricing). Where price databases are used, it is important to bear in mind that unless it specifies to the contrary, it may be that procurement prices are not true transactional prices because discounts and rebates are not factored in.

Misalignments amongst prescribers, dispensers and consumers

One key message is that in many LMICs, the lack of a comprehensive insurance scheme makes it extremely difficult for policy-makers to implement cost-saving measures. This is coupled with a host of economic, cultural and behavioural issues that must be overcome. This is an issue in both LMICs and high-income countries.

Clearly, increasing or, at worst, maintaining profit margins, will drive the agenda of almost everyone in the pharmaceutical value chain, except the consumer.

Legislation on when it is (or not) permitted to prescribe a generic or brand is often not written clearly enough, or perhaps more importantly, is perceived as not being written clearly enough. In this demand-side of the pharmaceutical value chain, perceptions will often define reality. Some prescribers (and obviously many consumers) continue to have a perception that generics are low quality.

Influencing prescribing behavior

Strategies that can undermine cost-saving

Generally, there are several reasons why cost savings amongst producers, prescribers and dispensers would not be passed onto patients. First, patients may decline generic substitution when the average saving per substitution is low, and conversely, generic substitution increases when the average saving per substitution is high (Andersson et al., 2005). Savings between branded and generic products can be smaller than estimated from wholesale prices because the branded product price is overstated and the cheapest generic

product is not available. In Sweden, there was evidence that the introduction of an internal reference pricing system decreased entry of generics after patent expiration. The number of branded generics entering the market after patent expiration was half the number in the six years preceding the use of the reference pricing system (Ekelund M, 2001). Further, the savings from the reference pricing system were less than the savings resulting from greater generic entry.

There are many other policies to influence prescribing. Such policies include removing or limiting incentives/the capacity of the industry to influence prescribers' behaviour with gifts and the like. Removing perverse incentives to prescribe higher-priced products might be more effective than giving positive incentives. Other policies to consider are providing information on prices and cost-effectiveness of substitutes, providing comparative/benchmark information on prescribing practices allowing the individual doctors to compare his/her behaviour with that of other doctors, pharmaceutical advisers/inspectors that regularly discuss prescribing behaviour with doctors, and regulating the promotion of medicines. A key message is that introducing legislation on generic prescribing might be a challenge since there is likely to be political opposition against it. Therefore, it is advised to bring all stakeholders, particularly doctors regarding generic prescribing, on board as soon as possible (Habl et al., 2008). The WHO recommends a phased introduction as the most feasible approach: "It is not advisable to jump from the first phase into a system of obligatory generic prescribing—countries which have tried that have all failed." (WHO, 2001).

Influencing dispensing behaviour

Introducing legislation on generic substitution might also be challenging. It would be inadvisable to initiate mandatory generic substitution without thorough policy and empirical review. Encouraging generic prescribing as an intermediary step prior to initiating mandatory generic substitution could be useful because there may be resistance from prescribers and originator companies in LMICs if mandatory generic substitution was put into place immediately. However, mandatory generic substitution could be problematic in LMICs, especially if the MRA is weak and distrusted and where the pharmacy personnel do not have sufficient knowledge to substitute equivalent products.¹²

An important lesson is that generic substitution does not necessarily correlate with market share for generics, since in the UK, substitution is forbidden, but a 49% generic market share by volume has been achieved (European Generic Medicines Association, 2007/2009) largely due to generic prescribing by doctors.

One question that policy-makers may ask is whether one needs INN prescribing if there already is a generic substitution policy operating. A widely cited report in Denmark (Danish

¹² In the US, where MRA procedures for generic medicines are sufficiently robust, many states have adopted mandatory generic substitution laws for patients on the federal Medicaid programme, requiring that the generic version of a medicine be dispensed when available. Under these mandatory generic substitution policies, the brand name medicine remains available to beneficiaries through prior authorisation by the prescriber. The most stringent form of such "prior authorisation" requires the prescriber to obtain permission from Medicaid. Many states have applied these principles to all patients, whether or not on Medicaid.

Medicines Agency, 2009) looked at this question. While in Denmark it was recommended that INN prescribing be voluntary, the key points of this report are relevant for LMICs were:

- The societal economic benefit of lower-priced generics was already gained via mandatory generic substitution in pharmacies. It is certainly arguable that, in the absence of a generic substitution arrangement, patients would receive savings through generic prescribing.
- A significant prerequisite for improving patient safety was the introduction of more stringent requirements for the generic name to be printed on product packs.

What might perhaps be added to these findings is that, in Denmark, the relationship between doctors and pharmacists is characterised by a good understanding of each other's roles. This is important to consider.

A situation of conflict between doctors and pharmacists (including the fear of doctors about limitation of their "therapeutic freedom") might be a barrier to pro-generics policies, particularly generic substitution. A key message is that Denmark (a country that switched from external to internal reference pricing in April 2005) had already set in place a reference price system for nearly two decades and a competitive tendering system, so it had already a well-functioning series of generics policies.

The role of education

Training of doctors on how to communicate to patients about the quality of generics, and why medicines are prescribed by INN, is of key importance as a policy lever.

Indeed, school- and home-based surveys in Nepal, Malaysia, Romania, Finland, Ireland and the US found that even young students are remarkably similar in their lack of knowledge about medicines, levels of autonomy in medicine use, and desires for information about medicines. These similarities suggested that a curriculum, with modest modifications for local practices, could be adapted to medicine education programmes in schools throughout the world.

A further important message is that there is often a lack of educational programmes targeted at informing people about generics, as well as a lack of incentives for consumers and patients to purchase generic medicines.

5. Recommendations

Key enabling conditions for low- and middle-income countries

5.1 Minimum set of pro-generics enabling conditions

Based on our review, and particularly the lack of research on the implementation of pro-generic medicines policies, it appears that three over-arching enabling conditions need to be introduced before any LMICs can effectively implement and enforce any one of a number of pro-generic medicines policies. These conditions are necessary, but may be insufficient. Other policies described in this review should be added once these first three policies are in place. The additional policies should be implemented in a provisional or incremental manner and, most importantly, ideally they should be monitored and evaluated before they are implemented for the long-term.

5.1.1 Medicines of assured quality: a critical component

The first requirement for a successful generics policy is a mechanism sufficient to provide certainty that generic products are of assured quality. Clearly, this involves having an effective regulatory system (and an effective enforcement of anti-counterfeiting policies). Assured quality of generic medicines is the pre-condition for all measures to take effect.

It follows that the public sector should not promote the uptake of generic medicines *per se*, but rather lower-priced and quality-assured generics. It is reasonable to speculate that promoting INN generics is beneficial by itself as this would be less confusing to patients and prescribers, but even it were the case in one country, the finding may not be generalisable to other countries with different pharmaceutical markets and policy structures. In Peru, for instance, there is greater variability in prices across outlets for individual INN generic products than for individual branded generic products. Retailers may sense latitude to add higher mark-ups to lower-priced products (a regressive mark-up), or they may apply a fixed mark-up, which translates into a larger percentage on lower-priced products (WHO/HAI, 2006c; Madden et al., 2010).

To achieve medicines of assured quality, WHO recommends that each country has a fully functioning and transparent MRA. This includes transparency surrounding the evidentiary basis for every generic marketing authorisation, as well as a publicly-accessible database of generic equivalents of nationally registered products (e.g., similar to the FDA Orange Book). All this continues to be a major challenge for many LMICs because the shortcomings of MRAs in many countries are well documented (Gray, 2004). A functioning and reliable MRA is necessary, but not entirely sufficient to overcome the psychological conflation of “price” with “quality”. This appears to be an extremely important barrier. Price should never be a proxy for quality of medicines. In part, successful implementation of our second necessary condition (see 5.1.2) may help to overcome the “price-quality” barrier. The MRA can play a very active role through communicating reliable information about generic medicines and their quality, and imposing tough sanctions on violations on pharmaceutical promotion.

Even though other policies may be proposed or even implemented, it appears that unless stakeholders believe that a generic medicine is a quality medicine, policy implementation may not substantially increase the uptake of generics. Economic incentives, such as higher mark-ups for originators might help, but such policies need to be tested.

5.1.2 Systems are needed to facilitate market entry of generics

For generics to be used, they must firstly be available in medicine outlets (e.g., pharmacies, public sector health facilities). This starts with removing unnecessary barriers to entry for generics. In addition, if governments try to control the prices of generics at too low a level they might remove the incentives for generic entry.

Supply side policies that improve market entry for generics include Bolar provisions and reduced fees for market authorisation applications (Kaplan and Laing, 2003). In the US, the Hatch-Waxman legislation provides an incentive for early market entry by protecting the first generic by a market exclusivity period of six months, but subsequent entrants into the market gain no additional advantage. Nonetheless, as a country's MRA takes on the tasks of regulating a larger and more sophisticated pharmaceutical industry, it will be necessary to try and balance the needs of the originator and generic components of the industry.

Strong competition policies are needed to counter any abuse of the dominant position maintained by the pharmaceutical industry through monopoly IP protection. Although producers of generic medicines take advantage of improved products or new therapeutic alternatives through the innovation of the first mover originator, generic manufacturers must still spend substantial sums to "reverse engineer" and create a formulation (Baker and Ombaka, 2009) and develop and scale-up production. Generic manufacturers also face regulatory barriers including the costs of proving bioequivalence (if required), regulatory fees and other costs, delays and other obstacles.

Generic producers must secure a viable local distribution system for their product in every country of sale because they often do not have in-country distribution channels, and to develop them is expensive and time-consuming (Baker and Ombaka, 2009).

Contrary to expectations, introducing additional competitors on the market does not necessarily promote price competition, as shown in Europe. A high level of government regulation of price and/or reimbursements may actually distort the salutary effect of price competition.

Tendering is but one of the approaches that can be used to procure generic medicines. Tenders can only be successful if there are enough competitors bidding, but authorities need to be careful not to have a tendering system that reduces the number of active, effective competitors. For small countries, having but a single supplier substantially exacerbates the security of supply of the tendered medicines so splitting the tender may be important in these circumstances.

5.1.3 Demand-side policies: align incentives

Demand-side policies are important, but often neglected. Attempts must be made to align the incentives of prescribers, dispensers and consumers to use generics.

The characteristics of the healthcare system in many LMICs suggest the value of demand-side policies. Many such countries contain large numbers of people who pay out-of-pocket for medicines. Hence, incentives, such as those listed below, may be needed.

There was insufficient evidence to suggest which demand-side policies will be most effective in LMICs, but experience in Europe suggests that aligning different users and consumers of generics can be vital when selecting policy options (Kanavos et al., 2008; Simoens, 2008). These include prescribing by the generic name, generic substitution, financial incentives for pharmacy and medicines outlet personnel to dispense/sell low-priced generic medicines, and continued education of consumers about generic medicines.

One might expect barriers to the implementation of demand-side policies, too. In the following section, we summarise the policy options (in no particular order of priority) that are considered relevant in the European context (see Kanavos et al., 2008, Simoens, 2008) and whether they would likely be relevant in the context of LMICs.

Encourage mandatory substitution of originators by generics. Pharmacy personnel or medicines sellers in many LMICs lack formal training. Substitution of the originator product for a generic product might be considered unsafe in such contexts. Adequate product labeling and lists of products available for substitution provide aids to the retail sector to implement substitution policies. More training for pharmacy personnel should be promoted in parallel.

Encourage pharmacists and others to dispense lowest-priced, quality-assured products This is likely to be more achievable through reimbursement systems, but may not be relevant in LMICs because many lack health insurance schemes.

Regulate discounts, but use caution. Pharmacists may be receiving discounts and rebates from wholesalers and/or manufacturers. Discounts typically provide incentives to dispense a particular product over another. The discounts would need to be arranged in a way that encourages the dispensing of the lowest-priced product (originator or generic) of assured quality.

Regulate profit margins, but use caution. As part of reimbursement policies, this may influence dispensing practices. Regulating mark-ups, in principle, can avoid excessive add-on costs in the supply chain. However, fixed percentage mark-ups provide incentives to sell higher-priced products to obtain a higher return. Regressive mark-up schemes, on the other hand, may avoid this problem by allowing higher mark-ups for lower-priced products.

Encourage patients to ask for generic products. This may take the form of financial incentives that reduce co-payment on generic medicines or impose higher co-payment on originator products. However, the relevance of this policy depends on the extent to which the

population has insurance coverage. Even where there is limited or no insurance coverage, patients can be encouraged to ask for generics through campaigns.

Develop a cost-sharing system that favours generic medicines. This may or may not work, depending on other parameters of the health care system, such as overall price levels for medicines and insurance coverage, if any. In LMICs that lack insurance systems, some type of cost-sharing system is of interest as most citizens have to cover the large majority of the cost of medicines on their own. The cost sharing should always be proportional to income with safety nets for very low income people.

Publish information on product approval processes, quality and price. MRAs in LMICs invariably have limited budgets. Increasing the market authorisation fee of originator products provides additional funds, which may allow MRAs to take a more active role in promoting generic medicines uptake through the publication of information about generics in general (such as the scientific basis for the granting of market authorisation) and, in particular, information on their quality. Publishing information on price would be extremely important, but unless price components (rebates, discounts and the like) are specifically extracted from the prices found in some databases, prices may not reflect the true price for comparative purposes.

In general, systems that either facilitate early market entry of generics and/or put in place financial incentives for their use, are, in principle, better able to achieve the dual aims of increasing generic consumption and creating a competitive market in which substantial differences in prices exist between generics and originators (Kanavos, 2008).

5.2 Monitoring and evaluating policy changes

A lack of studies undertake systematic evaluations of the impact of policy changes on the uptake, availability and prices of generic products. Simoens (2009) looked at generic medicines policies in Poland. Significantly, he noted the lack of studies evaluating the impact of policy measures (much more generally for LMICs as the findings of this review confirm) and suggested that "...researchers make sure that the introduction of new measures governing generic medicines is accompanied by an evaluation of their impact."

It is crucial to actively collect data before and after a change of policy occurs. However, a baseline is seldom used to measure the effects of a new policy coming into force; therefore, positive and negative effects of policy changes can only be tentatively explained. The need for experimental or quasi-experimental studies should be addressed to tease out the drivers of generic medicines uptake and prices. Studies should be carried out at least as pre- and post-change with a control group, or as a time-series analysis. Monitoring and evaluation measures need to be built in during the development of a policy (not an after-thought), and carried out throughout its implementation.

Concerted efforts to develop robust monitoring and evaluation initiatives in-country are important, largely as they appear to be consistently missing from the pro-generics repertoire of many countries. This is not a trivial goal as programme evaluation is complex and

requires input and financial resources from a variety of disciplines. Absence of data or limited access to data suitable to carry out these evaluations is only one obstacle amongst others, such as a lack of incentives for institutions to perform evaluations, absence of financial resources and, as others have pointed out, the need for capacity training (see La Fond and Brown, 2003).

In our view, the policies suggested here should be implemented in a provisional manner with a clear monitoring and evaluation system in place. If the research shows that a given policy does not yield the intended effects, then it should be reviewed for possible amendment and if appropriate, the policy should be modified accordingly.

6. Conclusions

Generic medicines are essential to treat and/or prevent disease by increasing the accessibility and affordability of pharmaceuticals in global healthcare systems. It is critical that the generic medicines sector be sustained to ensure that these benefits exist going forward. Essential medicines must continue to be made available to as many patients as possible. The importance of policies to incentivise both supply- and demand-side stakeholders to improve low-priced and quality assured generic medicine uptake and bolster patient access to and use of generics is critical.

There almost invariably exists a tension between promotion of R&D of new medicines and promoting the use of generic medicines. The former allows the originator to set the price at a level to maximise profits as soon as possible upon market approval and before patent expiry to create incentives for innovation. At the same time, producers of generics will normally have to wait until the patent on the originator expires or is declared invalid before they can be the “second movers”. Policies and procedures to promote generics (e.g., Bolar provisions, compulsory licensing of patents) have the objective to ensure rapid access to essential medicines at more affordable prices and allows generic medicine manufacturers some flexibility as to the timing of market entry. At the same time, public health-driven models that were reviewed recognised the importance of strengthening the role of consumers, people dispensing or selling medicines, and prescribers in promoting the uptake of generic medicines.

This review of policy options and the existing research of pro-generic policies in LMICs has highlighted the existence of a large amount of literature on generics policies and their effects in high-income countries. Most of the policies in high-income countries require insurance systems, such as co-payment policies to incentivise consumers to choose generics. For example, it has been argued that insurance systems play a crucial role in increasing the share of generics in the pharmaceutical market in the US as a measure to reduce costs (Generic Pharmaceutical Association, 2005). The literature on the effect of pro-generics policies in LMICs is much scarcer than for high-income countries. The difference in the contextual factors between high-income and LMICs that influence pro-generics policies make it difficult to predict which policies can be successfully translated from high-income countries to LMICs.

However, the paucity of literature evaluating the impact of pro-generics policies should not deter countries from promulgating them. The results of policy evaluations are important to re-adjust the policies in place to more effectively promote the uptake of generic medicines in each particular country setting. Indeed, current interest generated by this topic is beginning to translate into a small number of implementation studies outside of high-income countries.

More information on policy options and their impact in LMICs is particularly important in the following areas: procurement of generics in the public sector, encouraging prescribing and dispensing of generics in the private sector, and consumer education about generics.

Differences in policies across LMICs reflect the variety of their historical, political and socioeconomic trajectories and contexts; therefore, it cannot be emphasised enough that no single recommendation can be applied across all countries. However, the results of this

review show that some policies are of particular importance to LMICs, such as demand-side policies, specifically those related to the private market. This is because the private sector is the main way people access medicines in many LMICs, especially countries in which medicine availability is poor in the public sector. Hence, most LMICs will benefit from a series of measures in several of the policy dimensions described in this review, particularly from analysing policy options that promote the prescribing and dispensing of generic medicines in the private sector and the use of generics by consumers and patients.

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8. Appendices

Appendix 1: Examples of definitions of generic medicines and their differences

Author/ year	Pharma- ceutical equiv- alence ^a	Thera- peutically inter- changeable (therapeutic equivalent) ^b	Patent	Unbranded (INN name only)	Brand name	Multi source	Term used in the definition
UN organizations							
WHO (2006)	+	+	-	-	-	+	Generic product ^c
PAHO (2010)	+	+	-	-	-	+	Generic product ^d
Scientific publications							
King and Kanavos (2002)	-	+	+	+	+	-	Generic medicine ^e
Regulatory agencies							
FDA	-	+	-	-	-	-	Generic drug product ^f
EMA	-	+	+	+	+	-	Generic medicine ^g
Brazil MRA	-	+	+	+	-	-	Medicame nto genérico ^h
Bolivia MRA	-	-	-	+	-	-	Medicame nto genérico ⁱ

+ Concept included in the definition

- Concept not included in the definition

The above table gives examples of definitions of generic medicines. The rows list the various sources of definitions. The columns list the various specific terms and/or concepts that the authors included in their definition of the term generic. The + sign means that the term or concept is included in the definition. A – sign indicates that the term or concept is not included in the definition.

To illustrate, both the WHO and PAHO definitions are identical. Both use the term “generic product”, both include the same concepts as part of the definition, namely, pharmaceutical equivalence, therapeutically interchangeable, and multisource.

Explanations of the terms in the table:

a. Pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance¹.

b. Therapeutic equivalence

Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labeling. This can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies¹.

c. Generic product

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable¹.

d. Generic product

Uses the term multisource pharmaceutical products as pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable².

e. Generic medicines

A generic medicine is identical, or bioequivalent, to a brand name medicine in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. On expiration of the originator product's patent term protection, other manufacturing companies may file submissions to regulatory authorities for approval to market generic versions of the originator medicine. Generic medicines may be marketed under the non-proprietary (INN) name or as a branded generic. Branded generic medicines have names derived from a combination of the manufacturer's name and the non-proprietary name. This enables the manufacturer to market the product in a way similar to the proprietary product. Therapeutic and safety equivalence between products is assumed, from a regulatory perspective, on the basis of quality equivalence. This is evidenced from bioequivalence and chemical data. Products are considered to be bioequivalent if their rates and extent of absorption do not show a significant difference³.

f. Generic medicine product

Is one that is comparable to an originator medicine product in dosage form, strength, route of administration, quality, performance characteristics and intended use. Generic medicine applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead,

generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the originator medicine). One way scientists demonstrate bioequivalence is to measure the time it takes the generic medicine to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic medicine, which they can then compare to that of the originator medicine. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the originator medicine⁴.

g: Generic medicine

What is a generic medicine? A generic medicine is a medicine which is similar to a medicine that has already been authorised (the 'reference medicine'). A generic medicine contains the same quantity of active substance(s) as the reference medicine. Generic and reference medicines are used at the same dose to treat the same disease, and they are equally safe and effective. The name, appearance (such as its colour or shape) and packaging of a generic medicine differ to those of the reference medicine. It may also contain different inactive ingredients. As for all medicines, where precautions are necessary because of any inactive ingredient, these will be described both on the label and in the package leaflet of the medicine⁵.

How is a generic medicine authorised? Like originators, a generic medicine needs to receive a marketing authorisation before it can be marketed. A marketing authorisation is granted after a regulatory authority has conducted a scientific evaluation of the efficacy, safety and quality of the medicine. Originator medicines generally benefit from a period of data protection. After expiry of this period, companies can apply for a marketing authorisation for a generic medicine⁵.

How is a generic medicine evaluated? As the originator (reference) product has been authorised for several years, information is already available which does not need to be reproduced. Legislation defines the tests that must be carried out to demonstrate that the generic medicine is as safe and effective as the reference medicine. In the majority of cases, a bioequivalence study provides sufficient information. This is a study to show that there is the same quantity of the active substance in the human body whenever the same dose of generic medicine or reference medicine is taken. Generic medicines are manufactured according to the same quality standards as all other medicines⁵. Regulatory authorities also perform periodic inspections of the manufacturing site(s) as for all other medicines.

Is the safety of generic medicines monitored? The safety of all medicines, including generic medicines, is also monitored post-marketing. Each company is required to set up a system to monitor the safety of the products that it markets. Regulatory authorities may also perform an inspection of this monitoring system. If there are specific precautions to be considered when taking the reference medicine, the generic medicine will require in general the same safeguards⁵.

h. Medicamento genérico

A medicine interchangeable with its reference product, which has been proven to have the same efficacy, safety and quality. They are produced after the expiration of the patent and identified by their INN names⁶.

i. Medicamento genérico

Those medicines that have an INN name⁷.

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