

**WHO Guideline on
Country
Pharmaceutical
Pricing Policies**

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Overall coordination

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Executive summary

Medicines account for 20–60% of health spending in low- and middle-income countries, compared with 18% in countries of the Organisation for Economic Co-operation and Development. Up to 90% of the population in developing countries purchase medicines through out-of-pocket payments, making medicines the largest family expenditure item after food. As a result, medicines, particularly those with higher costs, may be unaffordable for large sections of the global population and are a major burden on government budgets. The Millennium Development Goals include the target: “[I]n cooperation with pharmaceutical companies, provide access to affordable, essential drugs in developing countries.”

Initiatives to stimulate availability and access through manufacturing innovations, procurement mechanisms, or supply chain improvements require management of pricing to have sustainable impact. The past ten years have seen the introduction of several initiatives at both global and regional levels to support countries in managing pharmaceutical prices. Despite some clear successes, many countries are still failing to implement the policy and programme changes needed to improve access to affordable medicines.

This guideline was developed to assist national policy-makers and other stakeholders in identifying and implementing policies to manage pharmaceutical prices. Although the feasibility of these policies in countries of all income levels was considered, special consideration was given to implementation needs in low- and middle-income countries, where the pharmaceutical sector may be less regulated. References to low- and middle-income countries are therefore intended to highlight specific implementation needs and do not to exclude the appropriateness for high-income settings.

WHO uses the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) for the development and review of recommendations. This guideline was developed with consideration to GRADE principles including development of PICO questions, systematic reviews of existing literature and consideration of the quality of the evidence; however, the available evidence did not support the development of functionally useful GRADE tables. The majority of the evidence was case descriptions and generally considered low-quality by experts. The recommendations included in this guideline are therefore mainly based on the experience of the Expert Panel and their review of the qualitative evidence, with note of the need to develop more quantitative evidence for future updates. The scope of this guideline is expressed in the three overarching policy questions below.

1. **Should countries use price control measures to manage medicine prices? If so:**

- Can external reference pricing be effective in low- and middle-income countries?
- Should health technology assessment be used in decision-making and/or price setting in low- and middle-income countries?
- Can cost-plus price setting be effective in low- and middle-income countries?

2. **Should countries adopt measures to control add-on costs in the supply chain? If so:**
 - Should wholesaler and dispenser mark-ups be controlled in low- and middle-income countries?
 - Should medicines be exempt from taxes and/or tariffs?

3. **Should countries promote the use of quality assured generic medicines as a strategy to manage medicine prices? If so:**
 - What prerequisites are needed to promote use?
 - Should strategies be used to facilitate/accelerate market entry of generics (e.g. TRIPS flexibilities and compulsory licensing, facilitated regulatory approval, fast-tracking and/or reduced fees)?
 - Should optional/mandatory generic substitution by dispensers be used?
 - What is the role of generic competition in the pharmaceutical market as part of a strategy for managing prices?
 - Should internal reference pricing by product or therapeutic group be used?
 - Should strategies be adopted to encourage the use of generic or lower-cost products by providers (prescribers and dispensers)?
 - Should strategies be adopted to encourage the use of generic or lower-cost products by consumers?

The WHO Department of Essential Medicines and Health Products led the development of the guideline, following the processes specified by the WHO Guideline Review Committee. A guideline panel was convened to define the scope of the guideline, review the evidence summaries, and develop the recommendations. An external consultation process was held with a targeted group of stakeholders to obtain input on draft recommendations and accompanying evidence summaries. The recommendations are listed below, together with a list of general considerations identified by the panel.

Box 1: Guideline recommendations and key principles

POLICY INTERVENTION	RECOMMENDATIONS
<p>Regulation of mark-ups in the pharmaceutical supply and distribution chain</p>	<ul style="list-style-type: none"> ➤ As part of an overall pharmaceutical pricing strategy, countries should consider regulating distribution chain mark-ups (distributors/wholesalers). ➤ As part of an overall pharmaceutical pricing strategy, countries should consider regulating retail chain mark-ups and fees (pharmacies, dispensing doctors, dispensaries). ➤ If mark-ups are regulated, countries should consider using regressive mark-ups (lower mark-up for higher-priced products) rather than fixed percentage mark-ups, given the incentive that the latter provides for higher-priced products to receive a higher net margin. ➤ Countries should consider using remuneration/mark-up regulation to provide incentives for supplying specific medicines (generics, low volume medicines, reimbursable medicines) or to protect specific patients or population groups (e.g., vulnerable groups, remote populations). ➤ In systems where rebates and discounts in the distribution chain occur, countries should consider regulating them and should make them transparent. The information should be taken into account when reviewing and regulating mark-ups and prices.
<p>Tax exemptions/reductions for pharmaceutical products</p>	<ul style="list-style-type: none"> ➤ Countries should consider exempting essential medicines from taxation. ➤ Countries should ensure any tax reductions or exemptions result in lowered prices to the patient/purchaser.
<p>Application of cost-plus pricing formulae for pharmaceutical price setting</p>	<ul style="list-style-type: none"> ➤ Countries generally should not use cost-plus as an overall pharmaceutical pricing policy. ➤ Countries using a cost-plus method as an overall policy that wish to change their strategy should consider replacing or complementing the cost-plus approach with other policies, including those covered in this guideline.
<p>Use of external reference pricing</p>	<ul style="list-style-type: none"> ➤ Countries should consider using external reference pricing as a method for negotiating or benchmarking the price of a medicine. ➤ Countries should consider using external reference pricing as part of an overall strategy, in combination with other methods, for setting the price of a medicine. ➤ In developing an external reference pricing system, countries should define transparent methods and processes to be used. ➤ Countries /payers should select comparator countries to use for ERP based on economic status, pharmaceutical pricing systems in place, the publication of actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease.
<p>Promotion of use of generic medicines</p>	<ul style="list-style-type: none"> ➤ Countries should enable the early market entry of generics through legislative and administrative measures that encourage early submission of regulatory applications, and allow for prompt and effective review. ➤ Countries should use multiple strategies to achieve low priced generics, depending on the system and market. These strategies may include: within-country reference pricing, tendering, and/or lower co-payments. ➤ In order to maximize uptake of generics, countries should implement (and enforce as appropriate) a mix of policies and strategies, including: <ul style="list-style-type: none"> ○ Legislation to allow generic substitution by dispensers; ○ Legislative structure and incentives for prescribers to prescribe by international nonproprietary name; ○ Dispensing fees that encourage use of low price generics; ○ Regressive margins and incentives for dispensers; and ○ Consumer and professional education regarding quality and price of generics.

POLICY INTERVENTION	RECOMMENDATIONS
Use of health technology assessment	<ul style="list-style-type: none"> ➤ Countries should use health technology assessment (HTA) as a tool to support reimbursement decision-making as well as price setting/negotiation. ➤ Countries should combine HTA with other policies and strategies, particularly within-country reference pricing (by chemical entity, pharmacological class, or indication). ➤ Countries should consider the following approaches for using HTA: review of applicability and adaptation of reports from other countries; review of reports submitted by pharmaceutical companies; conduct assessments based on local information and local data. The choice of approach depends on technical capacity and local decision-making structures. ➤ Countries could take a stepwise approach to develop legislative and technical capacity to take full advantage of the potential utility of HTA in pharmaceutical price setting. ➤ In establishing the legislative/administrative framework, countries should clearly define the roles and responsibilities of the decision-makers and other stakeholders, and the process of decision-making. ➤ Countries should ensure that HTA processes are transparent and that the assessment reports and decisions should be made publicly available and effectively disseminated to stakeholders. ➤ Countries should collaborate to promote exchange of information and develop common requirements for HTA.
KEY PRINCIPLES	
<ul style="list-style-type: none"> • Countries should use a combination of different pharmaceutical pricing policies that should be selected based on the objective, context and health system. • Countries should make their pricing policies, processes, and decisions transparent. • Pricing policies should have an appropriate legislative framework and governance and administrative structures, supported by technical capacity, and should be regularly reviewed, monitored (including actual prices) and evaluated and amended as necessary. • In promoting the use of affordable medicines, countries should employ a combination of pharmaceutical policies that address both supply and demand issues. • If regulation of pharmaceutical prices is introduced, effective implementation will be required to ensure compliance (e.g. incentives, enforcement, price monitoring system, fines). • Countries should adopt policies to promote the use of quality assured generic medicines in order to increase access and affordability. • Countries should collaborate to promote exchange of information about policies, their impacts, and pharmaceutical prices. 	

In developing the recommendations, the panel noted that the overall quality of research and evidence in relation to pharmaceutical policy implementation and impact is poor, especially in developing country settings. There are many areas where more descriptive studies and good quality research would allow better understanding of what policies should be chosen and how they should be implemented. However, it is clear that such research takes time to complete and therefore the panel recommended that the guideline should be reviewed for potential update in 5 years.

1. Introduction

Medicines account for 20–60% of health spending in low- and middle-income countries, compared with 18% in countries of the Organisation for Economic Co-operation and Development (OECD). Up to 90% of populations in developing countries buy medicines through out-of-pocket payments, making medication the largest family expenditure item after food. High prices of medicines might force people to forego treatment or go into debt. As a result, medicines are inaccessible to large sections of the global population and a major burden on government budgets.ⁱ This inequity is recognized in the Millennium Development Goal target: “[I]n cooperation with pharmaceutical companies, provide access to affordable, essential drugs in developing countries.”ⁱⁱ

Affordable prices are designated by WHO as a determinant of access to medicines – together with rational selection and use, sustainable financing, and reliable health and supply systems.ⁱⁱⁱ Despite some clear successes, many countries are still failing to implement policies and programmes to improve access to affordable medicines. The challenges faced differ by country but a common problem is the lack of technical capacity to analyse and interpret the relation between price data and local policies and to respond effectively to high prices or unusual price variations. A related issue is the paucity of published evidence on the effectiveness of policies in low- and middle-income countries. Lack of political commitment due, for example, to conflicting industrial or trade policies, can also act as a barrier to the adoption of strategies to reduce the price and improve the availability of medicines.^{iv}

The past ten years have seen the introduction of several global and regional initiatives, including a collaboration between WHO and the international nongovernmental organization Health Action International (HAI) to improve medicine availability and affordability in low- and middle-income countries. Project activities included development of a standard survey methodology for measuring medicine prices and availability, which has been applied in more than 50 countries. Medicine pricing activities are also under way in WHO regions, such as development of regional reporting systems for government pharmaceutical procurement prices. Several regional networks, such as the European-based Pharmaceutical Pricing and Reimbursement Information, have been established to share information on pharmaceutical pricing and reimbursement decisions. Efforts have also been made by the Pharmaceutical Pricing and Reimbursement Information, the OECD, and others to document the pharmaceutical pricing policies being implemented in countries. However, evidence of the impact of such policies is generally scarce, especially in low- and middle-income countries.

As part of the WHO/HAI project, a series of six reviews was completed to identify and describe policies used to manage medicine prices, increase availability, and make medicines more affordable, particularly in low- and middle-income countries. These WHO/HAI policy reviews include published and unpublished materials, country case studies, and key informant interviews. The topics of these reviews, plus the definitions used throughout this guideline, appear in Table 1.

Table 1: WHO/HAI review series – topics and definitions

Policy/intervention topic	Definition
Regulation of mark-ups in the pharmaceutical supply and distribution chain	A mark-up represents the additional charges and costs that are applied to the price of a commodity in order to cover overhead costs, distribution charges, and profit. In the context of the pharmaceutical supply chain, policies might involve regulation of wholesale and retail mark-ups as well as pharmaceutical remuneration.
Tax exemptions/reductions for pharmaceutical products	There are two main categories of tax: direct tax, levied by governments on the income of individuals and corporations, and indirect taxes, added to the prices of goods and services and collected through the businesses that provide them. Direct taxes, along with social security taxes, generally make up about two thirds of total government revenue in high-income countries. In low-income countries, indirect taxes, on international trade or on the purchase of goods and services, are the major sources of government revenue. Policies might involve the reduction of taxes on medicines, or the exemption of medicines from taxes, particularly sales taxes.
Application of cost-plus pricing formulae for pharmaceutical price setting	Cost-plus pricing is a method for setting retail prices of medicines by taking into account production cost of a medicine together with allowances for promotional expenses, manufacturer’s profit margins, and charges and profit margins in the supply chain.
Use of external reference pricing	External reference pricing (ERP; also known as international reference pricing) refers to the practice of using the price of a pharmaceutical product (generally ex-manufacturer price, or other common point within the distribution chain) in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. Reference may be made to single-source or multisource supply products.
Promotion of use of generic medicines	Generic medicines are produced and distributed without patent protection. Promotion of the use of quality assured generic medicines is a method of managing pharmaceutical prices. The various approaches used include facilitated market entry of generics, generic substitution by dispensers, ERP, strategies to foster competition in the market, and schemes to encourage use of generics among providers and consumers.
Use of health technology assessment (HTA)	The International Network of Agencies for Health Technology Assessment defines HTA as “The systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.” HTA in relation to pharmaceuticals encompasses evaluations relevant to price setting or pricing policies.

The purpose of this document is to provide advice for countries on managing pharmaceutical prices that: (i) consolidates the evidence from countries at all income levels; (ii) builds on the reviews done as part of the WHO/HAI project; and (iii) reflects experiences from a range of countries.

2. Target audience

The target audiences for this guideline are listed below.

- Policy-makers and decision-makers in countries that are considering introducing or revising their strategies to improve access to medicines through appropriate price-management policies.

- Decision-makers in countries who are involved in strategic and operational decisions relating to procurement and distribution of medicines or reimbursement decisions in national health insurance schemes.
- Donors, development partners, and other stakeholders who assist countries in development of the pharmaceutical sector and/or supply of medicines.

This guideline is intended for use in countries of all income levels. However, special consideration is given to implementation needs in low- and middle-income countries, where the pharmaceutical sector may be less regulated. References to low- and middle-income countries are therefore intended to highlight specific implementation needs and do not to exclude the appropriateness for high-income settings.

3. Scope of the guideline

The scope of this guideline focuses on three overarching policy questions, each with a series of more detailed sub-questions:

A. Should countries use price control measures to manage medicine prices? If so:

- Can ERP be an effective pricing strategy in low- and middle-income countries?
- Should HTA be considered as part of (i) decision-making and/or (ii) price setting in low- and middle-income countries?
- Can cost-plus price setting be an effective pricing strategy in low- and middle-income countries?

B. Should countries adopt measures to control add-on costs in the supply chain? If so:

- Should wholesaler and dispenser mark-ups be controlled in low- and middle-income countries?
- Should medicines be exempt from taxes and/or tariffs?

C. Should countries promote the use of quality assured generic medicines as a strategy to manage medicine prices? If so:

- What prerequisites are needed to promote increased use of generic medicines?
- Should strategies be used to facilitate/accelerate market entry of generics (e.g. trade-related aspects of intellectual property rights (TRIPS) flexibilities and compulsory licensing; facilitated regulatory approval; fast-tracking and/or reduced fees)?
- Should optional/mandatory generic substitution by dispensers be used to promote increased use of generic medicines?
- What is the role of generic competition in the pharmaceutical market as part of a strategy for managing prices?
- Should internal reference pricing (IRP), by product or therapeutic group, be used to promote increased use of generic medicines?

- Should strategies be adopted to encourage the use of generic/lower-cost products among prescribers and dispensers?
- Should strategies be adopted to encourage the use of generic/lower-cost products among consumers?

Although pharmaceutical procurement by governments, hospitals, and other organizations is relevant to pricing, this topic is extensively elsewhere and is not addressed in this guideline. Similarly, marketing and promotion practices by the pharmaceutical industry, which can have strong influences on prices, are outside the scope of this guideline.

4. How this guideline was developed

The WHO Department of Essential Medicines and Health Products led the development of the guidelines under the oversight of the WHO Guideline Review Committee. A WHO steering committee was responsible for overseeing and managing the guideline development process and comprised WHO staff from: Essential Medicines and Health Products, Public Health, Innovation and Intellectual Property, and Access to Medicines Policy Research, Alliance for Health Policy and Systems Research (HSR/HSS).

A guideline panel was convened to define the scope of the guideline, review the evidence summaries, and develop the recommendations. Panel members included content experts and academic personnel with expertise in the topic, potential end users, and experts skilled in guideline development methodology, in addition to experts from WHO Headquarters and Regional Offices ([Annex B](#)). Declarations of interest were collected from panel members and managed according to WHO requirements 2011 ([Annex C](#)). The guideline panel held one electronic meeting to agree on the scope of the guideline and one in-person three-day meeting to review the evidence summaries and develop the recommendations.

The guideline scope and development process is described in [Annex D](#), including a specific rationale for not including Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables in these recommendations. Developing an alternative table was not viewed by the panel as having the potential to add value to the usability and clarity of the recommendations.

The evidence considered for the development of the guideline was based on a series of literature reviews^{v-x} completed during 2010–11 by the WHO/HAI collaboration on pharmaceutical prices.^{xi} A global working group convened as part of the WHO/HAI pricing project responsible for oversight and peer review of the series. For each review, literature searches were specified as part of the protocol development and, in particular, searches were done to identify grey literature relevant to low- and middle-income countries. In addition to the WHO/HAI series of literature reviews, additional evidence was retrieved by searching relevant databases (PubMed, EconLit, ISI Web of Knowledge, Cochrane Library) for systematic reviews of pharmaceutical pricing policies identified in the guideline scope.

At the time of guideline protocol development, based on the absence of summary of findings tables in relevant Cochrane reviews, it was determined that that it would not be possible to prepare Grading of Recommendations Assessment, Development and Evaluation evidence

profiles, since few publications provided quantitative estimates of the impact of pricing policies on health outcomes or access to medicines. It was therefore predetermined that evidence summaries would be prepared as study-by-study tables from each WHO/HAI policy review, supplemented with any systematic reviews retrieved by the additional search.

The guideline development protocol initially proposed that methods used for assessment of the quality of the evidence would be based on advice from the Effective Practice and Organization of Care representative in the guideline panel, depending on the type of studies included. However, the qualitative and anecdotal nature of the evidence was such that formal assessment of the quality of the evidence was not deemed useful and GRADE evidence profiles were therefore not produced.

It was also pre-specified that in the expected absence of any experimental design studies of pharmaceutical policies, evidence from studies using time series design with repeated measures of either health outcomes or access to medicines would be considered as the most reliable basis to determine the estimate of effect of any policy. However, no such research was found; all studies were essentially case descriptions.

The evidence summaries were used as the basis for drafting recommendations and were also part of the review process. WHO staff with support of an expert consultant drafted the initial recommendations and evidence summaries, which were circulated to a separate group for external consultation. This group included experts and organizations representative of the relevant stakeholders, including pharmaceutical industry associations and nongovernmental organizations and international organizations working on access to medicines and pharmaceutical pricing issues. The feedback received from the consultation was considered by the guideline panel in formulating the recommendations. The recommendations and evidence summaries were circulated to the guideline panel prior to the in-person meeting.

The panel met in Geneva in November 2011. The panel determined that, in the absence of evidence-quality grading, it would not be possible to attribute a level of strength to individual recommendations.

The following approach for developing recommendations for each of the six policy topics was used. The panel reviewed the evidence summary, examined their own experience in different settings and countries in relation to the evidence provided, and reached consensus points, including the benefits and downsides of implementation of the policy. The recommendations for each of the six policies resulted from consensus based on the evidence and experiences noted above, with a caveat in each case regarding the paucity of research findings. There was also consensus on principles and considerations relevant to policy selection and implementation.

A full draft guideline was circulated for comment and final approval by the panel. No further peer review was sought at that time since all substantive comments from stakeholders had been considered in formulating the recommendations. The final draft was submitted for WHO publication approval according to the standard processes.

5. Recommendations

5.1 Regulation of mark-ups in the pharmaceutical supply and distribution chain

5.1.1 Definition of policy

A mark-up represents the additional charges and costs that are applied to the price of a commodity in order to cover overhead costs, distribution charges, and profit. In the context of the pharmaceutical supply chain, policies might involve regulation of wholesale and retail mark-ups as well as pharmaceutical remuneration.

5.1.2 Evidence

The panel considered the following information as the basis for the recommendations (see [Annex E](#)).

- The WHO/HAI policy review on this topic,^{vi} which identified reports from approximately 60 countries about aspects of mark-up regulation and its implementation (Annex E, Table ES1.1). The review noted that there were no formal assessments in low- and middle-income countries that could be used to evaluate the effect of mark-up regulation, whether used in isolation or in conjunction with other policies.
- Detailed case studies of Albania, South Africa, and Mali, which were done as part of the WHO/HAI project to supplement the review.
- An additional literature search retrieved no other evaluative studies or systematic reviews.

The evidence is primarily descriptive in nature, from case studies of different countries, surveys of pharmaceutical prices, and reviews of web sites. Information is provided the quantification of mark-ups that exist in supply chains relative to ex-manufacturer prices, in some cases in both public and private sectors of pharmaceutical supply chains. There are reports of mark-ups for specific products, e.g. for artemisinin combination treatments (see Patouillard et al, 2010^{xii}). Evidence on groups of products was also derived from the HAI country pricing survey reports.^{xiii} The degree of enforcement and regulation, whether dispensing fees are also regulated, and formulae used to calculate mark-ups are also described. The panel noted that the case studies of the three countries provided additional detail about the application of mark-ups but did not provide any information about the impact of the policy.

The policy review provided anecdotal information from a few countries about the impact of imposing or removing mark-ups (see Annex E). The effect of imposing or removing mark-ups on prices was inconsistent and had unpredictable effects on access to medicines. For example, the report from China indicated that enforced distribution mark-ups created an incentive to use high-cost medicines, thus presumably inhibiting access for some consumers. In Jordan, removal of mark-up regulation resulted in price increases, which led to the controls being re-imposed.

The WHO/HAI policy review noted that regulation of distribution mark-ups can have unintended impacts or consequences. Incentives and disincentives within a supply chain must be mapped and potential unexpected effects considered before controls are imposed. The review also suggested that mark-ups that include a regressive component (i.e. a lower mark-up

for higher-priced products) with or without fixed fees, as is done in countries such as Tunisia, Syria, and Lebanon, probably lead to better outcomes than fixed percentage mark-ups through their influence on financial incentives. However, fixed fee mark-ups can dramatically increase the price of otherwise low-cost medicines.

It is clear that mark-up controls are used in many countries, irrespective of income (see Annex E), although notable exceptions are the USA and the UK.^{xiv} However, there is no evidence comparing the use of mark-ups to other pricing policies with respect to comparative price or availability of and access to medicines. Nor is there evidence on the impact of mark-up regulation on medicine prices. The panel noted that systematic pre- and post-implementation studies, such as the case -study of Jordan noted above, would be very helpful as a minimum to document mark-up policy effects.

5.1.3 Findings of the panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. The consensus points are listed below.

- Mark-up controls are applied in many countries and appear to be one option to stop excessive charges being added to medicines as they move through the supply chain.
- There is variability in the methods for calculating and controlling the size of mark-ups – ranging from 0% mark-up allowed on hospital medicines in South Africa to more than 100% mark-ups in some private sector retail pharmacies (see Annex E). A single model does not fit all settings.
- While there is no evidence that directly describes the impact of enforcement of mark-ups, use of mark-ups without enforcement does not appear to be effective.
- If control of mark-ups is implemented, the effects on prices of pharmaceuticals to patients and payers must be monitored to ensure there are no adverse effects on affordability or access.
- Countries have a variety of starting-points within the pharmaceutical supply chain that are used as the base cost to which mark-ups are applied (see Annex E). The panel therefore defined the starting-point for calculation of mark-ups as the cost of goods that the first distributor has to pay.
- The structure of the health system and setting (e.g. urban/rural distribution chains) will determine how mark-ups can be applied and regulated. For example, private supply chains may be more prevalent in some areas and may also be more difficult to regulate.

5.1.4 Benefits and downsides

The panel considered the potential benefits and downsides of implementing mark-up regulation as a policy, noting that there is no evidence of the impact of this policy on health outcomes (see Annex E).

Benefits

- Regulation of mark-ups particularly in settings where there have been no price control strategies, may lead to lower prices of medicines.

- Regulation of mark-ups may be technically less complex to implement than other policy options as it require relatively limited information about cost of goods and the supply chain, and some enforcement capacity.

Downsides

- Regulation of mark-ups can have unintended negative consequences on availability and access through distortion of prices.
- There is potential for lack of transparency in the development of mark-up structures, which could allow higher prices.
- Regulation of mark-ups without adequate enforcement appears ineffective.
- Mark-up regulation can be relatively inflexible thus may not be sufficiently sensitive to market changes.

5.1.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the paucity of information on the impact of regulating pharmaceutical mark-ups on health outcomes but also that many countries use this policy; and made the recommendations below.

- ❖ As part of an overall pharmaceutical pricing strategy, countries should consider regulating distribution chain mark-ups (i.e. regulation of distributors and wholesalers).
- ❖ As part of an overall pharmaceutical pricing strategy, countries should consider regulating retail chain mark-ups and fees (i.e. regulation of pharmacies, dispensing doctors, and dispensaries).
- ❖ If mark-ups are regulated, countries should consider using regressive mark-ups (i.e. lower mark-up for higher-priced products) rather than fixed percentage mark-ups, given the incentive that the latter provide for higher-priced products to receive a higher net margin.
- ❖ Countries should consider using remuneration/mark-up regulation to provide incentives for supplying specific medicines (e.g. generics, low volume medicines, reimbursable medicines) or to protect specific patients or population groups (e.g. vulnerable groups, remote populations).
- ❖ In systems where rebates and discounts in the distribution chain occur, countries should consider regulation and should make them transparent. This information should be taken into account when reviewing and regulating mark-ups and prices.

5.1.6 Issues for implementation

The panel noted that the implementation of mark-up regulation needs high-level political support as well as a strategy for enforcement. The requirements for effective implementation identified are listed in Table 2.

Table 2: Implementation issues for mark-up regulation

Issues	Requirements
Technical capacity	<ul style="list-style-type: none"> • Statistical expertise to analyse commercial and/or medicine price data. • Medical and pharmaceutical expertise to assess incentives and disincentives in the supply chain and the effects on supply and rational use of medicines. • Economic expertise to analyse distribution costs and determine appropriate remuneration or budgetary requirements for stakeholders.
Data required	<ul style="list-style-type: none"> • Medicine prices; sales data.
Infrastructure	<ul style="list-style-type: none"> • Legislation setting up parameters for use. • Structures for consultation with concerned stakeholders. • A mechanism for monitoring medicine prices, use, and sales.
Methodological considerations	<ul style="list-style-type: none"> • Availability of resources and structures to implement mark-ups in a transparent manner.

5.2 Tax exemptions/reductions for pharmaceutical products

5.2.1 Definition of policy

There are two main categories of tax: direct tax, which are levied by governments on the income of individuals and corporations, and indirect taxes, which are added to the prices of goods and services. Direct taxes, along with social security taxes, generally make up about two-thirds of total government revenue in high-income countries. In low-income countries, indirect taxes, on international trade or on the purchase of goods and services, are major sources of government revenue. Policies relevant to pharmaceutical products might involve the reduction of taxes on medicines, or the exemption of medicines from taxes, particularly sales taxes.

5.2.2 Evidence

The panel considered the following information as the basis for the recommendations (see [Annex F](#)).

- The WHO/HAI policy review on this topic.^{vii} This review was based on two literature searches: (i) for publications relevant to medicines and taxation, and (ii) for papers assessing the relation between price changes and the use of medicines. The policy review notes that individual country web sites were useful sources of information (e.g. for information on national value added tax [VAT]). The HAI country pricing survey reports provided the most information about tax on medicines in low- and middle-income countries.^{xi}
- Two relevant studies were identified (see Annex F, Table ES2.1).
- An additional literature search retrieved no other evaluative studies or systematic reviews.

The WHO/HAI policy review highlights that indirect taxes on medicines, such as sales tax or VAT, are regressive and therefore inequitable, since the amount paid is a percentage of price and is the same for everyone, rich or poor. Consequently, a medicine tax will consume a larger share of a poor person's income than that of a rich person. However, since the early 1990s VAT has become a common revenue-raising strategy for low- and middle-income countries. The review states that there is a trend for VAT to replace sales tax, since it relieves governments of much of the responsibility of tax collection and allows relatively high rates of tax to be charged with a lower risk of evasion.

The policy review summarizes the use of VAT on medicines in high-income European countries, where VAT on medicines ranges from 0% to 25%. Many countries use a lower VAT rate on medicines than the standard VAT rate, while others exempt prescription medicines (see Annex F, Table ES2.2). In some high-income countries, such as Australia, Japan, and the Republic of Korea, medicines are tax-exempt. In the USA, the tax levied varies by state. Taxation on medicine in low- and middle-income countries ranges from 2.9% to 34%. Table ES2.3 in Annex F summarizes taxes on medicines based on material from the WHO/HAI database and medicine price surveys.

There are some descriptive studies assessing the rate of taxation (see Annex F) but only limited published evidence directly addresses the impact of tax reductions/exemptions in pharmaceutical price management. The policy review highlights some examples of the impact of taxes on access to care, and medicines use (Goldman 2007^{xv}). These tend to show that taxes on medicines disproportionately affect the poor. The policy review also estimates tax revenues derived from medicines and their proportion to overall national tax revenue.

5.2.3 Findings of the of panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. The consensus points are listed below.

- Choice of tax base for ensuring adequate revenue is an issue for national governments beyond simply medicines or health policy. While this is recognized by the panel, consideration should be given to ensuring that essential medicines are not taxed, for reasons of equity and safeguarding access to adequate care.
- Taxes on specific components of medicines, such as importation tax applied to the active pharmaceutical ingredients, can have a big impact on the price of the final product, and can affect capacity for local production.
- Medicines are taxed in many countries; however, the benefit of these taxes to the patient are unknown.

5.2.4 Benefits and downsides

The panel considered the potential benefits and downsides of tax exemptions/reductions for medicines, noting that there is no evidence of impact of this policy on pharmaceutical prices but some evidence of impact on access to medicines and appropriate use (see Annex F).

Benefits

- Most likely to have an equity impact on the poor.

Downsides

- Loss of revenue for national governments.
- Elimination or decrease of taxation revenue from medicines may have a negative impact on some aspects of the health care system.

5.2.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the paucity of information on the impact of reducing/exempting tax on

medicines on health outcomes but evidence of an impact on access to medicines, particularly for the poor; and made the recommendations below.

- ❖ Countries should consider exempting essential medicines from taxation.
- ❖ Countries should ensure any reductions or exemptions from taxes on medicines have the effect of reducing costs to the patient/purchaser.

5.2.6 Issues for implementation

The panel noted that the implementation of reduction or abolition of taxes on medicines requires high-level political support and legislation. The specific requirements for effective implementation of the policy that were identified by the panel are listed in Table 3.

Table 3: Implementation issues for medicine taxation policy

Issues	Taxes
Data required	<ul style="list-style-type: none"> • Assessment of the impact of taxation, or absence thereof, on medicine prices as well as the amount of revenue generated by taxes.
Infrastructure	<ul style="list-style-type: none"> • Legislation specific to medicine taxation. • Mechanism for monitoring medicine prices.
Methodological considerations	<ul style="list-style-type: none"> • Generation of revenue from other sources to replace that from taxes. • Mechanisms in place to avoid absorption of the savings by supply chain agents.

5.3 Application of cost-plus pricing formulae for pharmaceutical price setting

5.3.1 Definition of policy

Cost-plus pricing is a method for setting retail prices of medicines by taking into account production cost of a medicine together with allowances for promotional expenses, manufacturer’s profit margins, and charges and profit margins in the supply chain.

5.3.2 Evidence

The panel considered the following information as the basis for the recommendations (see [Annex G](#)).

- The WHO/HAI policy review on this topic,^{viii} which found no published studies that describe or evaluate cost-plus pricing. Based on a survey of personal contacts and web sites, the review author identified 13 countries apparently using cost-plus pricing as a method of price control. The review author devised and sent a questionnaire to contact persons in 10 countries, with a view to producing case studies. However, it is not clear which ten of the 13 countries using cost-plus pricing methods were included. There were three completed country responses, from Bangladesh, India, and the Islamic Republic of Iran. These are summarized in Annex G, together with the policy review author’s case study of his own country, Pakistan, and a case study of China derived from published papers and the National Development and Reforms Commission of China web site.

- An additional literature search retrieved no other evaluative studies or systematic reviews.

The country case studies provide limited descriptive information about the use of cost-plus price setting. Approaches to calculation of the cost-plus price clearly differ between countries. At least one country had previously used cost-plus pricing but stopped; the reasons for this change are not documented. It is very difficult to reach any conclusions about the likely impact of this policy, given the absence of detailed evaluation of the influence of these strategies on price over time and the lack of information on the effect on other outcomes, such as access to medicines.

5.3.3 Findings of the of panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. The consensus points are listed below.

- The available evidence is limited and anecdotal in nature.
- Cost-plus formulae are used in a few countries, for a selected group of drugs.
- One challenge in use of this method is that it requires reliable determination of manufacturing cost, which in turn is dependent on technical ability and resources to obtain this information.
- Cost-plus price setting might be an attractive policy option in settings where there is no other pricing regulation, because it appears “straightforward” to implement. However, determination of manufacturer costs can be very challenging and there are risks associated with the policy, as noted below).
- If cost-plus price setting were to be used, the country would have to determine what components should be included in the formulae. Application of the policy and verification of prices should be transparent. The policy should also be reviewed regularly, since prices can change in directions that may not be predicted based on market forces alone.

5.3.4 Benefits and downsides

The panel considered the potential benefits and downsides of implementing cost-plus pricing, noting that the information about the use of this policy is very limited (see Annex G).

Benefits

- Based on the experience of the panel members, it was suggested that cost-plus pricing might stabilize medicine prices in unregulated settings.
- The method might reduce out-of-pocket payments in an unregulated market.

Downsides

- Application of cost-plus pricing to medicines requires significant technical and human resources, particularly to obtain and validate reliable estimates of component prices such as active pharmaceutical ingredients.
- Formulae used by countries to calculate cost-plus prices can be manipulated to the advantage of manufacturers and disadvantage of patients.

- Application of the policy to only selected medicines in a market may result in patients and professionals switching to other, potentially inappropriate, medicines.
- Cost-plus pricing applied to selected medicines alone may disadvantage local manufacturers or population subgroups.

5.3.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the limited experience in use of cost-plus pricing and absence of information on the impact of this policy on health outcomes, prices, or access to medicines; and made the recommendations below.

- Countries generally should not use a cost-plus method as an overall pharmaceutical pricing policy.
- Countries using a cost-plus method as an overall policy that wish to change their strategy should consider replacing or complementing the cost-plus approach with other policies, including those covered in this guideline.

5.3.6 Issues for implementation

The panel noted that the implementation of cost-plus formulae requires legislation that mandates price setting for either a selection of medicines or all those supplied. For cost-plus pricing, it is important to obtain accurate information on material prices and obtaining this cost data may be difficult. The specific requirements for the policy are summarized in Table 4.

Table 4: Implementation issues for cost-plus formulae

Issues	Cost-plus formulae
Technical capacity	<ul style="list-style-type: none"> • Cost accounting. • Knowledge of manufacturing practices. • Market analysis.
Data required	<ul style="list-style-type: none"> • Prices of active pharmaceutical ingredients, excipients, packaging materials, wastages, cost of conversion, and profits and mark-ups in supply chain.
Infrastructure	<ul style="list-style-type: none"> • Legislation mandating price setting. • Information system for collecting the costs of price components. • Capacity to verify the information supplied by manufacturers. • A mechanism for monitoring the magnitude of applied mark-ups and medicine prices.
Methodological considerations	<ul style="list-style-type: none"> • Is the available cost information accurate? • There are various methods of costing that may be used (e.g. indirect cost allocation) and consistent application of methods is beneficial.

5.4 Use of external reference pricing

5.4.1 Definition of policy

ERP refers to the practice of using the price of a pharmaceutical product (generally ex-manufacturer price, or other common point within the distribution chain) in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. Reference may be made to single-source or multisource supply products.

5.4.2 Evidence

The panel considered the following information as the basis for the recommendations.

- The WHO/HAI policy review on this topic,^v which found 21 relevant articles from a literature search, mostly from high-income countries. There was little information available from low- or middle-income countries.
- The authors of the policy review did a survey of 14 countries that use ERP. Nine countries responded.
- An additional literature search retrieved no other evaluative studies or systematic reviews.

Full details of the policy review and survey are in Annex H. No studies report the impact of ERP on access to medicines or health outcomes. It is of note that 24 of 30 OECD countries and approximately 20 of 27 European Union countries use ERP, but use is mainly restricted on-patent medicines. For developing countries, the survey suggested that ERP is used for price setting of both on-patent and off-patent medicines. Sometimes ERP is used alone as the single method to determine prices, while other countries use ERP as one of several approaches. ERP is seen as a relatively simple method for countries to use because it does not require large amounts of information or extensive technical or analytical capability. However, certain technical issues need to be considered in the application of ERP, such as ensuring appropriate comparisons of formulations and adjustment for currency exchange rates.

Claims have been made that ERP has been effective in reducing the prices of medicines. However, the policy review found no supporting evidence from monitoring reports or rigorous analytical studies. The underlying assumption justifying the use of ERP is that prices in reference countries are somehow right, appropriate, or fair and thus by definition the ERP-derived local price structure will also be appropriate. This assertion is clearly very difficult to assess without objective criteria.

The policy review identifies potential indirect effects of ERP, including the design and implementation of international pricing and marketing strategies by the pharmaceutical industry to counteract the effects of ERP and maximize global profits. Advantages and disadvantages of ERP identified are listed below.

- ERP is a relatively simple and easy-to-apply system compared, for example, with economic evaluation. However, there are still requirements such as access to information about price components, determination of sample countries, and exchange rates that require some technical skills to manage.
- ERP implementation is feasible when resources are relatively limited and it provides quick information to regulators and other policy-makers. This aspect of ERP might justify its use by small countries with limited capacity to implement alternative pricing mechanisms.
- A main limitation is that price information is not always available, and the available prices are often heterogeneous and often difficult to adjust them to obtain the required type of price.

- Transaction prices are elusive – the prices that countries can access are often not real but virtual list/catalogue prices.
- Although there is no conclusive evidence about the impact of ERP, instances of launch delays and non-availability of new medicines in “low price” countries suggest there may be unintended negative effects.
- Price convergence, resulting from higher prices in lower-income countries and decreasing price transparency, is also a possible negative effect.

5.4.3 Findings of the of panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. The consensus points are listed below.

- There is extensive experience from many countries that use ERP and studies are under way.
- Use of ERP can be helpful for three aspects of management: price negotiation, setting, and verification.
- The biggest risk in ERP use is incorrect choice of reference countries, i.e. countries with substantially different market structures or prices (e.g. a low-income country using high-income countries as the sole reference).
- As described in the various reports, ERP is used in Europe for both multisource and single-source products and is also used as part of a series of price setting mechanisms. For example, ERP is used for setting prices of on-patent medicines, and subsequent price setting for generic products is referenced to the ERP prices.
- A challenge with use of ERP is to understand the nature of published medicine prices. Depending on the legislative framework or administrative arrangements in countries, published prices may not represent true prices paid. True prices may be concealed for purposes such as rebates or risk-sharing arrangements. The panel noted that it would be useful for countries to make public the *existence* of special pricing arrangements even if publication of actual prices is prohibited for legal reasons.
- ERP can be used in small markets, and this is particularly true for multisource (generic) products.
- ERP may be used for negotiation – the experience of several systems suggests that ERP can be an effective negotiation tool – or for checking prices.

5.4.4 Benefits and downsides

The panel considered the potential benefits and downsides of implementing ERP, noting that there is extensive experience in high-income countries (see [Annex H](#)).

Benefits

- May be simpler than some other methods for price setting.
- Allows international comparisons and benchmarking.

Downsides

- The choice of countries as reference countries may lead to inflated prices.
- If ERP used as the only method for price setting, entry of new products may be delayed and price manipulation may result.
- ERP use may result in higher-priced generic products.
- May be deceptively ‘simple’ and result in locally inappropriate prices, if incorrect reference countries selected and/or the comparator prices are not the real prices paid.
- Published prices may not reflect actual prices as these may be negotiated or conceal rebates, according to the legal systems in place. Countries need to know whether published prices are actual or special prices.
- Data sources for comparator prices may be difficult to verify.

5.4.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the experience in the use ERP; and made the recommendations below.

- ❖ Countries should consider using ERP as a method for negotiating or benchmarking the price of a medicine.
- ❖ Countries should consider using ERP as part of an overall strategy, in combination with other methods, for setting the price of a medicine.
- ❖ In developing an ERP system, countries should define transparent methods and processes to be used.
- ❖ Countries/payers should select comparator countries to use for ERP based on economic status, pharmaceutical pricing systems in place, published actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease.

5.4.6 Issues for implementation

The panel noted that the implementation of ERP requires a legislative framework. Experience has shown that there is a risk of use of high-income countries as reference countries for lower-income settings. Key considerations include access to actual prices and on-going monitoring. The specific requirements of the policy are summarized in Table 5.

Table 5: Implementation issues for ERP

Issues	ERP
Technical capacity	<ul style="list-style-type: none"> • Database management, data analysis.
Data required	<ul style="list-style-type: none"> • True negotiated prices rather than shadow prices.
Infrastructure	<ul style="list-style-type: none"> • Legislation framework for use of ERP. • Procedures on how to apply ERP, including criteria for choice of reference countries. • Procedures on how ERP feeds into the decision-making process. • A mechanism for monitoring the magnitude of applied mark-ups and medicine prices.
Methodological considerations	<ul style="list-style-type: none"> • Selection or calculation of the reference price (e.g. lowest price in the set, simple average of all products, weighted average). • Date of the price in the reference countries (e.g. current price versus price at launch). • Adjustments required (i) to account for confidential discounts or rebates in list prices and (ii) for level of economic development.

5.5 Promotion of the use of generic medicines

5.5.1 Definition of policy

Generic medicines are produced and distributed without patent protection. Promotion of the use of quality assured generic medicines is a method of managing pharmaceutical prices. The various approaches used include facilitated market entry of generics, generic substitution by dispensers, IRP, strategies to foster competition in the market, and schemes to encourage use of generics among providers and consumers. The assumption underpinning this policy is that use of generic medicines will result in lower prices and thus increase access.

5.5.2 Evidence

The panel considered the following information as the basis for the recommendations (see [Annex I](#), Tables ES5.1–5.3).

- The WHO/HAI policy review on this topic.^{ix}
- An additional literature search retrieved seven publications, some of which were included in the policy review. Each of these publications is described in more detail in Annex I, Table ES5.2.

This policy review identified an extensive literature on the use of generic medicines, which is summarized in Annex I. The panel noted that the information consisted mainly of descriptive studies, with no formal evaluative studies from low- and middle-income settings that document the impact of promoting use of generic medicines on health outcomes.

The policy review categorized approaches to promoting use of generic products as either supply-side or demand-side options (see Annex I, Box ES5.1).

Supply-side options include:

- Preferential and shortened licensing and/or registration review of product dossiers for generic products;
- Incentives to encourage generic manufacturers to develop and submit applications for licensing, such as reduced application fees and shortened data exclusivity periods;

- Legislative approaches that reduce patent barriers to supply of generics;
- Enforcement strategies to promote quality generic products, such as good manufacturing practice inspection; and
- Transparency of pricing information to allow effective competition.

Demand-side options identified in the review include:

- Preferential procurement of generic products by the national supply systems;
- Encouraging or mandating prescription and dispensing of generic products, for example through generic substitution by pharmacists or dispensers at the point of sale; and
- Education programmes to encourage consumer uptake.

There is considerable descriptive literature about most of these options. However, direct links between the promotion of supply and use of generic medicines and medicine price outcomes is limited, particularly for low- and middle-income countries (see Annex I). Much of the information that has been published is based on negative examples or descriptions of systems where generic medicine use has not been promoted, or theoretical arguments about market performance. A positive example is that of a 2010 campaign targeted raising patients' awareness in Estonia called "The difference is in the price of medicine". In a 2011 survey, almost half the patients who had bought pharmaceuticals said that, because of the campaign, they had chosen or were going to choose a cheaper product.^{xvi}

The panel noted that the evidence supporting use of generics was most compelling in the context of systems with reimbursement lists of medicines, where there is often a range price control mechanisms in place. In Turkey, for example, a generic substitution policy through a reimbursement scheme for diabetes medicines saved patients money. Several high-income countries using co-payments to promote generics have found that changing the co-payment is associated with increased uptake of generics. A prerequisite for all settings is that the generics available are of adequate quality, since several studies document consumer concerns about quality of generics in both regulated and unregulated markets.

5.5.3 Findings of the panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. The consensus points are listed below.

- The term "generic medicine" should encompass any product that contains an off-patent medicine. This definition is particularly important given that, in some markets, there are attempts to distinguish between so-called "branded generics" and "generic generics". This distinction is taken for promotional or sales advantage of problems in a given market resulting from inadequate quality of products, and should be discouraged or at least recognized as signalling the quality problem.

- For promotion of use of generics as a price-controlling strategy to succeed, generic equivalents of controlled pharmaceutical quality medicines **must** be available, preferably labelled as such.
- Monopoly supply of generic products seems to have no advantage to patent product supply in terms of reducing prices.
- Promoting use of generics is complex and requires many different pharmaceutical sector policy components to be in place, such as establishment of systems that facilitate market entry of generics; existence of a functioning and transparent medicines regulatory agency; adequate training of prescribers and dispensers for mandatory substitution of branded drugs by generics; etc.
- The general impression is that use of quality generics promotes access to medicines, although the panel acknowledged that this finding is not well supported by the evidence available.

5.5.4 Benefits and downsides

The panel considered the potential benefits and downsides of promoting generic medicine use, noting that in the descriptive studies of its use indicate that a complex set of strategies is required (see Annex I).

Benefits

- Medicine prices can be reduced through the promotion and use of generics via a range of approaches, which enables tailoring to different settings.

Downsides

- This is an approach to influence medicine prices that includes a number of policy options that can be combined to promote use of generics. The impact of the different individual aspects of generic medicines on pricing may not therefore be clearly identifiable.

5.5.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the complexity of promotion of use of generic medicines, and that the overall impact of this policy on health outcomes and prices is not well supported; and made the recommendations below.

- ❖ Countries should enable the early market entry of generics through legislative and administrative measures that encourage early submission of regulatory applications, and allow for prompt and effective review.
- ❖ Countries should use multiple strategies to achieve low priced generics, depending on the system and market. These strategies may include: within-country reference pricing, tendering, and/or lower co-payments.
- ❖ In order to maximize uptake of generics, countries should implement (and enforce as appropriate) a mix of policies and strategies, including:
 - ❖ Legislation to allow generic substitution by dispensers;
 - ❖ Legislative structure and incentives for prescribers to prescribe by international nonproprietary name;
 - ❖ Dispensing fees that encourage use of low price generics;
 - ❖ Regressive margins and incentives for dispensers; and
 - ❖ Consumer and professional education regarding quality and price of generics.

5.5.6 Issues for implementation

The panel noted that the promotion of the use of quality assured generic medicines requires consideration of a range of implementation issues, for each of the approaches identified, i.e. market entry; generic substitution by dispensers; IRP; competition; and strategies to encourage use of generics among providers and consumers. The specific requirements for each strategy are listed in Table 6.

Table 6: Implementation issues for use of generic medicines

Strategy	Technical capacity	Data required	Infrastructure	Methodological considerations
Facilitated/accelerated market entry	NA	Clear definition of evidence required to demonstrate bioequivalence and therapeutic equivalence.	Regulatory measures to allow earlier registration of generics.	Determination of change in market approval times and/or possible reduction in fees for generic medicines.
Generic substitution	Pharmacy personnel trained in appropriate substitution.	NA	<ul style="list-style-type: none"> • Legislation to allow substitution by dispenser. • If substitution is to be mandated, legislation is needed to define circumstances for substitution. 	When and how substitution will be made, i.e. allowed, encouraged, or mandated.
Promoting generic competition	Establishment of manufacturing and production facilities.	NA	<ul style="list-style-type: none"> • Systems in place regarding number of products available. • Systems in place to allow for joint manufacturing or pooled procurement. 	Whether competition will be promoted and where responsibility lies for promotion of competition.
IRP	Data analysis of prices.	Access to prices.	<ul style="list-style-type: none"> • Procedures on how to apply IRP. • Procedures on how IRP feeds into decision-making process, possibly supported by legislation. 	<ul style="list-style-type: none"> • Selection or calculation of the reference price (e.g. lowest price in the set, simple average of all products, weighted average). • Adjustments to account for confidential discounts or rebates in list prices.
Encouraging use of generics by prescribers/dispatchers	Determination of information to be provided.	NA	Establishment of systems, programmes, and regulations to encourage use of generic medicines.	Type, extent, and content of programmes.
Encouraging use of generics by consumers	Determination of information to be provided.	NA	Promotion of use of generic medicines by government required.	Type and extent of education campaigns.

NA = not applicable

5.6 Use of health technology assessment

5.6.1 Definition of policy

The International Network of Agencies for Health Technology Assessment defines HTA as “[t]he systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.”^{xvii}

This topic was included in the development of this guideline since HTA in relation to pharmaceuticals includes evaluations relevant to price setting or pricing policies. HTA encompasses assessment of a range of health-related technologies and has replaced the term 'pharmacoeconomics' in many contexts. HTA is used in several countries as a basis for setting prices of new pharmaceutical products (e.g. Australia, France, Sweden, UK).

5.6.2 Evidence

The panel considered the following information as the basis for the recommendations (see [Annex I](#)).

- The WHO/HAI policy review on this topic. This review identified limited information of relevance.
- An additional literature search retrieved eight relevant reviews. A comparison of IRP and HTA (Drummond et al, 2011^{xviii}), published after the WHO/HAI policy review was completed, was also retrieved. The papers are summarized in Annex J, Table ES6.1.

The panel noted that the literature about the use of HTA in relation to pharmaceuticals covers several aspects that may relate to price setting or policies. Of particular note was the study by Drummond et al that explicitly compared the use of IRP with that of HTA regarding the initial price and reimbursement status of innovative drugs in four countries – Germany, the Netherlands, Sweden, and the UK. The comparison considered drugs for four disease areas – hyperlipidaemia, diabetes, rheumatoid arthritis, and schizophrenia. The conclusions of Drummond et al appear below.

- No clear pattern of the impact of HTA on prices could be determined.
- The impact of reference pricing is only substantial when there are large differences in the prices of drugs in a given group or cluster.
- When one drug in a disease-area cluster becomes generic, reference pricing can have a major impact. Normally, one would expect the price of all drugs in the cluster to fall to the level of the reference price. However, in the case of the drug groups studied by Drummond et al, the manufacturers maintained their original price. In the case of atorvastatin, this led to increased patient co-payments; in the case of insulin analogues, the price was maintained by use of a subsidy.
- The focus of reference pricing is to set the reimbursement level for the cluster; however, in the absence of a generic, it is unclear how this level is set. By contrast, with HTA, reimbursement can be conditional or limited to certain indications of the drug or certain patient subgroups. Drummond et al propose that recommendations about price based on HTA potentially reward innovation while allowing consideration of value for money.

The panel noted that Drummond et al suggest that reference pricing alone does not represent a viable policy for obtaining value for money from pharmaceuticals, and HTA represents a better approach, given the reward for innovation and value for money. A dual policy approach, in which HTA is used for the primary policy for obtaining value for money from new drugs and is supported by reference pricing or another method, may be reasonable.

Although the study provides only descriptive assessments of four high-income countries, it appears to be unique in the literature at present in that it compares two policy options for setting prices. Drummond et al (2011) also provides an important model for future research studies.

For low- and middle-income countries, the evidence relates to how pharmacoeconomics/HTA has been used in different settings and its application in selecting medicines for reimbursement. Many publications describe challenges in the use of pharmacoeconomics in low-and middle-income countries, such as the lack of capacity/infrastructure to conduct economic evaluations, lack of local data, and lack of qualified researchers. Another key concern is the difficulty of generalizing or transferring results of economic evaluations based in developed countries to other settings.

Overall, the evidence relating to the use of HTA is descriptive in nature and primarily about the processes involved. The impact of HTA on medicine prices is not documented except in the one European study noted above.

5.6.3 Findings of the of panel

The panel examined their own experience from different settings and countries in relation to the evidence provided. In addition to the literature, some of the issues noted are listed below.

- There is increasing interest worldwide in the use of HTA in decision-making. for example, 13 Latin American countries are now collaborating on HTA in a regional network.
- HTA is a tool for decision-making and is often used for reimbursement decision-making.
- HTA should be implemented in a setting where there are other pricing policies and where there is sufficient technical capacity.
- There are several different models for undertaking HTA, with different resource implications. Full appraisal is the most sophisticated approach and demands the greatest technical resources, whereas evaluation of published HTA reports for local use is less resource intensive.
- A stepwise approach to capacity development is recommended for countries initiating HTA.
- A consistent framework for HTA worldwide would be beneficial.

5.6.4 Benefits and downsides

The panel considered the potential benefits and downsides of use of HTA as a policy option to manage medicine prices, noting that the evidence available provided some limited information about the impact of this approach but did not document impact on health outcomes (see Annex J).

Benefits

- HTA can potentially be used to assess value for money when making decisions on pharmaceutical prices.

Downsides

- HTA requires a high level of technical capacity.

5.6.5 Recommendations

The panel took account of the evidence and experiences documented above and in the evidence summary; noted the capacity requirements of HTA; and made the recommendations below.

- ❖ Countries should use HTA as a tool to support reimbursement decision-making as well as price setting/negotiation.
- ❖ Countries should combine HTA with other policies and strategies, particularly within-country reference pricing (by chemical entity, pharmacological class, or indication).
- ❖ Countries should consider the following actions when using HTA: review applicability and adaptation of reports from other countries; review reports submitted by pharmaceutical companies; and conduct assessments based on local information and local data. The choice of approach depends on technical capacity and local decision-making structures.
- ❖ Countries could take a stepwise approach to develop legislative and technical capacity to take full advantage of the potential utility of HTA in pharmaceutical price setting.
- ❖ In establishing the legislative/administrative framework, countries should clearly define the roles and responsibilities of the decision-makers and other stakeholders, and the process of decision-making.
- ❖ Countries should ensure that HTA processes are transparent and that the assessment reports and decisions are made publicly available and effectively disseminated to stakeholders.
- ❖ Countries should collaborate to promote exchange of information and develop common requirements for HTA.

5.6.6 Issues for implementation

The panel noted the following issues with respect to implementation. HTA is resource intensive in terms of the skills required and the processes involved. The specific requirements of the policy are summarized in Table 7.

Table 7: Implementation issues for HTA

Issues	HTA
Technical capacity	<ul style="list-style-type: none"> • Staff to assess or compile clinical and economic data. • Ability to assess or conduct statistical analyses of data; ability to assess or construct economic models.
Data required	<ul style="list-style-type: none"> • Clinical data on efficacy and safety of drugs. • Cost data. • Data used in economic modelling.
Infrastructure	<ul style="list-style-type: none"> • Legislation mandating use of HTA for reimbursement and price of pharmaceuticals. • System and resources to consider HTA evidence.
Methodological considerations	<ul style="list-style-type: none"> • The decision-making criteria to be used must be determined, as well as how analyses will be done or evaluated. • Determination of how results are to be communicated and whether fees will be charged.

6. Guideline use and adaptation – key principles and general considerations

In addition to the guidance on structures, processes, and methodological considerations documented above for each policy option included in the scope of this guideline, the panel identified the following key principles and considerations for any approach to pharmaceutical price intervention.

6.1 Key principles for policy planning and implementation

- Countries should use a combination of different pharmaceutical pricing policies that should be selected based on the objective, context and health system.
- Countries should make their pricing policies, processes, and decisions transparent.
- Pricing policies should have an appropriate legislative framework and governance and administrative structures, supported by technical capacity. They should be regularly reviewed, monitored (including actual prices), and evaluated and amended as necessary.
- In promoting the use of affordable medicines, countries should employ a combination of pharmaceutical policies that address both supply and demand issues.
- If regulation of pharmaceutical prices is introduced, effective implementation will be required to ensure compliance (e.g. incentives, enforcement, price monitoring system, fines).
- Countries should adopt policies to promote the use of quality assured generic medicines in order to increase access and affordability.
- Countries should collaborate to promote exchange of information about policies, and their impacts, and pharmaceutical prices.

6.2 Overarching considerations for policy selection

The policies considered in this guideline were selected primarily because of their potential in pharmaceutical price management. However, since a country's pharmaceutical sector interacts with the health and industrial sectors, wider principles need to be identified and considered when choosing between policy options, as listed below.

- Policy must be tailored to the local context.
- Preference should be considered for a policy that results in either clear consumer affordability or no payment by the patient.
- To promote health outcomes, the quality of prescription and dispensing practices should be enhanced, as should consumers’ use of medicines.
- Policies should be transparent to suppliers and consumers.
- Policy choice should not undermine a reliable supply of quality products.
- Policy choice should promote equitable access to drugs.
- Policy choice should ensure that prices provide value for money.
- Policy choices should promote improvement in health outcomes.
- Depending on the context, policy choices may take account need for a viable local production capacity.
- The impact of the policies should be monitored, not only their influence on prices but also their effect on other outcomes such as out-of-pocket payments and availability of essential medicines.

6.3 Health system and pharmaceutical sector considerations for policy implementation

The organization of, and interplay between, a country’s pharmaceutical sector and health care system can affect medicine availability, price, and affordability, as can the degree of public versus private sector funding. In “fully” public health care systems, medicines may be financed, procured, and distributed by a centralized government unit. In mixed systems, public funding from central budgets or social health insurance may be used to reimburse patients or private pharmacies, or medicines may be supplied through government medical stores and health facilities but paid for by patient fees. In fully private systems, patients or private insurance schemes usually pay the entire cost of medicines purchased from private providers. Most countries use a combination of these approaches. The selection and implementation of a policy to manage the price of medicines must take account of the wider health and pharmaceutical structures within which it will operate. Some of the characteristics that may need to be considered are listed in Table 8.

Table 8: Characteristics to consider when developing an implementation plan

Type of system	Characteristics
Overall health care system	<ul style="list-style-type: none"> • organization with private actors publicly funded • organization with private actors privately funded • public organization and funding of health care system
Primary ‘payer’	<ul style="list-style-type: none"> • social health insurance • public sector • consumers/private households (i.e. direct payment) • private actuarial insurance • government (via finance or taxation) • enterprises
Regulatory agency	<ul style="list-style-type: none"> • no regulatory agency • regulatory agency with limited capacity • stringent regulatory authority
Pharmaceutical sector	<ul style="list-style-type: none"> • unregulated with little scope for regulation within political environment • unregulated but regulation feasible within the political environment • regulated

Type of system	Characteristics
Pharmaceutical market	<ul style="list-style-type: none"> • primarily locally manufactured medicines • primarily imported medicines • mixed – local and imported medicines • role of generic medicines in market • local research and development
Supply chain and procurement	<ul style="list-style-type: none"> • number and nature of suppliers, wholesalers, and retailers
Legal enforcement	<ul style="list-style-type: none"> • limited capacity to enforce regulations • capacity to enforce regulations
Target for policy intervention	Characteristics
Type of product	<ul style="list-style-type: none"> • on-patent versus off-patent • single-source versus multisource • high-cost • reimbursed • essential versus non-essential • prescription versus over-the-counter
Sector	<ul style="list-style-type: none"> • public • private • other • all
Patient contribution	<ul style="list-style-type: none"> • co-payment • co-sharing

7. Research priorities and guideline update

In developing the recommendations, the panel noted that the overall quality of research and evidence in relation to pharmaceutical policy implementation and impact is poor, especially in developing country settings. There are many areas where more descriptive studies and good quality research would allow better understanding of what policies should be chosen and how they should be implemented. The lack of comparisons of different approaches is especially striking. The panel noted that Drummond et al (2011),^{xviii} which appears to be unique at present since it compares two policy options, provides an important model for future research.

The panel identified the research topics below as priorities.

- The effect of discounts and rebates on drug prices.
- The impact of mark-ups on price and access to medicines.
- Assessment of different methods for estimating distribution costs.
- Documentation of the experience of an insurance system that uses mark-up regulation.
- The impact of taxes on medicines on general revenue.
- The effect of rebates on overall drug prices.
- A comparison of the cost-plus approach with other policies for price setting.
- An evaluation of drug price databases.
- Comparisons of the effectiveness or impact of pricing policies.

The panel acknowledged that this research will take time to complete and recommended that the guideline should be reviewed for potential update in 5 years. An update to the guideline would also benefit from an evaluation of its impact.

Evaluation of the guideline would not intend to measure outcomes of the recommendations, but could consider the clarity and ability to translate the information into implementation or to support related activities, such as guiding the research areas or supporting development of tools. This may be challenging given with the lack of evidence favouring any specific method of implementation; however, evaluation of specific recommendations could be incorporated into the research topics identified and could also be undertaken with countries that opt to use the guideline in price management initiatives, procurement, reimbursement schemes and the like.

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9. Annexes

9.1 Annex A: Abbreviations and acronyms

ACT	Artemisinin combination therapy
AED	United Arab Emirates Dirham
API	Active pharmaceutical ingredient
CDR	Common Drug Review (Canada)
CEF	Cyclophosphamide, epirubicin, fluorouracil
CIF	Cost, insurance, and freight
CMF	Cyclophosphamide, methotrexate, fluorouracil
DALY	Disability-adjusted life year
ERP	External reference pricing
GDP	Gross domestic product
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAI	Health Action International
HIC	High-income country
HITAP	Health Intervention and Technology Assessment Program
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INN	International nonproprietary name
IRP	Internal reference pricing
LAC	Latin American and Caribbean
LIC	Low-income country
L-MIC	Lower-middle-income country
LMICs	Low- and middle-income countries
LPG	Lowest priced generic
MSP	Manufacturer's selling price
NHIS	National Health Insurance
NHS	National Health Service (UK)
NICE	National Institute for Clinical Excellence (UK)
OB	Originator brand
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PPRI	Prescription pricing and reimbursement information

QALY	Quality-adjusted life year
RDF	Revolving drug fund
SNS	Sistema Nacional de Salud (Spain)
SAARC	South Asian Association for Regional Cooperation
SP	Sulfadoxine-pyrimethamine
TRIPS	Trade-related aspects of intellectual property
UMIC	Upper-middle-income country
VAT	Value-added tax
WTO	World Trade Organization
ZAR	South Africa Rand

9.2 **Annex B: Lists of meeting participants and external experts/organizations**

Annex Box 1: List of guideline panel members and other meeting participants

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9.3 **Annex C: Summary of declared interests****Annex Box 3: Declared interests of panel**

Name	Designation	Interests	Decision
Lisa Bero	University of California, San Francisco	<ul style="list-style-type: none"> Editor of Cochrane Collaboration Review Group Effective Practice & Organization of Care, of which some reviews relate to pricing policy. Editor position is unpaid. 	No further action required
Sudip Chaudhuri	Indian Institute of Management, Calcutta	<ul style="list-style-type: none"> Study for United Nations Development Programme of industry response to product patent regime in India. Involved in a research project on non-government action to improve the poor's access to quality, cheap medicines. Economic and Social Research Council, UK. United Nations Industrial Development Organization project on local production in Ghana (on-going). 	No further action required
Mari Mathiesen	Estonian Health Insurance Fund	<ul style="list-style-type: none"> Provision/approval of expert opinion to state institutions related to the subject of the guideline as part of current employment at Estonian Health Insurance Fund. Married to a person actively involved in pharmaceutical consultancy business in Estonia (mainly regulatory and pre-marketing services to pharmaceutical manufacturers). 	No further action required
Jaime Espin Balbino	Andalusia School of Public Health (EASP)	<ul style="list-style-type: none"> EASP sponsorship and training – Eli Lilly, Sanofi-Aventis, Chiesi, Pfizer. Various honoraria for speaking on economic evaluation, pharmaceutical policies, risk sharing agreements, sponsored by Sanofi-Aventis, Novartis, Eli Lilly, Chiesi, Merck. 	No further action required
Prashant Yadav	MIT-Zaragoza International Logistics Centre	<p>Research or consulting directly related to the work:</p> <ul style="list-style-type: none"> Principal investigator for research on differential pricing sponsored by UK Department for International Development. External expert, differential pricing meeting, GlaxoSmithKline. WHO/Government of India/Centre for Trade & Development workshop on pharmaceutical pricing. <p>Other relevant disclosures:</p> <ul style="list-style-type: none"> Postgraduate students carried out research on pharmaceutical distribution in Africa, funded by Pfizer. 	No further action required

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Name	Designation	Interests	Decision
		<ul style="list-style-type: none"> • Assisted in a national Malaria Control Program Managers Best Practices Sharing seminar in Zambia funded by Novartis. • Presented “Multiple First Line Treatments for Malaria: Challenges and Opportunities” at conference of the Multi-lateral Initiative on Malaria in Kenya, sponsored by Pfizer. • Helped conduct a National Malaria Control Program Managers Best Practices Sharing seminar in Rwanda, sponsored by Novartis. <p>Testimony/public address related to guideline:</p> <ul style="list-style-type: none"> • Driving Malaria Reduction Globally: the role of supply chains, Congressional briefing, Washington, DC, USA. • Briefing on differential pricing of pharmaceuticals, the Industry Forum on Access to Medicines, London, UK. 	
Fatima Suleman	University of Kwazulu-Natal	<ul style="list-style-type: none"> • Member of pricing committee, Department of Health, South Africa. • Postgraduate bursaries for drug development and pharmacoeconomics awarded to the School of Pharmacy and Pharmacology by Aspen and Merck Foundation. • Travel to attend and present at a conference on pharmacy practice in New Zealand sponsored by Pfizer. 	No further action required
Sauwakon Ratanawijitrasin	Mahidol University	<ul style="list-style-type: none"> • Participated in a meeting as a pharmaceutical policy expert, Novartis and AstraZeneca. 	No further action required
Thamizhanban Pillay	Health Financing and Economics Cluster, National Department of Health, South Africa	<ul style="list-style-type: none"> • Wife employed as a clinical research associate with Roche. • Public statements. • Outcome of meeting could benefit government. 	No further action required
Suzanne Hill	Department Health and Aging, Australia	<ul style="list-style-type: none"> • Current position as Chair of the Australian Pharmaceutical Benefits Advisory Committee is a full paid position by the Australian Department of Health and requires public statements including pricing policy advice for the Australian Government. 	No further action required

9.4 **Annex D: Guideline scope and development process**

WHO uses the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) for the development and review of recommendations. The initial steps entail identifying key topics, formulating the Population, Intervention, Comparison and Outcomes (PICO) questions, scoping the literature to identify whether evidence reviews exist or recent evidence can be obtained, developing a comprehensive search strategy and identifying and retrieving relevant evidence, including evidence concerning both benefits and harms. Outcome frameworks are developed to ensure that outcomes are selected in a transparent and comprehensive manner and prior to reviewing the evidence. The first step of the GRADE approach is to rate the quality of evidence for each PICO question by outcome. The second step is to move from “evidence to recommendation” for each of the PICO questions. This process includes consideration of the quality of evidence, the balance of benefits and harms, community values and preferences and resource use. These factors affect both the recommendation’s direction (for or against) and its strength (strong or conditional). Decision tables summarize these factors.

At the preparatory phase of this guideline it was determined that for most questions it would not be possible to prepare functionally useful GRADE evidence profiles, since few publications provided quantitative estimates of the impact of pricing policies on health outcomes or access to medicines. In addition, existing Cochrane reviews (1-3) did not include summary of findings tables. It was therefore planned that evidence summaries would be prepared as study-by-study tables. The guideline development protocol proposed that methods used for assessment of the quality of the evidence would be based on advice from the Cochrane Collaboration Effective Practice and Organization of Care review group representative in the guideline panel, depending on the type of studies included. However, in the final evidence summaries the nature of the evidence was such that no grading of quality was possible. It was also pre-specified that in the expected absence of any experimental design studies of pharmaceutical policies, evidence from studies using time series design with repeated measures of either health outcomes or access to medicines would be considered as the most reliable basis to determine the estimate of effect of any policy. However, no such research was found; all studies were essentially case descriptions.

The remainder of this Annex describes the scope and development process for this guideline.

9.4.1 **PICO questions**

From the work to date, three main overarching policy questions were identified for the initial scope of the guidelines, each with a series of more detailed sub-questions. The structure for the questions was:

- **Population** – Country decision-makers (usually Ministry of Health officials)
- **Intervention** – Specified pricing or reimbursement policy
- **Comparison** – Existing practice or absence of policy
- **Outcomes** – Affordable prices and access to medicines as surrogates for health outcomes.

It was determined that, although pharmaceutical procurement by governments, hospitals, and other organizations is relevant to pricing, the topic is extensively covered elsewhere and would not be addressed in this guideline. Similarly, marketing and promotion practices by the pharmaceutical industry, which can have strong influences on prices, were determined as outside the scope of this guideline.

This guideline was planned for use in countries of all income levels. However, special consideration was to be given to implementation needs in low- and middle-income countries, where the pharmaceutical sector may be less regulated.

Preliminary work and discussion established questions for the guideline, which were structured as a decision-tree format (Annex Box 4); pricing policy options would be considered as complementary and not mutually exclusive.

Annex Box 4: Decision-tree of guideline questions

Should countries use price control measures to manage medicine prices? If yes →			
Can external (international) reference pricing (ERP) be an effective pharmaceutical pricing strategy (in low- and middle-income countries)?	If yes, then →	Under what conditions should it be considered for use?	
		What are the potential positive outcomes of using this strategy and what are the risks?	
		What best practices should be followed in the establishment of an effective external reference pricing system?	
		What are the resources and skills required for effective implementation?	
Should health technology assessment (HTA) be considered as part of 1) decision-making and/or 2) price setting in low- and middle-income countries?	If yes, then →	Under what conditions should it be considered for use?	
		What are the potential positive outcomes of using this strategy and what are the risks?	
		What best practices should be followed in an appraisal process, including submission requirements?	
		What are the resources and skills required for the appraisal process?	
		Should HTA appraisals from one country be adapted for use in another country?	If yes, then →
Can cost-plus price setting be an effective pharmaceutical pricing strategy (in low- and middle-income countries)?	If yes, then →	Under what conditions should it be considered for use?	
		What are the potential positive outcomes of using this strategy and what are the risks?	
		What best practices should be followed in the use of cost-plus price setting?	
		What are the resources and skills required for effective implementation?	

Overarching question 2 - should countries adopt measures to control add-on costs in the supply chain? If yes:			
Should wholesaler and dispenser mark-ups be controlled (in low- and middle-income countries)?	If yes, then →	Under what conditions should controlling the mark-ups of supply chain agents be considered?	And → What are the potential positive outcomes of each strategy and what are the risks?
		How can “reasonable” mark-ups be estimated?	
		What best practices should be followed in controlling supply chain mark-ups (flat, regressive, regressive but not applied across the total procurement price), fixed fees, mark-up/fixed fees combination, etc.?	
Should medicines be exempt from taxes and/or tariffs?	If yes, then →	What mechanisms are needed to ensure that cost savings obtained through exemptions are passed on to patients?	

Overarching question 3 - should countries promote the use of quality assured generic medicines as a strategy to manage medicine prices? If yes:			
What prerequisites are needed to promote increased use of generic medicines?			
Should strategies be used to facilitate/accelerate market entry of generics (e.g. Trade-related aspects of intellectual property rights (TRIPS) flexibilities and compulsory licensing; facilitated regulatory approval; fast-tracking and/or reduced fees)?	If yes, then →	Under what conditions should these strategies be considered for use?	
		What are the potential positive outcomes of using these strategies and what are the risks?	
		What best practices should be followed?	
		What are the resources and skills required for effective implementation?	
Should optional/mandatory generic substitution by dispensers be used to promote increased use of generic medicines?	If yes, then →	Under what conditions should this strategy be considered for use?	
		What are the potential positive outcomes of using this strategy and what are the risks?	
		What best practices should be followed?	
		What are the resources and skills required for effective implementation?	
What is the role of (generic) competition in the pharmaceutical market as part of a strategy for managing prices?	If yes, then →	Under what conditions should this strategy be considered for use?	
		What are the potential positive outcomes of using this strategy and what are the risks?	
		What best practices should be followed?	
		What are the resources and skills required for effective implementation?	

Overarching question 3 - should countries promote the use of quality assured generic medicines as a strategy to manage medicine prices? If yes:		
Should internal reference pricing (by product or therapeutic group) be used to promote increased use of generic medicines?	If yes, then →	Under what conditions should this strategy be considered for use?
		What are the potential positive outcomes of using this strategy and what are the risks?
		What best practices should be followed?
		What are the resources and skills required for effective implementation?
Should strategies be adopted to encourage the use of generic/lower-cost products among providers (prescribers and dispensers)?	If yes, then →	What strategies should be considered for use (e.g. payment structures (e.g. fee for service versus capitation or case-based), financial incentives to encourage prescribing and dispensing of lower-cost products, separation of prescribing and dispensing, education strategies)?
		Under what conditions should these strategies be considered for use?
		What are the potential positive outcomes of using these strategies and what are the risks?
		What best practices should be followed?
		What are the resources and skills required for effective implementation?
Should strategies be adopted to encourage the use of generic/lower-cost products among consumers?	If yes, then →	What strategies should be considered for use (e.g. generic restrictions and substitution requirements, internal/generic referencing pricing, education strategies, tiered copayments (with generics/lower-cost products on lower tier)?
		Under what conditions should these strategy be considered for use?
		What are the potential positive outcomes of using these strategies and what are the risks?
		What best practices should be followed?
		What are the resources and skills required for effective implementation?

9.4.2 Outcomes rating

GRADE specifies three categories of outcomes according to their importance: critical; important but not critical; and of limited importance, where the first two categories of outcomes bear on the development of recommendations and the third may or may not. To prioritize outcomes for the development of recommendations, a comprehensive list of outcomes related to pricing policies was developed. Members of the guideline panel were asked to rank outcomes on a 9-point scale according to the GRADE rating scheme:

- 1, 2, 3 – not important for decision-making
- 4, 5, 6 – important but not critical for decision-making
- 7, 8, 9 – critical for decision-making.

Fourteen panel members provided rankings and the average results and ranges are presented in Annex Box 5.

Annex Box 5: Results of outcomes rating exercise

Outcome	Average (minimum–	Outcome	Average (minimum–maximum) rating
Patient/retail price	8.4 (7–9)	% generic items claimed as part of an insurance scheme	6.9 (5–9)
Reimbursement price	8.1 (6–9)	Dispenser knowledge that generics are equivalent to brands	6.9 (4–9)
Out-of-pocket pharmaceutical expenditure as % of total	8.1 (6–9)	Wholesale price	6.9 (4–9)
Government (public) pharmaceutical expenditure	7.7 (6–9)	Prescriber knowledge that generics are equivalent to brands	6.8 (4–9)
Substitution of generics in place of branded medicines	7.7 (6–9)	Consumers request/purchase generic version or lower-cost	6.7 (3–9)
Total pharmaceutical expenditure	7.5 (5–9)	Consideration of price in prescribing	6.6 (4–9)
Availability at public sector facilities	7.4 (5–9)	Availability at private sector facilities	6.6 (3–9)
Price differences, e.g. between branded medicines and generics	7.4 (5–9)	Mortality	6.4 (3–9)
% prescriptions dispensed as generics	7.4 (5–9)	Number of manufacturers (competitors) registered/on the	6.4 (3–9)
Shift in use towards less-expensive items	7.3 (5–9)	Consumer knowledge that generics are equivalent to brands	6.4 (2–9)
% or fixed fee margin	7.2 (5–9)	Improved adherence to treatment	5.7 (3–9)
Volume purchased/sold	7.2 (3–9)	Disability-adjusted life years, quality-adjusted life years	5.5 (2–8)
Proportion of originator brands prescribed	7.2 (5–9)	Increased/decreased hospital admissions	5.4 (3–8)
Manufacturer’s selling price	7.1 (4–9)	Increased/decreased physician consultations	5.4 (3–8)
Time from patent expiry to generic market entry/market	7.1 (5–9)	Delay in launching of new products as a result of national pricing policies	5.3 (3–9)
Availability of information	6.9 (4–9)		

9.4.3 Evidence retrieval, synthesis and quality assessment

The evidence reviewed as part of the guideline process was largely based on a series of six reviews completed during 2010–11 by the WHO/HAI collaboration: regulation of mark-ups (4), tax exemptions/reductions (5), application of cost-plus pricing formulae (6), use of external reference pricing (7), promotion of the use of generic medicines (8), and use of health technology assessment/pharmacoeconomics (9). These WHO/HAI policy reviews included published and unpublished materials, country case studies, and key informant interviews. The policy reviews were overseen by a global working group convened through the WHO/HAI pricing project. Databases searches were specified as part of the protocol development for each review and there were searches to identify grey literature, since this is most relevant to the low- and middle-income country settings. As the study designs in the reviews are mostly observational, strict Cochrane methods were not been used. The quality of the reviews, in terms of adequacy of retrieval, inclusion/exclusion and other criteria was evaluated during the preparation process by the WHO/HAI working group members, who also acted as peer reviewers.

In addition to the reviews conducted as part of the WHO/HAI project, supplementary evidence was retrieved by searching relevant databases (PubMed, EconLit, ISI Web of Knowledge, Cochrane Library) for systematic reviews of pharmaceutical pricing policies identified in the guideline scope. Evidence summaries were prepared as study-by-study tables from each WHO/HAI policy review; any evidence retrieved during the supplementary search for systematic reviews was also included. As noted above, the nature of the evidence was such that no grading of quality was possible and all studies were essentially case descriptions.

The panel determined that, in the absence of evidence-quality grading, it would not be possible to attribute a level of strength to individual recommendations. The following approach for each of the six policy topics was used. The panel reviewed the evidence summary, examined their own experience in different settings and countries in relation to the evidence provided, and reached consensus points, including the benefits and downsides of implementation of the policy. The recommendations for each of the six policies resulted from consensus based on the evidence and experiences noted above, with caveats as appropriate regarding the paucity of research findings.

9.5 **Annex E: Evidence summary 1 – Regulation of mark-ups in the pharmaceutical supply chain**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: A mark-up represents the additional charges and costs that are applied to the price of a commodity in order to cover overhead costs, distribution charges, and profit. In the context of the pharmaceutical supply chain, policies might involve regulation of wholesale and retail mark-ups as well as pharmaceutical remuneration.

9.5.1 Overview of available evidence

Type of evidence

1. The WHO/HAI policy review (Ball 2010) (4) which provides definitions and descriptions of mark-ups and supply chains; a literature search for the evidence base on regulation of mark-ups on medicines and the impact of mark-ups on medicine prices in low- and middle-income countries (LMICs); and case studies of how three countries addressed price regulation.
2. An additional literature search retrieved no other evaluative studies or systematic reviews.

Quality of evidence

The WHO/HAI policy review concludes that the evidence for the regulation of mark-ups in the supply chain in LMICs is sparse, not systematically collected, and often of poor quality. The available evidence is primarily descriptive, and there is no evidence comparing the use of mark-ups with other pricing policies. The country case studies are descriptive, with little evidence available on the effects of mark-ups.

Outcomes

There is no information on the impact of mark-ups on medicine prices and other rated outcomes in the evidence identified, with the exception of some description of changes in medicine prices in the country case studies.

Results/conclusions

- Comparative evidence – LMICs; high-income countries (HICs) – none available.
- Descriptive evidence – LMICs; HICs – see below.

9.5.2 Descriptive evidence: WHO/HAI policy review – literature review

The PubMed and EconLit searches returned 31 and seven relevant publications, respectively. The number of relevant articles identified by searching the Internet and the grey literature is not specified, although the review states that “a wide range of articles and papers” was found. The policy review does not describe in detail the nature of the literature found (i.e. reviews, descriptions, opinion pieces, studies) but notes that the evidence is sparse, not systematically collected, and often of poor quality.

The policy review describes options for the regulation of mark-ups; the rationale behind distribution mark-up regulatory strategies; the breadth of use of mark-up regulation; the magnitude of regulated mark-ups; public versus private sector regulation; selective mark-up regulation; other add-ons in supply chain; discounts, rebates, and trade schemes; approaches to regulating wholesale and retail mark-ups; the impact of mark-up regulations on medicine prices; enforcement of mark-up regulations; and viability of wholesalers and retailers. Conclusions drawn by the WHO/HAI policy review are listed below.

- Regulation of mark-ups as part of a comprehensive price regulation strategy will probably lead to reduced medicine prices. However, regulation of mark-ups without

regulation of either the manufacturer or retail selling prices is unlikely to lower medicine prices.

- Regulation of mark-ups will probably have an effect on the viability of some operators in the pharmaceutical supply chain and may adversely affect operations in more remote areas or in other health services that are cross-subsidized through higher mark-ups.
- Regulation of distribution mark-ups can have unintended impacts or consequences. Incentives and disincentives need to be mapped and potential unexpected effects considered.
- A reliable mechanism for monitoring the prices and sales of medicines in the appropriate sector or market is essential to be able to judge the effects of pricing regulations, both intended and unintended.
- It is possible to use mark-up regulation as part of a generic medicine promotion policy, for example by providing higher remuneration for generic medicines or any other group of products, but this is not commonly practised, possibly due to the complexity of implementing differential mark-ups.
- Regulating mark-ups in the private sector is probably more complex than in the public sector.
- Regulating mark-ups without adequate enforcement is probably not effective and adequate enforcement in low-income countries (LICs) appears to be a challenge.
- Mark-ups that include a regressive component with or without fixed fees, as is practised in countries such as Lebanon, the Syrian Arab Republic, and Tunisia, probably lead to better outcomes than fixed percentage mark-ups through their influence on financial incentives. However, fixed fee mark-ups can dramatically increase the price of otherwise low-cost medicines.
- While bans on discounts, rebates, and bonuses in the supply chain probably increase transparency in medicine pricing, there is insufficient evidence to say whether reduced prices result.

Table ES1.1 summarizes the wholesale and retail mark-ups in LMICs, as presented in the WHO/HAI policy review. Tables ES1.2 and ES1.3 summarize wholesale and retail mark-up regulation strategies in HICs.

The policy review states that there are very few examples of the impact of regulating mark-ups in LMICs and all the information retrieved is anecdote or opinion. In China, distribution mark-ups are enforced, which has created an incentive to use higher-cost medicines. In Ecuador and Panama, there is mark-up regulation with resultant uniform prices and reduced speculation. In Honduras, mark-up regulation results in higher prices and suppliers over-invoice to recover margins. In Jordan, price controls including mark-ups were removed from 50 over-the-counter medicines with a resultant increase in prices; controls were subsequently re-imposed. In Kenya, price and mark-up regulations were removed and there is an anecdotal account that prices decreased, possibly due to a return to free-market principles from a situation where perverse incentives or other factors had led to unnecessary high prices. In South Africa, introduction of a 0% mark-up on hospital medicines resulted in a drop in the price index of 1000 medicines.

9.5.3 Descriptive evidence: WHO/HAI policy review – case studies

The WHO/HAI policy review includes case studies of two upper-middle-income countries (Albania and South Africa) and one low-income country (Mali), which are summarized below.

Albania

- Statutory mark-ups are used for remuneration of wholesale, distribution, and retail operations. There are no dispensing fees or other charges. The mark-ups as of 2007 are 12% for wholesalers for reimbursed medicines and 18% for non-reimbursed medicines; for retailers these mark-ups are 29% and 33%, respectively.
- There is no legal basis for discounts or rebates in the medicine supply chain with fixed manufacturer prices and wholesale and retail mark-ups.
- There is no evidence available on enforcements or effects of the mark-up regulations.

South Africa

- The 1996 national medicines policy addresses prices to “promote the availability of safe and effective drugs at the lowest possible cost”. Measures taken include : establishment of a multidisciplinary pricing committee; total transparency in the pricing structure of medicines; use of a non-discriminatory pricing system in the private sector; replacement of wholesale and retail mark-ups with a fixed professional fee; establishment of a system to support free or subsidized provision of medicines in the public sector; development of a price monitoring system compared to international medicine prices; regulation of medicine price increases; provision of priority medicines from public sector to private sector if needed; and promotion of use of generic medicines.
- There is a maximum single exit price, which is the “only price at which manufacturers shall sell medicines” in the private sector, which was set based on the average 2003 prices of medicines calculated on a unit basis. The single exit price can be increased on an annual basis to a level determined by the state, and the same price must be offered to all buyers.
- The standard exit price includes a logistics fee to cover the distribution costs and it is left to importers, manufacturers, and intermediate suppliers to negotiate how the fee is split.
- Retailer remuneration is based on a regressive percentage plus a fixed fee.
- Discounts, rebates, and other forms of commercial incentives are not permitted. The standard exit price is set irrespective of the volume of sales or package size.
- A five-year analysis of sales data demonstrated that sales of generic medicines, by volume, exceeded those of originator brands in 2007 for the first time. The policy review suggests that this is more likely the result of policies and laws promoting generic prescribing and substitution than pricing regulation.
- There is no difference between medicine prices in rural and urban areas and prices of medicines have reduced by an average of 19% (25–30% for generics and 12% for originator brands).

Mali

- Mali has implemented a series of national medicines policies, the latest of which, in 2006, set maximum prices for 107 essential medicines at wholesale and retail levels in the private sector.
- Mark-ups are not officially regulated in the private sector. As part of drug registration, manufacturers propose a retail selling price that is agreed with the Pharmacy and Medicines Department. Wholesalers then decide the wholesale selling price, which in effect determines the retailer's mark-up.
- Wholesale margins are not officially regulated for the 107 specified essential medicines. Instead, retail prices are set in consultation with manufacturers or importers. The wholesale selling prices are based on the formulae below.

Branded products:

Wholesale price before tax \times 1.97 = pharmacy price

Pharmacy price \times 0.75 = wholesaler transfer price

Generic products:

Wholesale Price before tax \times 2.05 = pharmacy price

Pharmacy price \times 0.65 = wholesaler transfer price

- The margin of private wholesalers is estimated to be 13–30% for branded products and 19–34% for generic products.
- The margin (or possibly mark-up) of private retailers is estimated to be 25% for branded products and 28–45% for generics.
- Discounts, trade schemes, and other practices are allowed and are unregulated. Wholesalers can sell to other wholesalers and may offer a discount of 10–12%.
- To ensure implementation of the 2006 national policy, these actions were taken: establishment of a formal committee representing all involved parties, public and private, with the exception of consumer representatives; definition of a mechanism for identifying the medicines and their current prices; fixing of maximum selling prices; informing the public of the initiative through mass media; implementation through issuing of the required decree; and monitoring of prices at wholesale and retail levels.
- The WHO/HAI policy review reports that one study demonstrated an average reduction in price of 25% was observed in 49 of the 107 essential medicines, three years after implementation of the policy.

9.5.4 Implementation requirements

The WHO/HAI policy review identified the following requirements for implementing regulation of distribution mark-ups.

- Knowledge of the costs of operating the various distribution functions.
- Economic expertise to analyse distribution costs and to determine appropriate remuneration of stakeholders or budgetary requirements.
- Medical and pharmaceutical expertise for assessing incentives and disincentives in the supply chain and effects on supply and rational use of medicines.

- Statistical expertise for analysis of commercial and/or medicine price data.
- Expert legal advice for drafting appropriate and sound legislation.
- Structures for consultation with concerned stakeholders.
- A mechanism for monitoring medicine prices and use/sales.
- A mechanism for regular review of regulated prices.
- A strategy and adequate resources and structures to enforce the regulations.
- A national medicines policy document providing a basis for the actions.
- High-level political support.

9.5.5 Feasibility

The WHO/HAI policy review indicates that if a number of the requirements listed above are lacking, as might be the case in many LMICs, it may not be appropriate to implement a mark-up policy. There is no clear guidance available on the minimum requirements for implementation in a resource-challenged setting.

9.5.6 Gaps, research needs, and comments

Quantitative assessment of the benefits of regulation of mark-ups is needed, preferably in comparison with other price control measures. The WHO/HAI policy review also suggests the research areas below.

- While mark-up regulation is aimed at reducing prices, there is a paucity of information as to whether the reduced prices lead to changes in consumption, or whether patients prefer higher-priced products because of a perceived relation between price and quality and/or efficacy. Examination of consumption patterns of low- and high-priced generic equivalents reimbursed by health insurance might produce useful data.
- Some studies have shown that high mark-ups may be required for sustainability of distribution operations or to cross-subsidize other services. Further information is needed to understand whether the high mark-ups in the supply chain in some countries reflect profiteering or actual high costs in the distribution chain.
- The enforcement of mark-up regulations – in terms of whether it occurs and the mechanism used – has not been well described. Information is also needed on the resources required for successful enforcement, especially in LMICs.
- Methods for monitoring the prices of medicines in a country are instrumental to monitoring the impact of regulatory/policy interventions. However, there is little detail available on mechanisms, such as the level of sophistication required, range of products covered, and analysis and interpretation of the data. This area needs further elucidation and development of guidance for policy-makers.
- More case studies of price regulation from LICs are needed to provide models for economies that face similar constraints in regulation and enforcement.

Table ES1.1: Summary of wholesale and retail mark-ups in low- and middle-income settings

Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Argentina	UMIC	–	–	60%	25%	–	1995	Sarmiento (1995) (10)
Armenia	L-MIC	25%	25%	25–30%	25–30%	–	2002	Key informant; Levison (2003) (11); WHO pharmaceutical profile 2010
Bolivia (Plurinational State of)	L-MIC	–	–	30–35%	–	–	1994	Sarmiento (1995) (10)
Bolivia (Plurinational State of)	L-MIC	184.8–488.3%	40.7–123.0%	144.0–228.1%	92.4–139.3%	–	2008	WHO/HAI survey report (12)
Brazil, Rio de Janeiro state	UMIC	–	–	See retail	27.1–28.8% combined wholesale and retail	–	2001	27.1–28.8% wholesale and retail mark-ups combined in private sector; WHO/HAI survey report (12)
Brazil	UMIC	–	–	7%	22%	–	2000	“Monitored freedom” in medicine pricing; Cohen (2000) (13); Levison (2003) (11)
Burkina Faso	LIC	–	–	30%	100%	–	2007	Antimalarials; document review and semi-structured interviews; Patouillard et al (2010) (14)
Burkina Faso, Cameroon, Kenya, Uganda	LIC	–	–	13% average	35% average	–	2007	AMFm technical proposal (2007) (15); average mark-ups across countries for ACTs
Cambodia	LIC	–	–	2–50%	3% (ACT)	–	2003	ACTs; interviews; Patouillard et al (2010) (14)
Cambodia	LIC	–	–	–	16–71% (ACT)	–	2007	ACTs in pharmacies and drug shops; interviews; Patouillard et al (2010) (14)
Cameroon	L-MIC	–	–	14% (ACT)	34% (ACT)	–	2007	ACTs; interviews; Patouillard et al (2010) (14)
Chad	LIC	~44% (importer + distributor)	~44%	~22%	~38%	No	2004	Estimates based on graphic in WHO/HAI survey report (12)
Chad	LIC	–	–	20%	30%	No	2004	Generic amitriptyline and OB ciprofloxacin; WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Chad	LIC	16% (CMS importer) + 25% (regional medical store) (regulated)	30% (regulated)	20% (unregulated)	30% (unregulated)	No	2004	Official mark-ups not respected in public sector; WHO/HAI survey report (12); and database (16)
China, Shandong province	L-MIC	To hospitals: 0.6–10.3% LPG; 6.2–13.7% OB	14.1–26.1% LPG; 17.1–18.8% OB	3% LPG; 2–3% OB	17.8–25.7% LPG; 4.5–22.3% OB	No	2004	WHO/HAI survey report (12)
China	L-MIC	–	–	15%	15%	–	up to 2000	Reports on pricing policy; Meng et al (2005)(17); Sun et al (2008) (18); Yu et al (2010) (19)
China, Hubei province	L-MIC	–	median 44.8% (range 15.6–177.8%)	–	–	–	2007	Observed prices of 25 medicines in public hospitals; Yang et al (2010) (20)
China	L-MIC	–	250–1000% (unregulated)	–	–	–	2005	Hospital data – source uncertain; Liang et al (2009) (21)
Costa Rica	UMIC	–	–	30% (25% essential drugs) (regulated)	30% (25% essential drugs) (regulated)	–	1994	Sarmiento (1995)(10)
Dominican Republic	UMIC	–	–	33–40%	30%	–	1994	Sarmiento (1995)(10)
Ecuador	L-MIC	–	–	20% (regulated)	25% (regulated)	–	1994	Sarmiento (1995)(10)
Ecuador	L-MIC	50–56% LPG	30–60% LPG	35–67.5% LPG	38–54% LPG	–	2008	WHO/HAI survey report (12)
El Salvador	L-MIC	–	–	380% LPG ceftriaxone	552% LPG ceftriaxone	No	2006	WHO/HAI survey report (12)
				179% LPG clotrimazole cream; 1702% LPG ciprofloxacin; 380% LPG ceftriaxone;	367% LPG clotrimazole cream; 226% LPG ciprofloxacin; 413%			Second set of values calculated from data in text and amended based on WHO/HAI database (16) and survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
				75% LPG ranitidine; 74% LPG fluconazole	LPG ceftriaxone ; 1228% LPG ranitidine; 30% LPG fluconazole			
Ethiopia	LIC	27–30% LPG	25% LPG	20% OB; 39% LPG	30%	No	2004	WHO/HAI survey report (12)
Ethiopia	LIC	–	25%	–	–	No	2002	“Special pharmacies” operating as revolving drug funds; Russell & Abdella (2002) (22)
Ethiopia	LIC	–	20–30% (official ?)	–	–	No	2007	“Special pharmacies” operating as revolving drug funds; Carasso et al (2009) (23)
Ghana	LIC	10% (regulated)	20% (regulated)	30–40% (unregulated)	30–40% (unregulated)	No	2004	Interviews; WHO/HAI survey report (12)
Ghana	LIC	20% (imported); 15% (local) + 10% for regional medical stores (regulated)	10% (regulated)	–	10–100% (unregulated)	–	2002; 2003	Data show regulated public sector mark-ups not known or enforced; Huff-Rouselle & Azeez (2002) (24); Sarley et al (2003) (25)
Ghana	LIC	–	–	10–30%	30–200%	No	2009	Interviews; McCabe (2009) (26)
Grenada	UMIC	–	–	20%	40%	–	2002	Snell (2003) (27)
Honduras	L-MIC	–	–	operating costs + 4% (regulated)	27% (regulated)	–	1994	Sarmiento (1995) (10)
India, Haryana state	L-MIC	–	–	8%	16%	No	2004	Hypothetical cases; WHO/HAI survey report (12)
India, Karnataka state	L-MIC	–	–	8–10% OB; 8.7–10% LPG	15.3–19.5% OB; 17.9–22.5% LPG	No	2004	Hypothetical cases; WHO/HAI survey report (12)
India, Maharashtra state (four regions)	L-MIC	–	–	9.5–9.7% LPG; 9.5% OB	19.1–20.3% LPG; 19.2–20.1% OB	No	2005	WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
India, Rajasthan state	L-MIC	–	–	10%	20%	No	2003	In general mark-up information from interviews; mark-ups vary and are lower for OBs; WHO/HAI survey report (12)
India, West Bengal state	L-MIC	–	–	8% scheduled; 10% non-scheduled (not regulated but by agreement)	16% scheduled (but 15–25% quoted and higher for slow-moving products; interviews)	No	2004	WHO/HAI survey report (12)
India	L-MIC	–	–	2–5% for superstockist; 8% minimum scheduled medicines (regulated): 7–11.1% measured; 10% non-scheduled (unregulated average): 9.7–11.5% measured (includes effect of trade schemes, regulated)	16% minimum scheduled medicines (regulated) : 17–30% for OB & 92–436% for LPG measured; 20% non-scheduled (unregulated average): 21.5–32.7% measured (includes effect of trade schemes, regulated)	No	2007 ^b	Minimum mark-ups; trade schemes increase effective mark-up; Kotwani & Levison (2007) (28)
India	L-MIC	–	–	–	25% retail margin estimated 25%; mark-ups of 150–200%	No	2007	No evidence to support; study examined only retail prices in various sectors; Godwin & Varatharajan (2007) (29)
Indonesia	L-MIC	–	–	6–15%	20–35%	Yes (100–500 rupiahs)	2004	Prices of some essential medicines list medicines regulated; WHO/HAI survey report (12)
Iran (Islamic Republic of)	UMIC	–	15% (regulated)	8–13.5%; lower for imported OB but 10–13% importer mark-up (regulated)	10–21%; lower for imported OB (regulated)	Yes (5000 rials)	2008	Public get medicines through private wholesalers; WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Jordan	L-MIC	–	–	19% (regulated)	26% (regulated)	No	2004	WHO/HAI survey report (12)
Kazakhstan	UMIC	–	–	5–50% LPG (15% measured)	20–30% LPG (measured)	No	2004	WHO/HAI survey report (12)
Kenya	LIC	–	–	15% (regulated)	20% (regulated)	No	2000	Fixed maximum mark-ups; Myhr (2000) (30). Reported as public sector mark-ups in Levison (2003) (11)
Kenya	LIC	0–15%	–	15–30%	20–100%	No	2001	WHO/HAI survey report (12)
Kenya	LIC	–	–	25% (regulated)	33% (regulated)	–	2001/02	Prices have dropped since regulations lifted; Snell (2003) (27)
Kenya	LIC	–	–	Regressive 10–22% (includes wholesale and retail?); 2% for ARVs	5% for ARVs	No	2003	Case-study from faith-based supplier (WHO 2004) (31)
Kenya	LIC	–	–	–	13–189%	–	2003	Antimalarials; interviews. Patouillard et al (2010) (14)
Kenya	LIC	–	–	15% measured (importer 30–40% fee) (15–34% hypothetical)	33% OB imported; 203% LPG local (33–308% hypothetical)	No	2004	15% and 33% voluntary agreement applied to OBs and high cost items; WHO/HAI survey report (12)
Kenya	LIC	–	–	15%	33% OB; 203% LPG	–	2004	Antimalarials; interviews. Patouillard et al (2010) (14)
Kenya	LIC	–	–	10%	33%	–	2007	Antimalarials; interviews. Patouillard et al (2010) (14)
Kenya	LIC	0%	–	(54–748% importer); 30% OB; 6% LPG	37% OB; 102% LPG	No	2007 ^b	WHO/HAI survey report (12)
Kenya	LIC	–	–	(15–200% importer); 3–23%; average 14%; see also retail	Average 28% retail; 5–22% mark-up in mission sector	No	2008 ^a	Interviews; Levison & Kimatu (2008) (32)
Kenya	LIC	–	–	–	38–113% (SP/AQ)	No	2002	Observed data on two most widely stocked products; Amin & Snow (2005) (33)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Kosovo (UN Administered Province of)	L-MIC	15% (see notes) (regulated)	15% (see notes) (regulated)	–	–	–	2002	Regulated mark-ups not observed; not certain whether public or private sector; Levison (2003) (11)
Kuwait	HIC	–	–	35% (regulated)	26% (regulated)	No	2004	In 2005 changed to 29% and 20% WHO/HAI survey report (12)
Kyrgyzstan	LIC	–	–	15–25% OB; 25–35% LPG	5–15% OB; 15–25% LPG	No	2005	WHO/HAI survey report (12)
Kyrgyzstan	LIC	–	–	–	32–244%	No	2007	Data from nongovernmental organization chain of pharmacies; Waning et al (2010) (34)
Lebanon	UMIC	–	–	10% (regulated)	30% (regulated)	No	2004	Regressive mark-ups have since been introduced; WHO/HAI survey report (12); Anon (2008) (35)
Lithuania	UMIC	See comments	–	–	–	–	2002	Formula with regressive percentage and fixed fee; Snell (2003) (27)
Malaysia	UMIC	17.5–20% (LPG and OB)	0%	5.8% LPG; 15% importer + 3.1–19.1% OB; (0% for locally made LPG)	100% LPG; 25.4–38.3% OB; 140% for locally made LPG	No	2004	Also dispensing doctors mark-up 5–75% for OB; 316% LPG. Importer 12%; distributor 0–15%; retailer 50–317%. WHO/HAI survey report (12) and Babar et al (2007) (36)
Malawi	LIC	–	–	10–30% (10–25% LPG; 30–35% OB)	50–100%	No	2009	Interviews; McCabe (2009) (26)
Mali	LIC	–	–	13.3–29.3% OB; 19.3–33.7% generics	25% OB; 28–45% generics	No	2004	Maiga & Diawara (2006) (37)
Mali	LIC	20–50% measured (regulated)	24–45% measured (regulated)	15% in theory at one wholesaler (23–30% measured)	100% (indicative price of one wholesaler) (45–78% measured) (33–55% from WHO/HAI database (16))	No	2004	Theoretical versus measured; Bamako public sector prices lower since no need for second wholesaler; might be cumulative values; public prices are regulated but not observed. WHO/HAI survey report (12) and WHO/HAI database (16)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Mali	LIC	–	–	–	45% max on listed medicines (price-regulated; not mark-up)	No	2009	Prices of 107 essential medicines fixed and wholesale and retail margins determined by negotiation. Maiga & William-Jones (2010) (38)
Mali	LIC	–	–	19–34% LPG; 13–30% OB (some prices regulated; not mark-up)	28–45% LPG; 25% OB (some prices regulated; not mark-up)	No	2009	Interviews; not clear whether these are margins or mark-ups; McCabe (2009) (26)
Mauritius	UMIC	14%	27%	–	–	–	2002	Levison (2003) (11)
Mongolia	L-MIC	15%	0%	25% LPG and OB	30% LPG; 10% OB	No	2004	WHO/HAI survey report (12)
Morocco	L-MIC	–	–	10% LPG & OB (regulated)	30% LPG & OB (regulated)	No	2004	WHO/HAI survey report (12)
Mozambique	LIC	–	–	13.5% importer + 9% warehousing + 5% distribution (all on CIF price) (regulated)	76.3% on CIF price (regulated)	No	2007	Regulated mark-ups not enforced; Russo & McPake (2009) (39)
Nepal	LIC	(see notes)	(see notes)	10–12%	16% (regulated)	–	2002	Reported as public sector but likely to be private sector; Levison (2003) (11)
Nepal	LIC	–	0% encouraged (unregulated)	7% importer + 8.5% wholesaler (regulated)	16% (regulated)	No	2005	Maximum prices and mark-ups not enforced. Rao & Thapa (2005) (40); Harper et al (2007) (41)
Nicaragua	L-MIC	–	–	35–67% generic; 30–128% OB	38–54% generic; 32–73% OB	–	2008	WHO/HAI survey report (12)
Niger	LIC	–	–	47.3% (importer) + 35% (wholesaler)	35%	No	2009	Abdou Sidikou et al (2009) (42)
Nigeria	L-MIC	–	–	20% importer+10%	30% (one example)	No	2004	WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Nigeria	L-MIC	–	5% profit margin from RDF	–	–	–	2005	University teaching hospital RDF; statement without supporting data; Mokuolu et al (2007) (43)
Oman	HIC	–	–	20.9% (regulated)	28.1% (regulated)	No	2007 ^a	WHO/HAI survey report (12)
Pakistan	L-MIC	–	–	6% imported; 2% local (regulated)	15% local and imported (regulated)	No	2004	821 controlled products; enforcement not rigorous WHO/HAI survey report (12)
Panama	UMIC	–	–	30% “ethical”; 25% other (regulated)	33% “ethical”; 30% other (regulated)	–	1994	Sarmiento (1995)(10)
Peru	UMIC	20% importer (unregulated)	25% (regulated)	25–40% importer + 20% (LPG) to 25% (OB) (unregulated)	11% (OB)–70% (LPG) (unregulated)	No	2005	Lower retail mark-ups for OB; importer gives public procurement less mark-up due to volume; interviews. WHO/HAI survey report (12). Mark-ups higher on lower-cost medicines; Madden et al (2010) (44)
Philippines	L-MIC	–	–	17.5–65%	20–50%	No	2005	Interviews; WHO/HAI survey report (12)
Philippines	L-MIC	–	30% maximum (regulated)	18.2–117% (LPG); 5–13% (OB; theoretical) (unregulated)	2.2–60% (OB); 5.1–355% (LPG) (unregulated)	No	2008 ^b	WHO/HAI survey report (12) with new methodology
Russian Federation	UMIC	–	–	25% maximum (regulated)	30% maximum for essential medicines; higher for others (regulated)	–	2009	World Bank (2009) (45)
Russian Federation	UMIC	–	–	15% (regulated)	25–35% (regulated)	–	2000	Bulgakov (2000) (46)
Senegal	L-MIC	–	–	15–18% quinine	30–41% quinine	–	2003	Interviews; Patouillard et al (2010) (14)
Senegal	L-MIC	15%	36%	19%	50%	No	2005	May be cumulative values; WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Senegal	L-MIC	–	–	15% ACTs	3–22% ACTs	–	2007	ACTs; interviews and mystery shopper; Patouillard et al (2010) (14)
Senegal	L-MIC	20% (regulated)	50% (regulated)	14.3% (OB/specialty medicine); 6.2% (social list); 18.2% (hospital pack) (regulated)	40.7% (OB/specialty medicine); 9.9% (social list); 56.3% (hospital pack) (regulated)	No	2000	Theoretical; Guimier et al (2005) (47)
Sierra Leone	LIC	–	–	33% own products; 25% third-party items	–	–	Pre-2002	Snell (2003) (27)
South Africa	UMIC	–	–	21.2%	50%	–	2003	Discounts affect final price. Gray & Matsebula (2000) (48). Reported as public sector in Levison (2003) (11)
South Africa, Gauteng	UMIC	–	–	Regulated fixed logistics fee (equivalent to approximately 2–20% of MSP OB; 15% for LPG) (regulated)	Fixed fee (regressive bands)	Yes	2004	Dispensing doctors have lower dispensing fee. WHO/HAI survey report (12)
South Africa	UMIC	–	–	–	46% + ZAR6 33% + ZAR15.75 15% + ZAR51 5% + ZAR121 (regulated)	Yes (captured in retail mark-up)	2010	Government of South Africa (2010) (49)
Sri Lanka	L-MIC	7%	12.5%	25% importer + 8%	16%	No	2001	Hypothetical; WHO/HAI survey report (12)
Sri Lanka	L-MIC	(see notes)	(see notes)	8.5%	16.25%	–	2002	Reported as public sector but likely to be private sector; Levison (2003) (11)
Sri Lanka	L-MIC	–	–	(see retail)	172% (includes taxes, import, wholesale, retail)	–	2000	Weerasuriya (2000) (50)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Sudan	L-MIC	20% + 28% (regional store) (regulated)	20% non-RDF (regulated)	15% (regulated)	20% (regulated)	No	2005 ^a	WHO/HAI survey report (12)
Sudan	L-MIC	64% (all mark-ups including retail for Khartoum RDF)	See wholesale	–	–	No	2006	E-Drug message Mohammed (2006) (51)
Syrian Arab Republic	L-MIC	–	–	8% (regulated)	Pharmacy mark-up applied regressively in increments at set bands of procurement price (regulated)	No	2003	WHO/HAI survey report (12)
Tajikistan	LIC	–	–	15%	15–30%	No	2005	WHO/HAI survey report (12)
United Republic of Tanzania	LIC	0%	50%	–	–	–	2000	Reported as public sector but source classified other data incorrectly; Levison (2003) (11)
United Republic of Tanzania	LIC	–	–	9–26%	150–669%	–	2004/2007	Antimalarials; interviews. Patouillard et al (2010) (14)
United Republic of Tanzania	LIC	–	–	48% + 13% (two wholesalers in chain)	100–233%	No	2003	Antimalarials; Battersby et al (2003) (52)
United Republic of Tanzania	LIC	–	–	27–56%	39–233%	–	2007	Antimalarials; interviews. Patouillard et al (2010) (14)
United Republic of Tanzania	LIC	–	–	18–41%	44–110%	–	2008	Antimalarials; interviews. Patouillard et al (2010) (14)
United Republic of Tanzania	LIC	16% (2.5% storage; 1% repackaging; 10% distribution; 2.5% administration)	0%	20%	30%	No	2004	WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
Thailand	L-MIC	–	31–41% OB; 20–567% LPG	0–1.6% OB; 6.7–31% LPG	13–40% OB; 20–150% LPG (includes tax)	No	2006	WHO/HAI survey report (12)
Thailand	L-MIC	–	15–30% scheduled up to 400% observed	–	–	–	1998	More expensive products tended to have lower mark-ups but not consistent; methodology not robust. Pitaknetinan et al (1999) (53)
Tunisia	L-MIC	10% (regulated)	0% (regulated)	8.7% (regulated)	31.6–42.9% regressive (regulated)	No	2004	WHO/HAI survey report (12)
Uganda	LIC	23% importer + 0% LPG	0%	23% importer + 2% OB; 6% importer + 0% LPG (imported); 4.2% LPG (local) (10–40% stated)	364% OB; 403% imported LPG; 233% local LPG (36–720% stated)	No	2004	WHO/HAI survey report (12)
Uganda	LIC	–	–	27% (importer) + 29%	410–501%	No	2004	Antimalarials. Patouillard et al (2010) (14) based on WHO/HAI survey report (12)
Uganda	LIC	–	–	25–33% OB; 6–91% LPG	28–365% OB; 30–720% LPG	No	2004	WHO/HAI database (16) importer and wholesaler mark-ups combined
Uganda	LIC	35%	–	(20–70% importer); 2–30% for imported or 15% for local	85–250% for imported; 105–145% for local	No	2007 ^b	Eight antimalarials and five other medicines; Auton et al (2008) (54); Coughlan et al (2008) (55)
Uganda	LIC	–	–	40–50%	38–100%	–	2007	Antimalarials; interviews. Patouillard et al (2010) (14)
Uganda	LIC	–	–	–	40% average (ACT); 190% average (SP)	No	2007	AMFm technical proposal (2007) (15)
Ukraine	L-MIC	–	–	10–12%	Up to 35%; up to 25% on some essential medicines (regulated)	No	2007	WHO/HAI survey report (12)

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Location	Income category	Public wholesale mark-up	Public retail mark-up	Private wholesale mark-up	Private retail mark-up	Dispensing fee	Date of survey/information	Source and comments
United Arab Emirates	HIC	–	–	20% (regulated)	20% (regulated)	No	2006	There have been reductions in mark-ups in recent times e.g. used to be 25% and 20%. WHO/HAI survey report (12)
United Arab Emirates	HIC	–	–	See retail	Combined profit margin for agents and retailers in three categories of selling price: >AED500 = 25–35% AED300–500 = 35–45% <AED300 = 50% (regulated)	No	2005	Change introduced November 2005; not mark-up regulation; Anon (2007) (56)
Yemen	LIC	10% (regulated)	–	10% (regulated)	20% (regulated)	No	2006	Not enforced or CIF not updated? WHO/HAI survey report (12)
Zaire (Democratic Republic of the Congo)	LIC	–	150%	–	–	No	1988	“Profit margin” at self-financing health centres; Courtois & Dumoulin (1995) (57)
Zambia	LIC	–	–	–	29–67% (ACTs) 25–300% (SP)	No	2008	Clinton Foundation (2008) (58)
Zambia	LIC	–	–	–	30%	–	2003	Antimalarials; interviews. Patouillard et al (2010) (14)

ACT = artemisinin combination therapy, AED = United Arab Emirates Dirham, CIF = cost, insurance, and freight, HIC = high-income country, LIC = low-income country, L-MIC = lower-middle-income country, LPG = lowest priced generic, MSP = manufacturer’s selling price, OB = originator brand, RDF = revolving drug fund, SP = sulfadoxine-pyrimethamine, ZAR = South Africa Rand, UMIC = upper-middle-income country.

^a Not publicly available at time of compilation.

^b Not a WHO/HAI-methodology survey (although these methods may have been used).

Notes: (1) Only WHO/HAI price studies with some data on mark-ups were included. (2) Importer mark-ups not reliably captured (unless stated). (3) “Regulated” refers to some form of mark-up regulation. Even where mark-ups are not regulated, there may be other price regulation mechanisms. (4) Individual sources should be consulted for greater detail and explanation.

Source: Ball D. Working paper 3: *Regulation of mark-ups in the pharmaceutical supply chain – review series on pharmaceutical pricing policies and interventions*. Geneva, World Health Organization and Health Action International, 2011. (4)

Table ES1.2: Summary of wholesale mark-up regulatory strategies in high-income countries

	Fixed fee (any format)	Regressive fixed fee	Fixed %	Regressive %	Cap? ^a	Notes
Albania	–	–	X	–	–	12%; lower on named high cost medicines
Australia^b				X	Y	
Austria	X	–	–	X	Y	9–17.5% or a progressive fixed fee; average wholesale margin 9%
Belgium	–	–	X	–	Y	13.1% up to €39 value, thereafter 31% of first €24 plus low percentage on remainder
Bulgaria	–	–	–	X	Y	7–10%
Canada^b	–	–	–	–	Y	Various mechanisms by region/plan
Cyprus	–	–	–	–	–	Unregulated. All imported medicine priced through international reference pricing. Fixed 20% for locally produced pharmaceuticals in private sector
Czech Republic^b			X		No	Total wholesale + retail mark-up of 29%
Denmark	–	–	–	–	No	Unregulated
Estonia	–	–	–	X	Y	3–20%
Finland	–	–	–	–	No	Unregulated; average margin 4%
France	–	–	–	X	No	Only reimbursed medicine; 2–10.3%
Germany	X	–	–	X	Y	Fixed fee acts as cap to percentage; 6–15%
Greece			X		No	8.43%
Hungary	X	–		X	No	5–12%
Iceland^b			X		No	Prescription-only medicines
Ireland			X		No	15%
Italy			X		No	6.65%

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	Fixed fee (any format)	Regressive fixed fee	Fixed %	Regressive %	Cap? ^a	Notes
Japan^b					No	Unregulated
Republic of Korea^b					No	Unregulated
Latvia				X		4–10%
Lithuania	X			X	Y	Regressive 5.5–14% or progressive fixed fees acting as caps. Maximum mark-ups used
Luxembourg^b			X		No	Domestic products only
Mexico^b					No	Unregulated. However, one citation that wholesale and retail margins are decided upon after negotiation between government and the manufacturer (US Dept. of Commerce 2004)
Netherlands^b					No	Unregulated
New Zealand^b			X		No	
Norway	–	–	–	–	No	Unregulated; average margin 5– 7%
Poland			X		No	Maximum mark-up, 9.8%
Portugal			X		No	18.25% of pharmacy retail price
Slovakia				X	No	Max mark-up, 4–11%; only two categories (other special cases)
Spain^b			X		Y	7.6%; fixed fee is a cap to the fixed percentage
Sweden	–	–	–	–	–	Unregulated; only two wholesalers with single channel distribution
Switzerland^b	X			X	Y	Total wholesale + retail mark-up shared between distributors. Fixed fee + regressive percentage 8–15%
Turkey				X	No	2–9%
UK	–	–	–	–	No	Negotiated; nominal 12.5% total distribution margin
USA^b	–	–	–	–	No	Unregulated

^a If there is a maximum value above which the mark-up should not exceed. This is not the same as having a maximum percentage mark-up.

^b From OECD (2008) report (59).

Notes: (1) This table is based on the information available in the OECD (2008) report (59) and the *Prescription pricing and reimbursement information* (PPRI) (2008) report (60), and focuses on the pricing regimen used for public national health systems. However, it is not possible to capture the intricacies of the pricing strategies, which may differ between public reimbursement systems and private sales, method of price caps, etc. Country PPRI reports should be consulted for these details. (2) Some flat fees may be regressive in nature. (3) “Unregulated” means there is no set mark-up; regulations may still exist as part of price regulation.

Source: Ball D. Working paper 3: *Regulation of mark-ups in the pharmaceutical supply chain – review series on pharmaceutical pricing policies and interventions*. Geneva, World Health Organization and Health Action International, 2011. (4)

Table ES1.3: Summary of retail mark-up regulatory strategies used in high-income countries

	Fixed fee (any format)	Regressive fixed fee	Fixed %	Regressive %	Cap? ^a	Dispensing fee?	Notes
Albania	–	–	X	–	No	No	29%; lower on selected high cost medicines
Australia^b	–	–	–	X	Yes	Yes	
Austria	X	–	–	X	No	Yes	3.9–37% or a progressive fixed fee; dispensing fee only for private clients; average retail margin 20%
Belgium	–	–	X	–	Yes	No	31% up to €39 value, thereafter 31% of first €24 plus low percentage on remainder
Bulgaria	–	–	–	X	Yes	No	7–10%
Canada^b	–	–	–	–	–	–	Various mechanisms by region/plan
Cyprus	–	–	–	–	–	–	38% in private sector
Czech Republic^b					No	No	Total wholesale + retail mark-up 29%
Denmark	X	–	X	–	No	Yes	progressive fixed fees and regressive factors built into formula; 55%
Estonia	X	–	–	X	Yes	No	0–40%; fixed fee not applied in all cases; higher fixed fee for most expensive products

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	Fixed fee (any format)	Regressive fixed fee	Fixed %	Regressive %	Cap? ^a	Dispensing fee?	Notes
Finland	X	–	–	X	No	Yes	12.5–50% plus progressive fixed fee
France	–	–	–	X	No	Yes	Only reimbursed medicines; 6–26.1%
Germany	X	–	X	–	Yes	Yes	3% (plus €8.10 per package)
Greece	–	–	X	–	No	No	35%
Hungary	X	–	–	X	Yes	No	17–26%; progressive fixed fee
Iceland^b	–	–	X	–	No	–	Prescription-only medicine
Ireland	–	–	–	–	No	Yes	Not officially regulated but agreements exist; 50% plus dispensing fee
Italy	–	–	X	–	No	No	Statutory discount creates regressive margin
Japan^b					No	Yes	Unregulated
Republic of Korea^b					No	Yes	Unregulated
Latvia	X	–	–	X	No	No	Formula incorporates regressive percentage and progressive fixed fee
Lithuania	X	–	–	X	Yes	No	Regressive 4–22% or progressive fixed fees acting as caps; maximum mark-ups used
Luxembourg^b			X		No	–	
^b					No	–	Unregulated; However one citation that wholesale and retail margins are decided upon after negotiation between government and the manufacturer (US Department of Commerce, 2004)
Netherlands^b			X		Yes	Yes	
New Zealand^b				X	No	Yes	

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	Fixed fee (any format)	Regressive fixed fee	Fixed %	Regressive %	Cap? ^a	Dispensing fee?	Notes
Norway	X	–	–	X	No	Yes	Maximum mark-ups; 5–8%; fixed fee could be considered a dispensing fee
Poland	X	–	–	X	Yes	No	Maximum mark-ups; 12–40% or progressive fixed fee; fixed fee acts as cap
Portugal	–	–	X		No	No	18.25% of pharmacy retail price
Slovakia	–	–		X	No	Yes	10–21%; only two categories; other special cases
Spain	–	–	X		Yes	No	27.9%; fixed fee is a cap to the fixed percentage
Sweden	X*	–	–	X	Yes	No	0–20% regressive percentage plus a progressive fixed fee; capped since highest category gets 0%
Switzerland^b	X			X	Yes	Yes	Total wholesale + retail mark-up
Turkey	–	–	–	X	No	No	10–25%
UK	–	–	–	–	No	Yes	Not regulated directly but target margin monitored
USA^b	–	–	–	–	No	No	Unregulated

^a If there is a maximum value above which the mark-up should not exceed. This is not the same as having a maximum percentage mark-up.

^b From OECD (2008) report (59).

Notes: (1) This table is based on the information available in the OECD (2008) report (59) and the *Prescription pricing and reimbursement information* (PPRI) (2008) report (60), and focuses on the pricing regimen used for public national health systems. However, it is not possible to capture the intricacies of the pricing strategies, which may differ between public reimbursement systems and private sales, method of price caps, etc. Country PPRI reports should be consulted for these details. (2) Some flat fees may be regressive in nature. Difference between a fixed fee and a dispensing fee at retail level not always clear (e.g. Germany, Norway). (3) “Unregulated” means there is no set mark-up; regulations may still exist as part of price regulation.

Source: Ball D. Working paper 3: *Regulation of mark-ups in the pharmaceutical supply chain – review series on pharmaceutical pricing policies and interventions*. Geneva, World Health Organization and Health Action International, 2011. (4)

9.6 **Annex E: Evidence summary 2: Tax exemptions/reductions for pharmaceutical products**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: There are two main categories of tax: direct tax, levied by governments on the income of individuals and corporations, and indirect taxes, added to the prices of goods and services and collected through the businesses that provide them. Direct taxes, along with social security taxes, generally make up about two-thirds of total government revenue in HICs. In LICs, indirect taxes, on international trade or on the purchase of goods and services, are the major sources of government revenue. Policies might involve the reduction of taxes on medicines, or the exemption of medicines from taxes, particularly sales taxes.

9.6.1 Overview of available evidence

Type of evidence

1. The WHO/HAI policy review (Creese, 2011) (5) on sales taxes on medicines; their impact on revenue generation and on medicine affordability; and their impact when reduced, abolished, or reintroduced. The policy review included two literature searches, one for papers on medicines and taxes, the second to investigate the relation between price changes and the use of medicines.
2. Two additional studies were identified: (i) an assessment of the impact of tariffs on pharmaceutical prices (Olcay and Laing, 2005) (61) that has some relevance to taxation and (ii) a European Commission study of duties and taxes on medicines for communicable diseases in 57 countries (62) (Table ES2.1).
3. An additional literature search retrieved no other evaluative studies or systematic reviews.

Quality of evidence

There is limited published evidence directly addressing the impact of reductions or exemptions for taxes in the management of pharmaceutical prices. There are some descriptive studies assessing the rate of taxation.

Outcomes

Direct information on the impact of reduction or exemptions for taxes and other government charges on pharmaceutical prices is not available for LMICs.

Results/conclusions

- Comparative evidence – LMICs; HICs – none available.
- Descriptive evidence – LMICs; HICs – see below.

9.6.2 Descriptive evidence: WHO/HAI policy review

Little material of direct relevance to medicines and taxes was found in the first literature review, with a PubMed search returning only 19 articles. Searches of other sources failed to identify additional material. Most of the articles retrieved concerned food, tobacco, alcohol, and related health problems. The searches concerning price changes and access to medicines returned 1475 articles. 356 were in free full text and 81 were review articles, with about half of the total being medicine or medical-condition specific studies, mostly from the UK and USA. The policy review also notes that individual country websites were useful sources of information, and that the publications and survey reports on the HAI web site provided the most information about tax on medicines in LMICs.

The WHO/HAI policy review discusses the principles of and current use of taxation, in particular the use of value-added tax (VAT). The following points are noted.

- Indirect taxes such as sales tax or VAT are regressive, which means they are inequitable, as the amount paid on a certain medicine is a percentage of its price and is the same for everyone, rich or poor. A medicine tax therefore consumes a larger share of a poor person's income than a rich person's.
- Since the early 1990s VAT has become a common revenue-raising strategy for LMICs. The review notes that VAT is tending to replace sales tax, since much of the responsibility for tax collection shifts from government to businesses. In addition, relatively high taxes can be charged with a lower risk of evasion than with sales tax.
- The review summarizes the situation in HICs. In Europe, VAT on medicines ranges from 0% to 25%. Many countries use a lower VAT rate on medicines than the standard VAT rate, while others exempt prescription medicines (Table ES2.2). In some HICs (e.g. Australia, Japan, the Republic of Korea) medicines are tax exempt, while in the USA the tax levied varies across the states.
- Taxation on medicine in LMICs is varied, ranging from 2.9% to 34%. Table ES2.3 provides a summary of taxes on medicines based on information from the WHO/HAI database and medicine price surveys.
- The policy review provides examples of the variation in tax rates and forms across LMICs and notes that in LMICs most private health spending is out-of-pocket as opposed to prepaid through some form of insurance.

The WHO/HAI policy review provides these literature-based examples of the impact of medicine taxes on access to care.

- Lower-income households rely more on over-the-counter (OTC) products than prescription medicines and some research has indicated patients shift to OTC medicines in the event of a price rise for prescription medicines.
- A systematic review of studies on increased prescription drug prices for patients in the USA (Goldman et al, 2007) (63) showed that a 10% increase in prices led to a 2–6% drop in medicine use as well as lower rates of treatment, poorer compliance, and more frequent discontinuation of treatment. Specifically, the price increases were associated with increased use of services for chronic conditions such as diabetes, congestive heart

failure, lipid disorders and schizophrenia. It was also noted that as co-payments rose, compliance fell, and chronically ill patients delayed starting treatment.

- An older study from the UK on the effects of increases in prescription charges from 1979 to 1982 showed a 7.5% fall in the per capita use of medicines in the population paying charges, while access to medicines in the charge-exempt group increased by 1% (Birch, 1986) (64).
- A 2008 review of 173 studies of the effect of prescription medicine charges in 15 HICs (Gemmill et al, 2008) (65) concluded that user charges are a regressive form of health-care finance, requiring the poor to pay more as a proportion of their income than the rich. Poorer people reduced their use of prescription drugs even when co-payment levels were very low.

The policy review states that evidence about the price of care and access is more fragmentary and of poorer quality. Most of the available evidence is concerned with user fees in general. The policy review also cites examples of the impact of the price of insecticide-treated bed nets in African countries and the impact of tariff and tax reductions on malaria. Two specific examples from Nigeria are reported. In one example, a reduction in tariffs from 42% to zero for insecticide and from 40% to 5% for netting materials may lead to an increase in bednet purchases of 9% to 27% (Simon et al, 2002) (66). In the second example, a 22% reduction in price led to an 11% increase in purchases (Simon et al, 2001) (67).

The policy review concludes that imposing or eliminating a 25% tax on prescribed medicines will reduce or increase demand, perhaps by 5–15% if elasticities are linear and similar to those in HICs. However, any fall in demand following a tax rise will be sharper among poorer households, for children, and for those with chronic illnesses. The policy review provides estimates of tax revenue from medicine sales in selected countries, with the tax on medicines ranging from 0.27% to 1.66% of total tax revenue. The review makes the point that while these proportions may seem small, the actual amounts can be substantial, depending on a country's gross domestic product (GDP).

The policy review provides arguments against taxing medicines, concluding that the taxation of medicines that restore and maintain peoples' health is a tax on economic potential, which is contrary to both economic development objectives and to public health goals. The review also states that public policy, including tax policy, should give priority to targeting the widespread 'diseconomies' of risky and unhealthy behaviour, rather than taxing medicines that directly promote health.

The policy review states commodities that promote public health objectives, such as access to essential medicines, should be supported by tax policies. In addition, use of commodities that damage human capital and public health objectives, such as tobacco and alcohol, should be discouraged by the tax system. The review suggests that in some circumstances the funds raised from taxes on unhealthy consumption patterns and behaviour can easily compensate for revenue lost through reduction or elimination of medicine taxes. The review cites the examples below.

- Total medicine sales in India in 2009 were US\$19 billion, with a VAT yield of just under \$1 billion. Doubling the tax on cigarettes would bring an additional \$3.1 billion in revenue to the Indian government, which would more than account for the \$1 billion lost if the VAT on medicines were to be waived. The policy review does not address the likelihood of such an increase in cigarette tax.
- Romania has been reported to be introducing a tax on food products that are high in fat, sugar, and salt, with an estimated revenue of \$1.3 billion annually. The policy review indicates this 'junk food' tax revenue would more than compensate the current 9% VAT on medicines, which brings in approximately \$200 million.

The review concludes that a simple principle would be that governments should tax the things that make people ill, not the things that make them well.

9.6.3 Descriptive evidence: Other literature

- Olcay and Laing (2005) (61) examined tariff rates levied and revenue generated in over 150 countries on pharmaceutical products. They found that pharmaceutical tariffs generate less than 0.1% of GDP in 92% of countries for which data was available and concluded that factors other than tariffs, such as manufacturer's prices, sales taxes including VAT, mark-ups, and other charges are likely to impact the price of medicines more than tariffs (Table ES2.1).
- In 2003, the European Commission published an assessment of the duties and taxes applied to pharmaceutical products used in the treatment of major communicable diseases (HIV, malaria, and tuberculosis) in 57 countries (62). The review found that rates of VAT vary from 0% to more than 20%. The average VAT rate is generally high (11–12%) compared with the European Union average (7%). Total duties and taxes (customs duty + VAT + other duties) applied to the products covered by the study varied from 0.01% in Malaysia to as high as 60% in India, with a global average of 18% (Table ES2.1).

9.6.4 Implementation requirements

Reduction or elimination of medicine taxes, perhaps countered by an increase in tax on unhealthy items.

9.6.5 Feasibility

The willingness of governments to decrease or eliminate taxes is unknown, and in many cases may not be probable.

9.6.6 Gaps, research needs, and comments

Quantitative assessment of reduction in taxes and its impact on medicine prices.

Table ES2.1: Summary of literature on tariffs and taxation

Review	Aim	Outcomes
Olcay & Laing (2005) (61)	Examination of tariff rates levied on pharmaceutical products and revenue generated by more than 150 countries. The study was undertaken as part of the Commission on Intellectual Property Rights, Innovation and Public Health's work on factors that determine access to medicines.	<ul style="list-style-type: none"> • 59% of countries for which data are available levy tariffs on pharmaceutical active ingredients and 61% levy tariffs on finished pharmaceutical products. • 90% of countries apply tariff rates of less than 10% on medicines. • Pharmaceutical tariffs generate less than 0.1% of gross domestic product in 92% of countries for which data are available. • The authors conclude that factors other than tariffs – such as manufacturer's prices, sales taxes including VAT, mark-ups, and other charges – are likely to have a greater impact on medicine process than tariffs. Nevertheless, tariffs remain a regressive form of taxation that targets the sick, and the authors state that pharmaceutical tariffs could be eliminated without adverse revenue or industrial policy impacts.
European Commission (2003) (62)	Assessment of the duties and taxes applied to pharmaceutical products used in the treatment of major communicable diseases (HIV, malaria, and tuberculosis) in 57 countries. ^a	<ul style="list-style-type: none"> • Customs duties vary significantly between 0 and 35% for compounds as well as for medicines and vaccines. The average customs duty rate levied on these products is 5–7% of the price of the imported products. • Customs duties represent one-third of the total taxes and duties applied to pharmaceutical products. The rates of “other duties” vary between 0 and 22% on compounds and between 0 and 15% on medicines and vaccines. • Rates of VAT vary between 0 to >20%. The average VAT rate is generally high (11–12%) compared with the European Union average of 7%. • Based on data from European Union exports, total duties and taxes (customs duty + VAT + other duties) applied to the products covered in the study vary from 0.01% in Malaysia to as high as 60% in India, with a global average of 18%. • Least Developed Countries have lower rates of duties and taxes, on average 14%, compared with the global average of 18%. • Applied total duties and taxes on compounds are generally higher than on manufactured medicines. • No systematic correlation can be drawn from the study between the value of imports (weighted per inhabitant) and the rates of customs duties and taxes. • Taxes and duties collected on these products represent 17% of the public health expenditure of Least Developed Countries and 9% on average for the countries covered by the study.

^a Included countries: Algeria, Angola, Bangladesh, Benin, Botswana, Brazil, Burkina Faso, Cameroon, Central African Republic, Chad, China, Côte d'Ivoire, Cuba, Dominican Republic, Egypt, El Salvador, Eritrea, Gabon, Georgia, Ghana, Guatemala, Haiti, Honduras, India, Indonesia, Iran, Jamaica, Kenya, Kyrgyzstan, Lesotho, Liberia, Malaysia, Mali, Mauritius, Mexico, Morocco, Namibia, Nicaragua, Niger, Nigeria, Pakistan, Philippines, Plurinational State of Bolivia, Republic of Moldova, Senegal, Sierra Leone, South Africa, Sri Lanka, Syrian Arab Republic, Thailand, Togo, Turkmenistan, Uganda, United Republic of Tanzania, Uzbekistan, Viet Nam, Yemen.

Table ES2.2: Medicine taxes in Europe in 2010

Country	Standard VAT %	Medicine VAT % (differential VAT for medicines)	Country	Standard VAT %	Medicine VAT % (differential VAT for medicines)
Norway	25	25	Finland	23	9
Sweden	25	25 (0 prescription- only medicines)	Slovenia	20	8.5
Denmark	25	25	Turkey	18	8
Ireland	21	21.5 (0 oral medicines)	Poland	22	7
Bulgaria	20	20	Belgium	21	6
Germany	19	19	Netherlands	19	6
UK	17.5	17.5 OTC products (0 NHS products)	Portugal	21	6
Greece	23	11	Lithuania	21	5 reimbursables (21 OTC products)
Latvia	21	10	Hungary	25	5
Italy	20	10	Spain	18	4
Austria	20	10	Luxembourg	15	3
Slovakia	19	10	Switzerland	7.6	2.4
Czech Republic	20	10	France	19.6	2.1 reimbursables (5.5 non- reimbursables)
Romania	24	9 prescription- only medicines (12 OTC products)	Malta	18	0
Estonia	20	9	Cyprus	15	0 (15 diagnostic agents)

OTC = over-the-counter, NHS = National Health Service.

Source: Creese A. *Working paper 5: Sales taxes on medicines – review series on pharmaceutical pricing policies and interventions.* Geneva, World Health Organization and Health Action International, 2011. (68)

Table ES2.3: Domestic tax rates on medicines in selected low- and middle-income countries

Country and survey year	VAT or sales tax	Other taxes on medicines	Total domestic tax
Armenia, 2001 ^a	20%		20%
Plurinational State of Bolivia, 2008	13%		13%
Brazil, 2001 ^a	18%	6% state tax	24%
Chad 2004		2% statistical tax (public & private sectors), 0.9% purchase verification tax (private sector)	2.9%
China, 2004 & 2006	17%	3% regional sales tax	20%
Congo, 2007	18% (unclear whether medicines exempt)	1% community tax	19%
Democratic Republic of the Congo, 2007	0%	17% turnover + other taxes	17%
El Salvador, 2006	13%		13%
Ghana, 2004	15% + national health insurance levy		15%
India, 2003 & 2004	Was 6.5–9.8% sales tax, currently 5% VAT on most medicines	5–16% state excise duty 3% national education “cess”	13–24%
Indonesia, 2004	10%		10%
Jordan, 2007	4% sales tax		4%
Kyrgyzstan, 2005	4% sales tax		4%
Mali, 2004		8% taxes and fees	8%
Mongolia, 2004	15%	6% stamp duty and other fees	21%
Morocco, 2004	7% (some exemptions)		7%
Nigeria, 2004		“Multiple tax regimes” >30% other fees	30%
Peru, 2005	12% (some exceptions)	19% goods & services tax + 2% local tax, some exemptions	34%
Philippines, 2008	12%		12%
South Africa, 2004	14%		14%
Tajikistan, 2005	20%	1–5% sales tax	21–25%
Tunisia, 2004	6% (locally made)		6%
Yemen, 2006	5%		5%
All 23 countries			Approximate average = 14.8% Range = 2.9–34%

^a Data from Levison L, Laing R. The hidden costs of essential medicines. *Essential Drugs Monitor*. 2003, (33):20–21. (69)

Source: Creese A. *Working paper 5: Sales taxes on medicines – review series on pharmaceutical pricing policies and interventions*. Geneva, World Health Organization and Health Action International, 2011. (68)

9.7 **Annex G: Evidence summary 3 – Application of cost-plus pricing formulae for pharmaceutical products**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: Cost-plus pricing is a method for setting retail prices of medicines by taking into account production cost of a medicine together with allowances for promotional expenses, manufacturer's profit margins, and charges and profit margins in the supply chain.

9.7.1 Overview of evidence available

Type of evidence

1. The unpublished WHO/HAI policy review (Saif 2011) (6), which provides a description of cost-plus pricing, a review of available evidence, results of case studies of countries using cost-plus pricing, and a discussion of the issues surrounding use.
2. An additional literature search retrieved no evaluative studies or systematic reviews.

Quality of evidence

The policy review indicates that there is no literature available assessing cost-plus pricing. The reviewer undertook sent a questionnaire to contact persons in 10 of 13 countries identified as using cost-plus pricing methods but it is unclear which 10 countries were included. Only three countries returned a completed response. The sample may not therefore be representative but are the only data available. The review indicates that the country case studies were drafted from the completed questionnaires, published articles, and information available on the web sites of regulators, while the impact of cost-plus pricing was analysed by assessing the results of pricing surveys conducted by HAI/WHO and/or any other published report or authentic data.

Outcomes

The impact of cost-plus formulae on medicine prices are provided for three countries included in the WHO/HAI policy review survey, however the data are not current (based on report dated from 2002 to 2007). The majority of evidence available provides a descriptive summary of characteristics of cost-plus formulae systems.

Results/conclusions

- Comparative evidence – LMICs; HICs – none available.
- Descriptive evidence – LMICs; HICs – see below.

9.7.2 Descriptive evidence: WHO/HAI policy review – case studies

The WHO/HAI policy review undertook a search for literature on cost-plus pricing on the Internet, in published country reports, material available from HAI, the WHO and the Ministry of Health in Pakistan. The review reports that no global studies on cost-plus pricing could be found. However, the review does not provide any further details of the search conducted or indicate if any other relevant literature is available, even though it states that published literature is used.

The authors of the review drafted a questionnaire to identify which countries were using, or had used, the cost-plus pricing method. The questionnaire was sent to survey managers of HAI/WHO project on medicine prices as well as contact persons in health ministries of the WHO EMRO region and regional advisers in WHO regional offices for Europe and the Western Pacific. 67 individuals in 46 countries were sent the questionnaire and 26 (39%) responded. Information obtained from the questionnaire indicated that 12 countries used the cost-plus pricing method, and one country (Colombia) was identified as having used cost-plus pricing but had discontinued. Another country using cost-plus pricing was identified at time of writing the policy review, making 13 countries in total.

The policy review provides country profiles of three countries that returned questionnaires – Bangladesh, India, and the Islamic Republic of Iran as well as Pakistan (based on policy review authors' input) and China (based on published papers and the National Development and Reforms Commission of China web site). The country profiles are summarized below.

Bangladesh

- Under the Drugs Control Ordinance 1982, a cost-plus pricing mechanism was adopted to ensure access to essential medicines. The policy identified 150 medicines, which were subsequently reduced to 117. The review states that cost-plus pricing is applicable on generic molecules, whether locally manufactured or imported.
- Prices are determined by an expert committee using the formulae below.

Local manufactured retail price = (RM+PM) × factor (mark-up)

Imported medicines retail price = C+F × exchange rate × factor (mark-up)

The review does not define the letters used in these equations; however, RM may mean raw materials and PM packaging materials.

- The impact of the use of cost-plus methods on access to essential medicines is described based on a report that cites 2002 data and indicates an increase in share of essential medicines on the pharmaceutical list. However the report also indicates that inadequate implementation of the policy over the years has diluted its effect.
- There is no information of a more recent nature provided assessing the impact of cost-plus methods in Bangladesh.

China

- Maximum retail prices are set by the National Development and Reform Commission.
- Prices are set on the basis of declared costs submitted by manufacturers and are calculated as factory prices with duty/taxes and retail distribution profits incorporated. The prices submitted by manufacturers are not checked for accuracy.
- In terms of impact of the use of cost-plus methodology in China, the review notes the following points.
 - Availability of medicines is low.
 - Public sector patient prices are 21–75% higher than public sector procurement prices.
 - Public sector medicines are more expensive and mark-ups higher than those in the private sector.

- Prices are 5.6–8.8 times greater than international reference prices for originator brands and 1.2–2.0 times greater for generic medicines.
- Prices of originator brands are 2.5–14 times greater than prices of generics.

India

- A Drugs (Price Control) Order in 1979 specified 342 medicines under price control. The number of medicines was reduced to 74 in 1995. The review does not indicate the current number of medicines under price control in India.
- Price of bulk drugs is fixed by specifying a maximum rate of return to bulk drug manufacturers. The maximum retail prices are fixed using cost-plus methods and are determined by use of data submitted by companies and by comparing elements of cost of each company. The formula used is:

$$RP = (MC + CC + PM + RC) \times (1 + MAPE/100) + ED$$

[RP = retail price; MC = material cost; CC = conversion cost; PM = cost of packing material; PC = packing charges; MAPE = maximum allowable post-manufacturing expenses; ED=excise duty].

- The policy review indicates that between 1996 and 2006 the rise in prices of all medicines was 39.93% and for price-controlled medicines was 0.02%.
- The prices of medicines in the private sector are 3 to 5 times the procurement prices in the public sector.

Islamic Republic of Iran

- Retail, ex-factory, and wholesale prices are set using the cost-plus method.
- This method is applied to all domestically produced medicines, about 1030 items. For imported medicines, a combination of reference pricing and negotiation is used.
- The distributor price is set at ex-factory price $\times 1.12$ and the user price is set at distributor price $\times 1.21$.
- A 2007 survey using WHO/HAI medicine prices survey methodology reported efficient public sector procurement, with generic prices similar to international reference prices. For a few medicines, the government buys higher-priced originator brands as well as lower-priced generics. In the public sector, patients pay government procurement prices without additional charges or mark-ups. Few originator brands are marketed but they are on average 3 to 7 times the price of generic equivalents, depending on sector.

Pakistan

- The Ministry of Health is responsible for implementing the cost-plus pricing policy. The Ministry of Health fixes maximum retail prices for private sector pharmacies and manufacturers/importers can sell the drugs up to the fixed price. The cost components included in the prices are raw materials, packaging materials, labour costs, and taxes and tariffs on materials. Distribution, wholesale, and retail mark-ups are included as supply chain components when setting the retail price.
- For non-sterile products, the manufacturer's retail price is prime cost + 75% mark-up, while sterile products are priced at prime cost + 90% mark-up.

In 1994, the government introduced a formula for the annual price increase for controlled drugs:

$$(DI \times CPI) + (MI \times ER)$$

[DI = domestic inputs of industrial costs; MI = imported inputs in total industrial costs; CPI = consumer price index; and ER = exchange rate of Pakistan rupee to USA dollar].

- Prices of all drugs with a few exceptions were frozen until 2007. In 2008, the pharmaceutical industry demanded price increases using the 1994 formula. While the Ministry of Health did not agree with the demand, it advised companies to submit justifications for price increases.
- Cost-plus pricing is not the only method used by the Price Advisory Committee in Pakistan – for the pricing of new chemical entities, the reference prices of the innovative brand in South Asian Association for Regional Cooperation (SAARC) countries are considered. If reference prices are not available, the price is negotiated with companies in pricing committee meetings. Cost-benefit analyses are also considered in these meetings.
- An HAI survey in 2004 found that prices of medicines in private pharmacies in Pakistan are generally lower than other developing countries, but higher than in India; certain medicines are unaffordable to the poor; public procurement of medicines is efficient in acquiring low-priced medicines but inadequate in supplying government health facilities with the quantities needed.
- The average increase in the prices of medicines from 2000–01 to 2008–09 was 7.7%.

9.7.3 Implementation requirements

The following requirements were identified for implementing cost-plus methods.

- Legislation mandating price setting
- Information system for collecting the costs of price components (e.g. active pharmaceutical ingredient [API] prices)
- Capacity to verify information supplied by manufacturers
- Price monitoring system
- Well-defined methodology, including pricing formulae and guidelines on how to ascertain prices of APIs, excipients, packaging material, wastages and cost of conversion and profits and mark-ups in the supply chain.
- Expertise in cost accounting, manufacturing practices, market analysis, pharmacy, and economics.
- Sufficient personnel for enforcement (e.g. field inspectors).

9.7.4 Feasibility

There is a lack of evidence supporting the use of cost-plus formulae. Obtaining accurate information on material prices and cost data in order to implement cost-plus pricing is difficult. The manipulation of costing data by the manufacturers may result in higher prices.

9.7.5 Gaps, research needs, and comments

There is a lack of comparative, analytical evidence assessing the use and impact of cost-plus formulae methodology. There is a need for a more rigorous assessment of cost-plus formulae using current data and including consideration of the impact on drug prices and other key outcomes.

9.8 **Annex H: Evidence summary 4 – Use of external reference pricing**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: External reference pricing (ERP; also known as international reference pricing) refers to the practice of using the price of a pharmaceutical product (generally ex-manufacturer price, or other common point within the distribution chain) in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. Reference may be made to single-source or multisource supply products.

9.8.1 Overview of evidence available

Type of evidence

1. WHO/HAI policy review (Espin et al, 2011) (7), which provides an overview of external reference pricing and results of a literature search seeking papers describing the use of ERP. Given the relative lack of literature, a survey was undertaken in a sample of countries to obtain an understanding of how ERP is applied in a variety of (mainly low- and middle-income) settings.
2. An additional literature search retrieved no other evaluative studies or systematic reviews. Table ES4.1 provides details of two articles that were included in the policy review (Richter, 2008 (70); Stargardt and Schreyogg, 2006 (71)), a recently published mathematical model (Marinosa et al, 2011 (72)), and a description of price control strategies in Norway (Håkonsen et al, 2009 (73)).

Quality of evidence

The WHO/HAI policy review notes that the available literature is limited and is largely comprised of review or opinion articles, with no comparative analyses available. Of the available literature, most focuses on developed countries, with little information available from LMICs. The survey conducted by the policy review authors received responses from nine countries (69%) and was descriptive in nature.

Outcomes

The impact of ERP on medicine prices and other rated outcomes is not provided in the identified evidence.

Results/conclusions

Comparative evidence – LMICs; HICs – none available.
Descriptive evidence – LMICs; HICs – see below.

9.8.2 Descriptive evidence: WHO/HAI policy review – literature review

The policy review states that assessing the impact of ERP is difficult, given that controlled experimental designs are not feasible and comparisons across countries based on observational studies are problematic because of the differences in ERP systems. In addition, it is difficult to separate the effects of ERP from other policies that are applied simultaneously within countries.

The policy review conducted a literature search looking for articles addressing the consequences, impact, scope, and limitations of using ERP as a criterion to set medicine prices. Twenty-one relevant articles were identified in the search, the majority focusing on OECD countries, with little information available from LMICs. Of the 21 articles, the majority were review or opinion articles (13; 61.9%), while four (19.04%) used a theoretical model, three (14.28%) used databases, and one (4.76%) applied a questionnaire across different countries. Findings from the literature are listed below.

- European countries tend to select as reference countries those that share economic similarities or geographical proximity, however many differences were found between countries regarding the methodology used.
- Japan uses a formula to adjust prices upwards or downwards and as a consequence prices can vary between 150% or 75% below the reference countries' prices. Mexico uses a weighted average of ex-factory prices with respect to the previous quarter in six countries with bigger sales. A formula is used to determine the price for sales to the public ($ERP \times 1.72$). In Slovakia, pharmaceutical companies must provide information about the price of a medicine in the country of origin plus eight European countries before market introduction. In Estonia, ERP is used for reimbursed originator and generic medicines using the manufacturer price level. The ERP explicitly examines the prices of Latvia, Lithuania, and Hungary and may include all EU Member States.
- The review notes that the literature indicates that countries with lower prices or lower market volume had fewer medicines available and had longer delays in medicine launches.
- The alleged negative effects of ERP include higher prices in LICs and delays in launching of new medicines in countries with low-priced medicines.

9.8.3 Descriptive evidence: WHO/HAI policy review – country survey

A survey of countries using ERP was conducted in 2009. 14 countries received the survey, including Brazil, Colombia, Czech Republic, Hungary, Indonesia, the Islamic Republic of Iran, Italy, Jordan, Lebanon, Mexico, Oman, South Africa, the United Arab Emirates, and Yemen. The survey included 27 questions, with an additional four questions for Italy as an example of a country that had stopped using ERP.

- Nine (69%) surveys were returned.
- Countries stated that they combine between two and five criteria to set prices. The second most used method is the cost of existing treatment for the same condition or disease within the same country.
- The average number of countries used as a reference was 7.75 (range 4–8 countries).

- The most frequent justifications for selection of countries were: country in the same region (55.5%); products usually have market authorization when the price information is searched (33.3%); and availability of price information (22.2%).
- The most commonly used criterion for arriving at the reference price was the minimum price of the set of reference countries (six countries) followed by average price (two countries).
- The price used as reference is usually the ex-factory or manufacturer's selling price.
- Most of the countries surveyed use ERP for all products.
- The countries used as reference are usually selected from within the region and with similar income levels.

9.8.4 Descriptive evidence: WHO/HAI policy review – additional notes

The policy review also makes the following observations.

- 24 of 30 OECD countries and approximately 20 of the 27 EU countries use ERP.
- Developed countries usually restrict the use of ERP to on-patent medicines. Developing countries included in the survey apply ERP to both on-patent and off-patent medicines.
- Some countries use ERP as the single criterion to determine prices, while other countries use ERP as just one in a battery of approaches.
- While some countries claim ERP has had positive effects in reducing the prices of medicines there is no evidence from monitoring reports or rigorous analytical studies to support such claims.
- ERP or any other policy option cannot be assessed meaningfully in isolation – it needs to be considered as one of a variety of pricing tools that can be used.
- ERP is a relatively simple method for countries to use because it does not require large amounts of information or an extensive technical/analytical capability.
- One of the shortcomings of ERP is the lack of a clear rationale or theoretical foundation.
- The underlying assumption justifying the use of ERP is that the prices in the reference countries are somehow right, appropriate, or fair. ERP then tries to ensure that the country does not pay more than other countries or that it pays less.
- It is difficult to assess whether prices resulting from ERP will be appropriate, efficient, or optimal in accordance with any objective criterion.

The policy review identifies potential indirect effects of ERP, including the design and implementation of international pricing and marketing strategies by the pharmaceutical industry to counteract the effects of ERP and maximize global profits.

The review identifies the following advantages and disadvantages of ERP.

- ERP is a relatively simple and easy-to-apply system compared, for example, with economic evaluation. Its implementation is feasible when resources are relatively limited and it provides quick information to regulators and other policy-makers. This might justify its use by small countries with limited capacity to implement alternative pricing mechanisms.

- A main limitation is that price information is not always available, and the available prices are often heterogeneous and it can be difficult to make the adjustments to obtain the required type of price.
- Transaction prices are difficult to obtain; the prices to which countries have access are often not real but virtual list/catalogue prices.
- Although there is no conclusive evidence about the impact of ERP, launch delays and the non-availability of new medicines in low-price countries may be a likely effect. Price convergence, resulting from higher prices in lower-income countries, and decreasing price transparency are possible additional negative effects.

The policy review provides a checklist of the issues and options to be considered when designing an ERP system. These include: single or multiple approaches to setting the regulated price; types of products regulated by ERP; criteria for deciding the number of countries and for selecting the specific countries used as reference countries; sources of price information; types of price used for setting the national target price; formula or procedure to derive the national target price from the prices in reference countries; exchange rate; procedure to follow if international prices are not available at the time they are needed; updating/revisions of the target national price based on ERP; enforcement; and monitoring and evaluation.

9.8.5 Implementation requirements

- Criteria and process for selection of reference countries, including determination of the number and specific set of countries to be used as references, as well as adequacy of their medicine regulatory system.
- Access to prices from reference countries and date of the available price, e.g. current price versus price at launch.
- Determination of what type of reference will be used (e.g. minimum price of set of reference countries, average price of reference countries).
- Procedures for when the relevant price data are not available, and use of adjustments to account for confidential discounts or rebates in list prices or for differences in income levels.
- Adequate staff to compile and analyse data, sufficient personnel for enforcement (e.g. field inspectors).
- Procedures for how ERP feeds into the decision-making process, perhaps supported by legislation.

9.8.6 Feasibility

Applicability to LMICs is unknown given a lack of evidence. Although ERP is used in developed countries, there is little analytical, comparative evidence to support claims that it reduces medicine prices. However, it is an option in situations where there is limited capacity to implement other pricing strategies.

9.8.7 Gaps, research needs, and comments

There is a lack of comparative, analytical evidence assessing the use and impact of ERP, particularly in LMICs. More rigorous assessments of ERP are needed, including the impact on drug prices and other outcomes, such as product launches.

Table ES4.1: Summary of literature relevant to external reference pricing

Article	Aim	Outcomes
Håkonsen et al (2009) (73)	Description and assessment of price control strategies used in Norway from 1994 to 2004.	<ul style="list-style-type: none"> • International reference pricing (or ERP) based on prices in 9 European countries was introduced in 2000 as the main method for price setting of patented and off-patent drugs. • Price revisions of new drugs occurred every 6 months for the first two years after initial marketing. • Authors claim that consistent use of ERP and subsequent price revisions led to substantial price reductions on many drugs. However, the amount of the price reductions is not provided.
Mariño et al (2011) (72)	Use of a mathematical model to assess the influence of ERP on reference countries and pharmaceutical companies.	<ul style="list-style-type: none"> • Use of a model where a pharmaceutical firm sells a drug in two countries, a home country and a foreign country. Each country can either negotiate a price directly with the firm or engage in ERP. If no country engages in ERP, then each country negotiates prices independently. • Three scenarios are used to analyse how the commitment by a country to engage in ERP affects the negotiations in the reference country and ultimately determines the firm’s total profit. The paper assumes that in Europe price-negotiating agencies have a minor role in the authorization of drugs, and therefore countries in Europe are in a ‘weak threats’ scenario. In contrast, in countries such as Canada or Brazil where agencies can threaten to ban the drug when negotiations fail a ‘tough threats’ scenario exists. The first scenario suggested by Mariño focuses on the weak threats scenario and ignores the existence of possible therapeutic substitutes. This scenario represents a first step to understand the effects driven by ERP only. The second scenario extends the first to account for competition between the firm’s pharmaceutical product and a therapeutic substitute that is already in the market in both countries. The third scenario maintains the initial monopoly setting but allows for tough threats by the agencies. • The main results are as follows. <ul style="list-style-type: none"> ◦ Under weak threats and no therapeutic competition, an ERP policy by the home country increases the negotiated foreign price, which harms the foreign country. Despite this price increase, the home country prefers ERP to an independent price negotiation if the consumer co-payment in the home country is relatively high. However, this preference diminishes as the demand size grows in the home country relative to the foreign country, although this preference does not disappear. When compared with the profits resulting from independent price negotiation, an ERP policy brings an increase in the profits derived from the foreign country and a decrease in those derived from the home country. The second effect is strong enough such that overall profits decrease. ◦ The above results are confirmed for the case of therapeutic competition between drugs, except for the size effect that is absent because, for simplicity, the asymmetry in country size is ignored.

Article	Aim	Outcomes
		<ul style="list-style-type: none"> ○ In for the tough threats scenario, the home country benefits while ERP harms the firm, as in the weak threats scenario. However, in contrast to the weak threats scenario, the negotiated price in the foreign country is unaffected by ERP, such that ERP does not affect the foreign country. • The authors conclude that their analysis offers insights on the direction of the effects of an ERP policy, with the fact that a reference country can be harmed one of the key outcomes of their model. They indicate that this type of policy externality suggests pharmaceutical pricing policies should be internationally coordinated.
<p>Richter (2008) (70)</p>	<p>Use of a theoretical mixed integer linear model to examine the issue of ERP and product launch decisions from a pharmaceutical firm’s perspective, with discussion of how results might be useful to individual countries in their price and reimbursement negotiations.</p>	<ul style="list-style-type: none"> • A theoretical model was designed to examine the launch of an innovative, first-in-class medication for outpatient use in a collection of countries implementing a variety of ERP regulations. Characteristics of the model are summarized below. <ul style="list-style-type: none"> ○ A pharmaceutical company wishes to maximize total revenue and return on investment for a new medicine across all countries in which it has been launched. As ERP introduces limits on what price can be charged in each country these are included in the model as a series of pricing constraints. ○ Parallel trade (which causes a loss of income in the country into which the goods are brought since the demand is satisfied by a lower-priced product from another country) is considered as a loss of revenue and is included in the model as a penalty. ○ Four basic types of ERP are considered. In type 1, the price of a product in country i must be a given percentage lower than the price of the product in a set of reference countries. In type 2, the price of a product in country i must be less than or equal to the average price in a set of reference countries. In type 3, the price of a product in country i must be the lowest price of the product in a set of reference countries. In type 4, the ratio of the price of the product and its closest competitor(s) in country i must be less than or equal to the ratio of the price of the product and its closest competition in the reference countries in which the product is sold. ○ Prices must be positive and may only decrease over time. ○ The quantity of the product demanded is fixed at the expected market share of the product. ○ The model can be used to determine all possible combinations of launch sequence and price to determine the optimal solution. • The paper does not provide results of the model; it is simply a ‘theoretical’ model. The author states that the model provides a structured analysis of the global strategic pricing problem faced by pharmaceutical companies at a macro level, and takes into account interdependencies that arise during pricing decisions due to ERP and parallel trade. The author claims the model can help countries understand the implications of their individual external pricing policies on the global repeated pricing game. The author also claims

Article	Aim	Outcomes
		<p>that understanding how a pharmaceutical company is likely to act will help countries better prepare to counter potentially unwanted actions.</p> <ul style="list-style-type: none"> • Real-world examples of the use of ERP in British Columbia, Canada; New Zealand; and Germany and other European countries are provided.
Stargardt & Schreyogg (2006) (71)	<p>(1) Summary of ERP in European countries.</p> <p>(2) Assessment of the impact of pharmaceutical price changes in Germany on prices in other countries using ERP, considering both direct impact (from referencing to Germany directly) and indirect impact (from referencing to other countries that conduct their own ERP schemes).</p>	<ul style="list-style-type: none"> • Assumptions used when calculating price changes were: the referenced drug in the sensitivity analysis is marketed in Germany; a reduction in maximum reimbursement prices due to ERP leads to similar price cuts in selling prices; the manufacturer has to bear the full cost of a price reduction; and updating of all ERP schemes will occur immediately. • A price reduction of €1.00 in Germany will reduce maximum reimbursement prices from €0.15 in Austria to €0.36 in Italy. • The authors note that they assumed that prices are updated simultaneously in all countries once per year. In addition, parallel trade between European countries will create spill-over effects of price changes, and the effects of ERP and parallel trade cannot be separated. • The inclusion of countries that use ERP increases the weight of non-referencing countries. This may lead to strategic manufacturer behaviour that affects price and availability of drugs in some markets. Countries with small market volumes, especially with lower price levels, may have to agree to higher price levels than originally intended by national market regulation and, in some cases, a launch delay. • The authors suggest that to avoid the negative effects of ERP a weighted index of prices from as many countries as possible should be used to determine reimbursement prices thereby reducing the direct and indirect impact of individual countries.

ERP = external reference pricing, HTA = health technology assessment.

9.9 **Annex I: Evidence summary 5 – Promotion of the use of generic medicines**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: Generic medicines are produced and distributed without patent protection. Promotion of the use of quality assured generic medicines is a method of managing pharmaceutical prices. The various approaches used include facilitated market entry of generics, generic substitution by dispensers, ERP, strategies to foster competition in the market, and schemes to encourage use of generics among providers and consumers.

9.9.1 Overview of available evidence

Type of evidence

1. The WHO/HAI policy review (Kaplan et al, 2011) (8), which was at the working-draft stage when this evidence summary was prepared. A version of the policy review, with additional information derived from a repeated literature search in January 2012, was published in August 2012.

The WHO/HAI policy review stated that it sought to:

- Provide a brief introduction to policies that can be used to address enhancing uptake of generic medicines in the pharmaceutical sector.
 - Review existing literature on generic medicines policies with an emphasis on LMICs, particularly as it relates to research on interventions and outcomes designed to assess the impact of such policies.
 - Create a synthesized set of conclusions about what might be the core/necessary and jointly sufficient elements of generics policies for LMICs, plus useful complementary policies.
2. An additional literature search retrieved seven publications, some of which were included in the WHO/HAI policy review. Each of these publications is described in more detail in Table ES5.2.

Quality of evidence

There is considerable literature on generic medicines and strategies associated with their use, however much of the literature is descriptive and focused on HICs.

Outcomes

Evidence demonstrating the impact of the use of generic medicines as an indirect method for managing pharmaceutical prices is available for some aspects of generic medicine use, however direct links between generic policies and price outcomes is limited, particularly for LMICs.

Results/conclusions

- Comparative evidence – LMICs; HICs – none available.
- Descriptive evidence – LMICs; HICs – see below.

9.9.2 Descriptive evidence: WHO/HAI policy review

Literature published in English, French, Spanish, and Portuguese between 2000 and March 2010 was searched to identify policy options to promote the use of generic medicines in LMICs. HICs were not excluded because it was assumed there would be limited literature on LMICs. To identify ‘interventional studies’ assessing the effect of implementation of policies promoting the uptake of generics, the following inclusion criteria were used.

- Study objective – to study the impact of a policy or a set of policies to promote the use of generic medicines. All policies in the following policy domains were considered: competition, consumer education, dispensing, marketing authorization and labelling, prescribing, price regulations, reimbursement, trade-related/intellectual property.
- Study design – Interrupted time series analysis, and/or repeated measures studies, and/or controlled or uncontrolled before-and-after studies.
- Study sites – LMICs (World Bank classification or, if not included in the database as search term, the International Monetary Fund 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.

The policy review states that the majority of publications discussing the policy options were based on descriptive research, particularly for LMICs. The policy review provides a summary of policy options for supply-side policies and demand-side policies, for both HICs and LMICs. The policy options described by the review are summarized in Annex Box ES5.1 and evidence available for these options is provided in Table ES5.1.

Annex Box ES5.1 Supply-side and demand-side policy options to promote uptake of generics

A: Supply-side policy options to promote uptake of generics via market authorization and regulation requirements	
Policy objective	Policy
Reducing time of market authorization:	<ul style="list-style-type: none"> • shortening application review time • Bolar-type provision^a
Encouraging generic manufacturers to apply for market authorization:	<ul style="list-style-type: none"> • reducing registration fees • exclusivity period to first on market
Reducing information asymmetry:	<ul style="list-style-type: none"> • labelling of generic medicines
Ensure quality and safety:	<ul style="list-style-type: none"> • monitoring of good manufacturing practice (GMP) • publication of inspection reports • post-market surveys • sanctions for false quality claims • surveys of health providers, drug sellers, and consumers • therapeutic equivalence
<p>Evidence: The available evidence (Sub-table ES5.1A) is based largely on surveys and is limited for LMICs. The policy review does not describe the type of study or quality of evidence on reducing time to market authorization and ensuring quality for LMICs. Of the sources cited, one study was a survey; other types could not be determined.</p> <p>^a In Bolar-type provisions, countries permit the manufacturers of generic pharmaceuticals to use the technology of a patented pharmaceutical to perform work that would assist in the marketing or regulatory approval of the generic product, while the patent is in force. This then allows the generic producer to market and manufacture their goods as soon as the patent expires.</p>	
B: Supply-side policy options to promote uptake of generics via trade and intellectual property policies	
Policy objective	Policy
Protection against undue monopoly created by use of patent:	<ul style="list-style-type: none"> • pre-grant opposition • definition of patentable products
Protection against undue bar to entry of generic medicines to market:	<ul style="list-style-type: none"> • transparency of patient information
Measure to ensure medicines supply for public if patented product not accessible:	<ul style="list-style-type: none"> • compulsory licensing • voluntary licensing • Bolar provision • parallel importation
<p>Evidence: The available evidence (Sub-table ES5.1B) does not directly address the TRIPS-related policy options identified.</p>	

C: Supply-side policy options to promote uptake of generics via generic price competition policy

Policy objective

Increase competition of generic products on the market

Policy

- joint manufacturing
- increase number of manufacturers
- ‘me-too’ products as a strategy to increase competition
- limiting number of products on market
- pooled procurement
- price information
- competition between wholesalers and retail pharmacies
- collectively managing intellectual property: patent pools

Evidence: Limited evidence is provided assessing the impact of generic price competition, since this topic was covered by another review paper. One study assessing the price of antiretroviral medicines found that pooled procurement resulted in lower prices for generics compared to branded products, although impact on overall prices was not clear (Sub-table ES5.1C).

D: Supply-side policy options to promote uptake of generics via pricing and purchasing policies

Policy objective

Direct price control:

Policy

- external reference pricing (ERP)
- internal reference pricing (IRP)
- originator price control
- setting generic medicines prices relative to originator products

Regulate profits:

- cost-plus pricing
- regulating mark-ups

Indirect price controls:

- government subsidies

Decrease information asymmetries:

- publication of generic medicine prices

Optimize public purchasing:

- open tender
- restricted tender

Evidence: Little evidence regarding purchasing and pricing policies is provided, possibly owing to a lack of evidence in this area. There is some evidence indicating that internal reference pricing in HICs has a positive impact on the prices of generic medicines, but the long-term impact of this strategy, and its relevance to LMICs, has not been demonstrated (Sub-table ES5.1D).

E: Supply-side policy options to promote uptake of generics via reimbursement policies

Policy objective

Cost-saving for payers while ensuring medicine access:

Policy

- positive reimbursement list
- co-payments

Evidence: The policy review states that there is little direct evidence that policies on reimbursement of generic medicines will increase the number of competitors and assist in lowering prices and or assist in increasing market penetration of generics (Sub-table ES5.1E).

F: Demand-side policy options to promote uptake of generics via prescribing policies	
<p>Policy objective Promote the prescribing of generic medicines among physicians:</p> <p>Decrease information asymmetry:</p>	<p>Policy</p> <ul style="list-style-type: none"> • regulations to mandate prescribing medicines by INN • requesting extra note on prescription if only originator product can be dispensed • training of prescribers and other health providers using INN only • financial incentives <p>• campaign directed towards prescribers regarding generic medicines and quality</p>
<p>Evidence: There is little evidence for the impact of prescribing policies in LMICs (Sub-table ES5.1F). In HICs there is some evidence that prescribing policies have increased use of generics, but the evidence is limited.</p>	
G: Demand-side policy options to promote uptake of generics via dispensing policies	
<p>Policy objective Increase dispensing or selling of generic Medicines:</p> <p>Decrease information asymmetry:</p>	<p>Policy</p> <ul style="list-style-type: none"> • substitution • reimbursement of pharmacies • manipulating mark-ups, margins and/or dispensing fees • financial incentives <p>• educational campaigns</p>
<p>Evidence: The available evidence, in both LMICs and HICs, addresses generic substitution. There is some indication that generic substitution has increased use of generic medicines. Evidence relative to policies affecting consumers and patients is based on small studies and is dated, i.e. more than 10 years old. It is therefore difficult to draw firm conclusions on the impact of policies on consumers/patients (Sub-table ES5.1G and Sub-table ES5.1H).</p>	

9.9.3 Descriptive evidence: Other literature

Several reviews assessing generic medicine policies are summarized in Table ES5.2. These studies focused on developed countries, however the results should be considered with regard to LMICs.

9.9.4 Implementation requirements

The policy review lists a number of implementation barriers to generic medicines in Europe, commenting that these may provide a starting-point to consider which barriers apply to LMICs. Currently, there is inadequate research to determine their importance in LMICs. Table ES5.3 provides a summary of the implementation barriers identified in the policy review. Below are listed key implementation requirements.

- Mechanisms sufficient to provide certainty that the generic medicines are of assured quality.
- Functioning and transparent medicines regulatory agency.
- Systems that facilitate market entry of generics (e.g. Bolar-type provisions, abbreviated registration processes, and fee reductions/exemptions).
- Consideration of demand-side policies.

- Mandatory substitution of originators by generics, with adequate training for prescribers and pharmacy personnel.
- Regulate discounts, but with caution. Discounts should be arranged such that pharmacies and medicine sellers are encouraged to dispense the least expensive originators and generic products, but quality must be assured.
- Regulate profit margins with caution.
- Develop a cost-sharing system that favours generics.
- Publish information on medicine quality, e.g. post-marketing surveillance data.

9.9.5 Feasibility

The policy review suggests that before any LMIC can effectively implement and enforce any of the pro-generic medicines policies, three ‘enabling conditions’ must met. These conditions are: assured quality of medicines; systems for facilitated market entry; and alignment of incentives for users and consumers of generics. Once these conditions are in place, the policies discussed in the review could be implemented in a provisional manner. Monitoring and evaluation for long-term use would be essential.

9.9.6 Gaps, research needs, and comments

Quantitative assessment of the impact of policy changes on the uptake, availability, and prices of generic medicines. This would benefit from an assessment of data prior to and following a change in policy using an experimental or quasi-experimental design. The policy review suggests that the policies identified should be implemented in a provisional manner with a clear monitoring and evaluation system in place. If analysis of the data indicates that the policy has not provided the intended results, then it should be reviewed and amended, if appropriate.

Table ES5.1: Evidence summary for supply-side and demand-side policy options to promote uptake of generic medicines

Sub-table ES5.1A: Supply-side policy options to promote uptake of generics via market authorization and regulation requirements

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Reduce time to market:</p> <ul style="list-style-type: none"> • shortening review time • Bolar provision 	<p>Short market approval times In Brazil, generic registration takes 6–8 months compared with 8–14 months for originators. In Colombia, approvals are 3 months for generics and 6 months for originators. Argentina, the Bolivarian Republic of Venezuela, Brazil, and Chile have lower registration fees for generics (74)</p> <p>Bolar provision In Mexico, generic producers can ask for registration of generics for products under patent 3 years prior to patent expiration.</p>	<p>Short market approval times In the USA, a manufacturer can submit an Abbreviated New Drug Application demonstrating bioequivalence, without the need to replicate original clinical tests.</p> <p>Bolar provision – USA</p> <ul style="list-style-type: none"> • 180-day market exclusivity right for the first manufacturer • Policy review claims evidence suggests that policies in the USA promoting generics have reduced delay between patent expiry and generic product market entry from >3 years to <3 months for high revenue medicines. • Generic medicines have increased from 19% of the total USA pharmaceutical market by volume to 56% in 2005. • Policy review indicates that pressure by Medicaid and private insurers for use of generics and state laws requiring generic substitution have increased generic penetration in the USA. <p>Bolar provision – Europe Measures such as abridged marketing applications and Bolar-type provisions are in place in Europe to facilitate market entry.</p>
<p>Encourage applications:</p> <ul style="list-style-type: none"> • reducing registration fees • exclusivity period 	<p>No evidence provided, possibly owing to a lack of evidence in this area.</p>	
<p>Reduce information asymmetry:</p> <ul style="list-style-type: none"> • labelling of generics 	<p>No evidence provided, possibly owing to a lack of evidence in this area.</p>	
<p>Quality assurance:</p> <ul style="list-style-type: none"> • monitoring GMP • publication inspection reports • post-market surveys • sanctions for false claims • surveys of stakeholders • therapeutic equivalence 	<p>Publication of inspection reports Between July 2000 and July 2002 only 20 of 3529 generic medicine samples in Delhi were found to be of substandard quality.</p> <p>Demonstration of therapeutic equivalence Brazil and Mexico have schemes for demonstration of therapeutic equivalence that restrict generic substitution. In Mexico, all registered medicines must have demonstrated therapeutic equivalence.</p>	<p>The USA Food and Drug Administration actively promotes the quality of generics.</p>

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Policy objectives/options	Low- and middle-income countries	High-income countries
	<p>Other efforts to regulate quality The WHO Prequalification Programme, which facilitates access to medicines that meet standards of quality, safety, and efficacy. Prequalification entails assessment of quality standards, technical competence, and financial viability of a supplier.</p>	
Overall conclusions		
<p>There is no evidence provided regarding regulation/registration/quality assurance for most LMICs, with the evidence provided for Latin American countries not quantifiable or strong.</p> <p>Evidence for HICs indicates use of generic has increased, however the evidence for claims of faster market entry cannot be quantified.</p>		

Sub-table ES5.1B: Supply-side policy options to promote uptake of generics via trade and intellectual property policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Protect against undue monopoly created by use of patent:</p> <ul style="list-style-type: none"> • pre-grant opposition • definition patentable products <p>Protect against bar to market entry:</p> <ul style="list-style-type: none"> • transparency of patent information <p>Ensure supply if patented product not available:</p> <ul style="list-style-type: none"> • compulsory licensing • voluntary licensing • Bolar provision • parallel importation 	<ul style="list-style-type: none"> • Policy review cites two models: <ul style="list-style-type: none"> ◦ Simulation model of price and quantity costing between innovative medicines and their generics using data from Thailand. The model indicated that the TRIPS-plus provision of the Thailand–USA free trade agreement was estimated to increase medicine expense by extending market exclusivity – \$6.2 million in the first year, increasing to \$5215.8 million in the tenth year. The model also predicted a delay in increase in medicine accessibility of generics (Akalephan et al, 2009) (75). ◦ An econometric scenario model based on the Thailand-USA free trade agreement found that prices would increase due to delay in generic entry to the market (Kessomboon et al, 2010). • Policy review states that an analysis of antiretroviral prices before and after policy changes in Brazil and Thailand showed some success (Ford et al, 2007) (76). The review goes on to state that the Brazilian experience shows that negotiations with pharmaceutical companies have largely failed to secure optimal prices, and Brazil paid up to four times more than international prices for second-line antiretrovirals. • A study of the Thailand pharmaceutical sector (Supakankunti et al, 2001) (77) found the price of originator medicines did not change due to imposition of TRIPS, however there were few data available for generic medicines. 	<p>Data exclusivity</p> <ul style="list-style-type: none"> • The policy review cites a number of free trade agreements that contain data exclusivity, whereby, for a fixed period, medicine regulatory authorities do not allow the registration files of an originator drug to be used to register a therapeutically equivalent generic version. Data exclusivity laws may encompass medicines that would otherwise be open to generic competition. <p>Linkage</p> <ul style="list-style-type: none"> • Some LMICs have created patent linkage schemes that impose a requirement on generic companies to make a mandatory statement about the patent status as part of a regulatory dossier submission. The policy review gives the example of Slovakia, which requires that market authorization given to a generic medicine is suspended until patent expiry.
<p>Overall conclusions</p>		
<p>Evidence for LMICs is limited. The Ford et al (2007) (76) review provides a summary of some aspects of TRIPS in Brazil and Thailand.</p>		

Sub-table ES5.1C: Supply-side policy options to promote uptake of generics via generic price competition policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Increase competition of generic products on the market through:</p> <ul style="list-style-type: none"> • joint manufacturing • increasing numbers of generic manufacturers • ‘me-too’ products to increase competition • limiting number of products on the market • pooled procurement • price information • competition between wholesalers and retailers • collectively managing intellectual property: patent pools 	<p>Joint manufacturing A proposed method is that small countries form regional cooperative ventures for generic manufacture in an attempt to achieve sufficient volumes. The policy review states that this may not be economically feasible since cost of goods may still be higher than those available by international tender. In China, the number of local generic competitors had decreased local product price.</p> <p>Pooled procurement</p> <ul style="list-style-type: none"> • Pooled procurement is done in the Organisation of Eastern Caribbean States and the Gulf Cooperation Council – whether such procurement is effective in increasing generic penetration is not clear. • The policy review states that Waning et al (2009) (78) used data from 7253 procurement transactions for antiretrovirals from WHO and GFATM databases and found that large purchase volumes did not necessarily result in lower antiretroviral prices. <p>Limiting number of products on market This option is defined, but no evidence provided, possibly owing to a lack of evidence in this area.</p> <p>Price information to increase competition Policy review cites a number of countries that have made procurement prices public. However, no evidence relating to the impact of this is provided, possibly owing to a lack of evidence in this area.</p> <p>Competition between wholesalers and retailers</p> <ul style="list-style-type: none"> • Policy review that evidence for reduction of prices due to competition is available in analyses and case reports of competition and anti-trust authorities. • Waning et al (2009) (78) reports that presence of a new pharmacy in villages that previously had none led to competitive pressure on pharmacies at a distance of up to 15km away in Kyrgyzstan. <p>Creating a patent pool Policy review describes this option but evidence relating to impact is not yet available, since this is a new approach.</p>	<p>Increasing number of generic manufacturers Policy review states that various studies estimating the discount in price offered by the first generic entrant on the market find discounts of 15–40% when there is only one generic competitor, and generic prices reduce as more generics enter the market. A 1991 study by Caves, Whinston, and Hurwitz (79) found the average generic wholesale price to be 60% of originator price for medicines with only one generic entrant, dropping to an average of 29% with 10 generic entrants and 17% with 20 generic entrants.</p> <p>‘Me-too’ medicines as strategy to increase competition The policy review states that competitive pressure from ‘me-too’ products, even for medicines still on patent can place downward pressure on prices, and this has been demonstrated in a number of countries, including the Australia, New Zealand, Norway, and the USA.</p>
<p>Overall conclusions</p>		
<p>Limited evidence is presented assessing the impact of generic price competition. One study (Waning et al, 2009) (78) looking at antiretroviral prices found that pooled procurement resulted in lower prices for generics compared to branded products, although the impact on overall prices is not clear.</p>		

Sub-table ES5.1D: Supply-side policy options to promote uptake of generics via pricing and purchasing policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Direct price control:</p> <ul style="list-style-type: none"> • external reference pricing • Internal reference pricing • originator price control • generic prices set relative to originator prices 	<p>Reference pricing Assessment of a South African programme covering items for which appropriate generic equivalents are available found that the rate of medicines inflation lowered as a result of switching from original or branded products to generics or switching from higher-priced to lower-priced generics</p> <p>Regulation of originator products</p> <ul style="list-style-type: none"> • In Mexico, market authorized products that lose their patient protection are excluded from governmental price controls, as are all existing generic products. • The Philippines has a price control policy that uses a maximum retail price for a list of medicines. <p>Generic prices relative to originator products In Indonesia, ratios are used to set the price of the generic relative to the branded product.</p>	<p>Generic prices relative to originator products Several countries in the <i>Prescription pricing and reimbursement information</i> (PPRI) (2008) report (60) set the price of a generic considerably lower than that of the original product, and some countries provide mechanisms for reducing the prices of the second and further generics.</p> <p>External reference pricing The policy review states that external reference pricing is common among developed countries other than Sweden, UK, Germany, Denmark, and Malta.</p> <p>Internal reference pricing</p> <ul style="list-style-type: none"> • The policy review provides an example of Germany, where the change from a system in which patients paid a flat prescription fee to one in which social insurers paid the same maximum reimbursement for all generic equivalents and patients paid the difference between the reimbursement and producer's price led to a 10–25% reduction in prices by the producers. • A study by Kanavos et al (2008) (80) concluded that although reference pricing led to a decline in lowest generic prices by up to 47%, the average generic prices showed a significantly lower price decline over time. • Portela (2009) (81) examined market share for medicines in Portugal before and after the introduction of internal reference pricing. The market share for generics increased but less so for branded medicines. Reference pricing in Portugal tended to promote consumption of medicines that had the lowest co-payment for consumers. • In Hungary, therapeutic reference pricing decreased the prices for generic statins, but the average unit price of statins did not change and the price of patented statins did not change.

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Policy objectives/options	Low- and middle-income countries	High-income countries
Regulating profits: <ul style="list-style-type: none"> • cost-plus pricing • regulating mark-ups 	Cost-plus pricing Policy review states that in India a cost-plus formula is used where the retail price is calculated as the cost of production plus post-manufacturing costs including trade margins and manufacturer’s margin. The policy review indicates that in West Bengal the price of ciprofloxacin remained high even off-patent, in contrast to generic omeprazole, which was less than half the reference price. The policy review comments on the poor availability of medicines in the public sector of West Bengal but does not provide direct evidence relating to the impact of cost-plus pricing.	Cost-plus pricing is no longer used in Europe.
Indirect price controls: <ul style="list-style-type: none"> • government subsidies 	Government subsidies The review cites the example of Peru, where exemption of medicines from import taxes has not had an effect on wholesaler or consumer prices.	No evidence provided, possibly owing to a lack of evidence in this area.
Decrease information asymmetries: <ul style="list-style-type: none"> • publication of prices 	No evidence provided, possibly owing to a lack of evidence in this area.	No evidence provided, possibly owing to a lack of evidence in this area.
Regulating public purchasing: <ul style="list-style-type: none"> • open tender 	Purchasing The policy review provides examples of tendering used in Serbia, South Africa, West Bengal, and Sudan. In Serbia, it is estimated that the aggregate tender used resulted in 4.6% and 17.2% cost savings in comparison with minimal tender price and free-market price, respectively. In South Africa, the most recent tender will result in antiretroviral medicines at or about the best prices available globally, with the costs of tenofovir and efavirenz reduced significantly.	Purchasing The policy review states that insurance companies in the Netherlands and sickness funds in Germany have developed tender procedures for medicines in ambulatory care and that such procedures show that significant cost savings can be achieved through purchasing mostly generic medicines. The policy review also states that the European Generics Medicines Association does not have a good opinion of tendering “....such initiatives do not support long-term competition in the pharmaceutical market or provide access to medicines and may jeopardize the sustainability of the generic medicines industry”. The policy review indicates that the research on which this claim was based was not evaluated.
Overall conclusions		
While some examples are provided illustrating pricing and purchasing policies, there is little evidence addressing their impact. There is, however, some evidence indicating internal reference pricing in HICs has a positive impact on prices of generic medicines, but the long-term impact of this strategy has not been demonstrated.		

Sub-table ES5.1E: Supply-side policy options to promote uptake of generics via reimbursement policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Cost savings for payers while ensuring medicine access:</p> <ul style="list-style-type: none"> • positive reimbursement list of medicines • copayments 	<p>Reimbursement</p> <ul style="list-style-type: none"> • A generic substitution policy in Turkey for medication costs for diabetes patients resulted in a mean annual saving per patient equivalent to the cost of 1 month’s medication for patients using insulin and 2 months’ medication supply for patients not using insulin. • Reductions in daily expenses in medicines occurred after changes to reimbursement rates in Taiwan, China, in which prices for bioequivalent generics could not exceed 80% of prices for corresponding branded medicines, and such a medicine being registered for the first time could not be priced higher than the lowest among prices of existing generics in the same group (Chen et al, 2008) (82). However, hospitals expanded the volume of medicines prescribed and the total costs for three classes of medicines grew following the reimbursement change. • In the Republic of Moldova, there is 100% reimbursement of medicines for children 0 to 5 years old. However, for paracetamol, the only form on the reimbursement list is 500 mg, which means that caregivers pay out-of-pocket for doses that are more convenient. 	<p>Reimbursement through a positive list</p> <p>The policy review states that a conditional or limited form of reimbursement for pharmaceuticals exists in most developed countries</p> <p>Co-payments</p> <ul style="list-style-type: none"> • A Cochrane review by Austvoll-Dahlgren et al (2008) (2) found that cap and co-payment policies can decrease overall medicine use and decrease third-party medicine spending. However, reductions in medicine use were found for life-sustaining medicines and those that are used to treat chronic conditions. Tiered co-payments may reduce medicine use if patients are not willing to substitute for other medicines or if changes included increased co-payments for generics. The review was based on 13 studies and the quality of research in the included studies was rated to be low to moderate. • A review of 30 studies (Gibson et al, 2005) (83) reported that few substitutions for generics resulted from plans introducing or increasing generics versus a brand cost-sharing differential. • 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 observed when substitution with patient consent was allowed in 1994 (McManus et al, 2001) (84). • A Swedish study has indicated that co-payments have a large effect over consumer choices (Andersson et al, 2005) (85). • A US study (O’Malley et al, 2006) (86) demonstrated that co-payment was the intervention that most affected patients’ change from originator to generic products compared with advertisement campaigns, member mailing, and free generic samples.
<p>Overall conclusions</p>		
<p>The policy review states that there is little direct evidence that policies on reimbursement of generic medicines will increase the number of competitors and assist in lowering prices and or assist in increasing market penetration of generics.</p>		

Sub-table ES5.1F: Demand-side policy options to promote uptake of generics via prescribing policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Promote prescribing of generics among physicians:</p> <ul style="list-style-type: none"> • regulations to mandate prescribing medicines by INN • requesting extra note on prescription if only originator can be prescribed • training prescribers using INN only • financial incentives 	<p>Regulatory policies to request prescribing by INN</p> <ul style="list-style-type: none"> • Prescribing by generic name has been implemented but not enforced in Argentina, Ecuador, Peru, Panama, and Paraguay and therefore shows little effect. • In Pakistan, physicians were required to write the name of the generic medicine on prescriptions. <p>Campaigns to promote generic uptake</p> <ul style="list-style-type: none"> • In the Philippines, information was provided to the public as part of the deployment of the Generics Act of 1988. In 1992, resistance was being voiced by medical associations and in 2007 resistance remained. The policy review states that public awareness of generics remains low. <p>Other factors influencing policies</p> <ul style="list-style-type: none"> • A systematic review by Lim et al (2009) (87) based on 21 studies in LMICs and HICs found that dispensing prescribers were more likely to prescribe originator product. • An interventional study from South Africa (Meyer et al, 2001) (88) assessed the effect of a training course to promote prescribing of generics found a substantial increase in the use of the generics 3 months after the programme; however long-term impact was expected to be low. 	<p>Financial incentives</p> <ul style="list-style-type: none"> • A systematic review by Sturm et al (2009) (3) found that, based on five studies measuring generic medicine use, the presence of financial incentives increased prescribing of generic medicines by 10.6%. • Implementation of physician budgets appears to have boosted the German generic market, since actual generic prescriptions as percentage of potential generic prescriptions increased from 60% in 1992 to 75% in 2003. <p>Campaigns targeting prescribers</p> <ul style="list-style-type: none"> • Provision of information to physicians in the UK and Spain that indicates where physicians can achieve cost savings reduces prescriptions for originators more than complex incentive schemes. • Most US hospitals prescribe generically and this has been accepted by staff who have confidence that the products will be of good quality. • In other countries, such as countries of the former Soviet Union, the perceptions of generics are largely negative. <p>Training of prescribers to use INN</p> <ul style="list-style-type: none"> • The review claims that medical students are taught to prescribe by INN in medical school and INN prescribing is common even for branded items. In 2008, 82.6% of all prescription items in the UK were prescribed by INN. <p>Other factors</p> <ul style="list-style-type: none"> • A study from Greece found that around half of 1204 physicians surveyed thought that generic medicines were of high or very high quality, safety, and effectiveness and 70.8% reported prescribing the originator product (Tsiantou et al, 2009) (89). • A retrospective study from Republic of Korea assessed the effect of a policy to separate prescribing from dispensing roles on the use of generic medicines and found that the use of originator products increased.
<p>Overall conclusions</p>		
<p>There is little evidence for the impact of prescribing policies in LMICs. In HICs there is some evidence that prescribing policies have increased use of generics, but the evidence is limited.</p>		

Sub-table ES5.1G: Demand-side policy options to promote uptake of generics via dispensing policies

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Increasing dispensing or selling of generic medicines:</p> <ul style="list-style-type: none"> • substitution • reimbursement of pharmacies • manipulating mark-ups, margins and/or dispensing fees 	<p>Generic substitution</p> <ul style="list-style-type: none"> • Generic substitution policies exist in Ghana, Uganda, South Africa, and other countries. • Data from a medical scheme in South Africa indicate that in 2009 the total insured market was between 7 and 8 million individuals and the generic utilization rate, or percentage of generic items claimed in the scheme, increased from 48.1% in 2007 to 48.7% in 2008 and 48.8% in 2009 (Bester and Badenhorst, 2010) (90). • Data from WHO 1997 indicates on overall generic dispensing rate of 15% of prescriptions in Indonesia. These data may not represent the current situation. • The policy review states that in Latin America, the substitution of medicines has been restricted to a certain list of medicines for which therapeutic equivalence is proven, and therefore the impact of promoting the uptake of generic medicines depends on the number of products for which substitution is authorized. <p>Factors influencing dispensing or sales</p> <ul style="list-style-type: none"> • A literature review of pharmacists' perception of generic medicines demonstrated that pharmacists were largely guided by economic considerations such as the profit margin between generic versus originator product; perceived quality of the generic product; perceived risk of substitution depending on the therapeutic class of the medicine (narrow therapeutic index products were less likely to substituted); and the customer and physician factors (good communication with the physician facilitated substitution). The studies included in this review were largely from the USA, with only one LMIC country represented – Malaysia (Al-Gedadi and Hassali, 2008) (91). • A study from West Malaysia surveying 40 pharmacists found that the main driver for generic substitution was the high profit margin by pharmacists (Din Babar et al, 2010) (92). • A study from the United Republic of Tanzania assessed the proportion of generic medicines sold out of all products in 39 private pharmacies and 11 medicine stores and found that 14% of all medicines were generics without brand (Nsimba et al, 2007) (93). • Research in Mail suggests that the probability of acquiring a generic medicine following an appointment at a public health facility was significantly higher than after an appointment with a private provider (Maiga et al, 2003) (94). • A study in the Philippines found that patients using pharmacies with links to public sector 	<p>Generic substitution</p> <ul style="list-style-type: none"> • In the UK, generic substitution is forbidden, except in an emergency or under strict hospital control. In Italy and France, generic substitution is limited, and Germany made generic substitution mandatory in 2001. • Sweden introduced a mandatory generic substitution policy in 2002. Analysis of sales volume of substitutable and non-substitutable products demonstrated that the sales volume of substitutable products increased (Andersson et al, 2008) (97). • A survey of 16 originator companies and seven generic companies in Finland found that after the introduction of generic substitution, producers of originator products had decreased profit margins (Timonen et al, 2009) (98). • An Australian study (McManus et al, 2001) (84) showed that the dispensing of generic fluoxetine and ranitidine increased significantly after the introduction of a substitution policy. <p>Regressive margins</p> <ul style="list-style-type: none"> • The policy review defines regressive margin models as functions of margins according to either public price, ex-factory price, or intermediary price. The simplest regressive model is one where margins in percentage are constant over a given price interval, and decrease at each price interval.

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Policy objectives/options	Low- and middle-income countries	High-income countries
	<p>physicians spent 49.3% more on medicines than those using unlinked pharmacies and that a switch to generic medicines could save patients up to 58% of their expenditure (James et al, 2009 (95)).</p> <ul style="list-style-type: none"> • An older study in Sierra Leone (Palmer and Lisk, 1997) (96) found that dispensers dispensed generics more than doctors (59% versus 45%) and made more use of the essential medicines list. The authors of the paper argued this was because dispensers were less influenced by medical representatives and had more experience in state facilities where medicines were dispensed and sold predominantly as generics. 	
<p>Decreasing information asymmetry:</p> <ul style="list-style-type: none"> • educational campaigns 	No evidence provided, possibly owing to a lack of evidence in this area.	
Overall conclusions		
<p>Most available evidence, across LMICs and HICs, addresses generic substitution. There is some indication that generic substitution has increased use of generic medicines.</p>		

Sub-table ES5.1H: Demand-side policy options to promote uptake of generics via consumer/patient consumption

Policy objectives/options	Low- and middle-income countries	High-income countries
<p>Increasing consumption of generic medicines:</p> <ul style="list-style-type: none"> • communication between health care providers and consumers • public education campaigns • limitation on free samples of originator products • prohibition or limited direct advertising of originator products • price information accessible to consumers 	<p>Labelling of generic medicines</p> <ul style="list-style-type: none"> • A survey conducted in Brazil (Bertoldi et al, 2005) (99) evaluated the knowledge and use of generic drugs by adults in a southern Brazilian city. The proportion of generic use was 3.9%. While 86.0% knew that generics cost less and 70.0% knew that the quality is similar to brand-name medicines, only 57.0% knew any packaging characteristics that distinguished generics from other medicines. When photographs were used, a brand-name medicine (with a brand similar to the generic name) was mistakenly classified as a generic by 48.0% of the subjects. Among subjects who bought medicines in the 15-day study period, 18.9% reported buying a generic, but the authors indicated this result should be interpreted with caution since the population frequently fails to differentiate between generics and other medicines. <p>Factors influencing consumer behaviour change</p> <ul style="list-style-type: none"> • A South African study (Patel et al, 2010) (100) assessed the perceptions of generic medicines held by 73 consumers in two different regions of the country. The study found that consumers defined ‘quality’ as the effect the medicines had on their symptoms. Consumer choice of care was mainly influenced by cost, choice, and receipt of individualized attention. The results of this study should be interpreted with caution, given the relatively small sample size. • A survey of 3967 consumers in Malaysia found that 32% believed that generic products caused more side-effects and 64% knew that generic products were less expensive than originator products (Al-Gedadi et al, 2008) (101). • The policy review indicates that schoolchildren can be effective change agents in improving community medicine use. This is based on the impact of school-based programmes addressing inappropriate use of antibiotics. 	<p>Promotion campaigns to increase generic use</p> <ul style="list-style-type: none"> • While promotion campaigns have been undertaken in Belgium, Italy, Portugal, Spain, and the UK, there have been no formal evaluations of the impact of these campaigns. • In the USA, a study 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 generics can increase the rate of generic substitution (Sedjo et al, 2009) (102). <p>Communication by health providers about generics</p> <ul style="list-style-type: none"> • A 1995 study (Dowell et al) (103) found that 20% of patients (n=167) who reported they were ‘very unhappy’ with their generic medications did so because of the nature of communication they received rather than the change in medication itself. This was a small study at one general practice in the UK more than 15 years ago, thus the results should be interpreted with caution. • Research in Spain indicates that patient education is successful in increasing patients’ acceptance of generic medicines and their satisfaction with the medicines (Valles et al, 2002) (104). <p>Factors influencing consumer behaviour change</p> <ul style="list-style-type: none"> • A survey of 1047 adults commercially insured by a large pharmaceutical benefit manager in the USA found that only 30% believed that branded medicines are more effective than generic medicines. However, 63% of them preferred to take originator medicines. • A survey of 800 patients recruited from general practitioners in three regions in Germany found that 37% were sceptical about generics because they were cheaper than originators (Himmel et al, 2005) (105).

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Policy objectives/options	Low- and middle-income countries	High-income countries
		<ul style="list-style-type: none"> • The policy review also cites a 1998 USA study in which more than 60% of respondents indicated that generics are as safe and effective as brand medicines and equivalent in quality, but only 24% asked their physician or pharmacist for generics when receiving a prescription. • The policy review describes a 1990 New Zealand study, which indicated that providing a guarantee of the acceptance of generic medicines by patients is problematic. In New Zealand in 1990, 56% of physicians in a survey reported problems associated with the use of generics. 88% of these problems were due to patient confusion over size, shape, and taste (Tilyard et al, 1990) (106). Since these data are more than 20 years old, their relevance is limited. The policy review does state that patient awareness has improved in many countries because patent-protected and marketed medicines often have a unique shape or colour (Garattini and Tediosi, 2000) (107).
Overall conclusions		
<p>Some evidence is available but it is mainly based on small studies from more than a decade ago. It is therefore difficult to draw firm conclusions on the impact of policies targeted at consumers/patients.</p>		

GFATM = Global Fund to Fight AIDS, Tuberculosis and Malaria, INN = international nonproprietary name.

Source: Kaplan WA et al. *Policy options for promoting the use of generic medicines in low- and middle-income countries – WHO/HAI review series on pharmaceutical pricing policies and interventions*. Unpublished. (8)

Table ES5.2: Summary of additional literature on generic medicines policies

Review	Design	Aim	Outcomes
Aaserud et al (2006) (1)	Systematic review	To determine effects of pharmaceutical pricing and purchasing policies on drug use, health-care utilization, health outcomes and costs.	<ul style="list-style-type: none"> • 10 studies of reference pricing and one study of index pricing were included in the review. • Data relative to generic drugs was provided in one study of reference pricing: Pavcnik (2002) (108) indicated that the prices of generics reduced by an average of 11%, whereas the decline in brand prices was an additional 26%. The single study included on index pricing (Brekke et al, 2003 (109)) demonstrated that brand and generic drug prices were both reduced. The reduction in brand drug prices was not statistically significant. Generic drug prices were reduced (relatively) more than the brand drugs. The long-term effects were slightly larger than the short-term effects (-1.1% versus -0.8% for brand drugs; -5.3% versus -4.0% for generic drugs).
Bardey et al (2010) (110)	Dynamic model of pharmaceutical sector	Evaluation of long-term impact of reference pricing on pharmaceutical innovation, health, and expenditures.	<ul style="list-style-type: none"> • A model was constructed based on a dynamic game involving three players: pharmaceutical firms, consumers, and a regulatory entity. The model was calibrated with data on statins from France. • The model indicates that reference pricing negatively affects the intensity of research and also modifies the types of innovations that are brought to market, deterring small innovations. Reference pricing also typically generates a decline in health, while discounted expenditures may decrease or increase. This model has limited applicability to generic medicines
Dylst & Simoens (2010) (111)	Review, survey	<p>(1) Assessment of current generic medicine pricing policies in ambulatory care in Europe.</p> <p>(2) Literature review investigated policies relating to free-pricing systems, price-regulated systems, price differentiation, price competition, and discounts and tendering procedures.</p> <p>(3) A survey of member associations of the European Generic Medicines Association was also done to document the current standard of generic medicine pricing policies in Europe.</p>	<ul style="list-style-type: none"> • There is no single approach on developing generic medicine pricing policies in Europe. A number of generic pricing policies have been implemented, although there is little evidence regarding the impact of these policies.

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Review	Design	Aim	Outcomes
King & Kanavos 2002 (112)	Policy review	Review of policies implemented in Canada, Denmark, Germany, the Netherlands, the UK, and the USA.	<ul style="list-style-type: none"> • Savings in the countries reviewed are realized through increases in the volume of generic medicines used and the differences in price between generics and originator medicines. • Key supply-side policies include generic drug marketing regulation that facilitates market entry soon after patent expiry; reference pricing; pricing of originator products; and degree of price competition in pharmaceutical markets. • Demand-side policies include influencing prescribing and dispensing patterns and copayments. • Quality of generic medicines is a precondition for all other measures to take effect. • Policies implemented in developed countries must be adapted and take into account local conditions in order to have maximum impact in transitional countries.
Puig-Junoy (2010) (113)	Literature review	Assessment of European pharmaceutical price regulation on generic price competition. Focus on direct price-cap regulation of generic drugs and implementation of systems regulating the reimbursement rate, particularly through reference pricing and similar mechanisms.	<ul style="list-style-type: none"> • A total of 16 studies were included in the review. Only descriptive results were provided; no analyses were undertaken. • The available evidence indicates that price-cap regulation leads to a levelling of generic prices at a higher level than would occur in the absence of this regulation. • Reference pricing systems cause a reduction in the consumer price of all pharmaceuticals subject to the system, with the reductions varying across countries and time periods. The reductions were found to be greater for originator products than for generics. • The percentage discount offered to pharmacies in a country that uses a price-cap system combined with reference pricing is positively and significantly related to the number of generic competitors for the pharmaceutical in the market.
Puig-Junoy & Moreno-Torres (2010) (114)	Descriptive analysis of time trend in consumer prices before and after application of reference pricing in Spain	Assessment of the impact of competition on the consumer price and average price paid by the national health system (Sistema Nacional de Salud, SNS) under reference pricing in the Spanish generic market.	<ul style="list-style-type: none"> • Entry of a generic at a lower consumer price than that of the brand-name medicine or the first generic does not cause a voluntary reduction in the consumer price of the branded medicine or the first generic, either before or after the application of reference pricing. • Generic entry at a lower consumer price than previously existing drugs always causes a slight reduction in the average price paid by the SNS. However, the average price paid by the SNS is always higher than the lowest, with the difference being greater in relative terms under reference pricing.

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Review	Design	Aim	Outcomes
			<ul style="list-style-type: none"> •The authors concluded that the Spanish reference pricing system results in very little consumer price competition between generic firms, with price reduction being limited to regulatory measures.
Simoens et al (2005) (115)	Descriptive review of pharmaceutical policy regarding generic drugs in Belgium	Discussion of Belgian pharmaceutical policy regarding generic drugs and analysis of how the Belgian drug market has evolved following initiation of a reference pricing scheme in 2001.	<ul style="list-style-type: none"> • The market share held by generic drugs in Belgium increased following implementation of reference pricing. Average market share was 2.05% from January 1998 to June 2001 and increased to 6.11% from July 2001 to December 2003. • The introduction of the reference pricing scheme was associated with savings of 1.8% of pharmaceutical expenditure by third-party payers in 2001 and 2.1% in 2002. •The authors indicate that the existing policy has failed to take into account the role that physicians and pharmacists can play in stimulating generic drug use. They anticipate that future development of the Belgian generic drug market may hinge on the creation of incentives for physicians to prescribe, and pharmacists to dispense, generic medicines.

Table ES5.3: Barriers to implementation of generic medicines policies

Barrier	Relevance to low- and middle-income countries
Supply-side barriers	
Lack of transparency on prices and availability of generic medicines	The situation has changed due to WHO/HAI and various pricing databases such as the Global Price Reporting Mechanism (Waning et al, 2009) (78) achieving more price transparency. Various LMICs are promoting the publication of medicines prices to consumers but those efforts still seem insufficient.
Delays to market caused by post-market authorization procedures for establishing price and reimbursement status	Medicine registration authorities in many LMICs are weak. Regulation is also generally weak or non-existent.
Market entry delays originated by patent linkage in marketing authorization	TRIPS requirements go into effect for all World Trade Organization (WTO) members by 2016. Whether patents will be applied for and granted in many countries is unknown but for major emerging markets (Brazil, Thailand, India, China) this may be an issue unless such linkage is eliminated by legislation. “Linkage” requirements are not mandatory but have been negotiated in many free trade agreements. Such “linkage” does not have to be a foregone conclusion.
Evergreening of medicines (patent coverage for ‘new uses’ of existing, already patented substances) / switching patient demands by launching second-generation products with little or no added therapeutic value	TRIPS requirements go into effect for all WTO members by 2016. Whether ‘me-too’ patents designed to extend monopoly will be applied for and granted in many countries is an open question but for major emerging markets (Brazil, Thailand, India, China) this may be an issue.
Seeking weak or invalid patents, particularly second-generation patents – which may form part of a ‘patent thicket’ or be used to block the entry of generic medicines in other ways	TRIPS requirements go into effect for all WTO members by 2016. Whether or not patents will be applied for and granted in many countries is an open question but for major emerging markets (Brazil, Thailand, India, China) this may be an issue.
Reference pricing at a level of the cheapest medicine which inhibits economic viability of generic producers	Not clear, as no research on the effect of internal ‘reference pricing’ in such countries was identified.
Demand-side barriers	
<ul style="list-style-type: none"> • Lack of incentives for physicians to prescribe generic medicines • Economic disincentives for pharmacies to dispense generic medicines • Limited incentives for patients to request generic medicines. • Cultural and political factors such as opposition of physicians who value their prescribing freedom and their tradition to prescribe originator medicines • Pharmacies are not viewed as part of the health care system 	Yes, but little research regarding effective interventions to counter demand-side barriers. There is survey and other qualitative evidence from LMICs supporting the existence of these barriers, especially with regard to the limited incentives for patients to request generics and the cultural and political forces acting to disincentivize physicians and pharmacists to prescribe and dispense generics.

Source: Kaplan WA et al. *Policy options for promoting the use of generic medicines in low- and middle-income countries – WHO/HAI review series on pharmaceutical pricing policies and interventions*. Unpublished. (8)

9.10 **Annex J: Evidence summary 6 – Use of health technology assessment**

Note: This Annex replicates the evidence summary prepared in October 2011, with textual and presentational modifications for publication purposes.

Topic: The International Network of Agencies for Health Technology Assessment defines HTA as “[t]he systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.” HTA in relation to pharmaceuticals encompasses evaluations relevant to price setting or pricing policies

9.10.1 Overview of evidence available

Type of evidence

1. The unpublished WHO/HAI policy review (Pillay 2011) (9), which provides an overview of pharmacoeconomics and includes a literature review of studies that reported on the use of cost-effectiveness as a criterion used in drug selection and the role of pharmacoeconomics in the allocation of resources. Case studies of the systems in New Zealand and Australia were also presented. As the WHO/HAI policy review used the term ‘pharmacoeconomics’ instead of the term ‘health technology assessment’, both terms are used in this summary.
2. An additional literature search retrieved eight relevant reviews. A comparison of IRP and HTA (Drummond et al, 2011) (116), published after the WHO/HAI policy review was completed, was also retrieved. The papers are summarized in Table ES6.1.
3. In November 2009 the journal *Pharmacoeconomics* published a special issue addressing the use of cost-effectiveness analyses for health-care policy decisions in developing countries. These articles, together with other literature relevant to developing countries are summarized in Table ES6.2.

Quality of evidence

Overall, the evidence relating to the use of HTA is descriptive in nature, based on systematic reviews, other literature reviews, surveys, and opinion pieces. While there are a number of systematic reviews of various aspects of HTA, all are descriptive, not comparative. Many reviews raise common themes, including generalizability of economic evaluations and barriers faced when instituting economic evaluation (e.g. lack of technical knowledge, lack of local data, and lack of guidelines).

One publication, which is not a systematic review (Drummond et al, 2011) (116), provides a comparison of internal reference pricing and HTA in regard to initial price and reimbursement status of innovative drugs in four countries, Germany, the Netherlands, Sweden and the UK. Another descriptive analysis of retrospective data from the Common Drug Review in Canada (CDR), National Institute for Clinical Excellence (NICE) in the UK, and the Pharmaceutical Benefits Advisory Committee in Australia (PBAC) described how clinical and cost-effectiveness evidence is used in coverage decisions within and across jurisdictions, and identified common issues in the process of evidence-based coverage (Clement et al, 2009) (117).

The analysis found that a key issue in coverage decisions was the significant uncertainty around clinical effectiveness, usually resulting from inadequate study design, the use of inappropriate comparators, or unvalidated surrogate endpoints. The authors concluded that the results of the evaluation process in different countries are influenced by the context, agency processes, ability to engage in price negotiation, and perhaps differences in social values.

Outcomes

The impact of HTA on medicine prices and other rated outcomes is not provided in the identified evidence, with the exception of the paper by Drummond et al (2011) (116).

Results/conclusions

- Comparative evidence – HICs – see below
- Comparative evidence – LMICs – none available.
- Descriptive evidence – LMICs; HICs – see below.

9.10.2 Comparative evidence – High-income countries

Drummond et al (2011) (116) compared the use of internal reference pricing and HTA with regard to initial price and reimbursement status of innovative drugs in four countries, Germany, the Netherlands, Sweden, and the UK. The comparison considered drugs for four disease areas – hyperlipidaemia, diabetes, rheumatoid arthritis, and schizophrenia. The paper provides the cost of drugs considered and their reimbursement status. The authors draw the following conclusions.

- No clear pattern of the impact of HTA on prices could be determined.
- The impact of reference pricing is substantial only when there are large differences in the prices of drugs in a given group or cluster.
- When one drug in a disease-area cluster becomes generic, reference pricing can have a major impact. Normally, one would expect the price of all drugs in the cluster to fall to the level of the reference price. However, in the drug groups studied, the manufacturers maintained their original price. In the case of atorvastatin, this led to increased patient co-payments; in the case of insulin analogues, the price was maintained by use of a subsidy.
- The focus of reference pricing is to set the reimbursement level for the cluster; however, in the absence of a generic, it is unclear how this level is set. In contrast, with HTA, reimbursement can be conditional or limited to certain indications of the drug or certain patient subgroups. The authors indicate that recommendations following HTAs potentially reward innovation, while allowing consideration of value for money.
- The authors suggest that reference pricing alone does not represent a viable policy for obtaining value for money from pharmaceuticals, and HTA represents a much better approach, given the reward for innovation and value for money. A dual policy, in which the primary policy for obtaining value for money from new drugs is based on HTA, supported by reference pricing or another approach, may be emerging.

9.10.3 Descriptive evidence: WHO/HAI policy review

This WHO/HAI policy review used the term ‘pharmacoeconomics’ instead of HTA, therefore the former term is used in the summary below. The policy review provides an overview of pharmacoeconomics in terms of the components of a pharmacoeconomic study (assessing benefits of a drug, assessing costs of a drug) as well as definitions of the four types of economic analyses – cost-minimization, cost-benefit, cost-effectiveness, and cost-utility.

The policy review included a literature search designed to identify studies that reported on cost-effectiveness as a criterion for drug selection; the role of pharmacoeconomics in the allocation of resources; and knowledge and understanding of terms used in economic analyses. The review does not provide a summary of literature search results in terms of number of relevant articles found, however it does note that the published literature on drug selection is dominated by surveys and personal opinion pieces from developed countries.

The policy review summarizes five studies that assess drug selection criteria; seven studies assessing incentive schemes for prescribers, budget allocation, consumer participation, and scoring systems to determine resource allocation; and seven studies on the application of pharmacoeconomics in various settings and problems associated with its use. The following conclusions were reached.

- Literature on drug selection criteria suggests that efficacy, safety, and cost remain key issues in drug selection; however, there are other factors that have not been reported. These factors are not described. The review also states that there appears to be no literature on the role of pharmacoeconomics in developing countries.
- Rationing of drugs is extremely difficult for a drug selection committee.
- Several countries use some type of formal economic evaluation of pharmaceuticals for policy purposes but there is no standardized pharmacoeconomic methodology.
- Pharmacoeconomic analysis is resource intensive and requires a range of skills.

The policy review describes a survey of the economic assessment of pharmaceuticals conducted in 2001 among 11 OECD countries. The policy review also describes the HTA systems used in Australia and New Zealand.

The policy review includes a discussion of the sequencing of cost-containment measures and indicates that given the limited impact pharmacoeconomics has on cost containment relative to other interventions (generics, price control measures such as reference pricing, removal or reduction of taxes and tariffs) it should be done only when other interventions have been successfully implemented. The review also notes the resources required to implement a pharmacoeconomics policy are significant, including establishment of a regulatory system, technical expertise, and financial resources to support operations of the unit.

The review indicates that the use of pharmacoeconomics would require the introduction of new legislation to formalize the process. The review suggests that a more pragmatic approach would be to introduce the policy on a voluntary basis for a few years before the final structure is legislated. The review also recommends that the legislation should clearly define how the analysis will be evaluated, the decision-making criteria to be used, the roles and composition of

committees, the route to appeal or reapplication, how findings will be made public, and fees that may be levied for each application. The review provides further comments on structure of guidelines, the structure and operation of a pharmacoeconomics unit, and stakeholder relationships.

9.10.4 Descriptive evidence – Systematic reviews

The aim, number, and type of studies included and key results of the systematic reviews are provided in Table ES6.1 below. None of the reviews was comparative. One review assessed compliance and methodological quality of pharmacoeconomic studies (Anis et al, 2000) (118) and reported that the majority (74%) of submissions were not compliant with guidelines. Two reviews assessed economic evaluations in an Asian context, one assessing economic evaluations in the Republic of Korea (Lee et al, 2005) (119), the second assessing economic evaluation literature of health technology in Thailand (Teerawattananon et al, 2007) (120), and the third on uses and potential barriers to use of economic evaluation in an Asian context (Yothasamut et al, 2009) (121). Williams et al (2008) (122) looked at the extent of use of health economic information in health policy decision-making in the UK. Mason and Mason (2006) (123) updated an earlier review assessing generalizability of economic evaluation, and a large review by Sculpher et al (2004) (124) included three systematic reviews addressing generalizability as well as case studies looking at use of multilevel modelling. Neumann et al (2009) (125) provided a summary of cost-utility analyses pertaining to pharmaceuticals over the past 30 years.

9.10.5 Descriptive evidence – Developing countries

There is considerable literature on HTA in developing countries, including examples of economic evaluations as well as a number of discussion and opinion pieces. In November 2009, the journal *PharmacoEconomics* published a “developing nations special issue”. The editorial of the special issue discussed the issues facing the use of pharmacoeconomics in developing nations, including the lack of capacity to conduct economic evaluations within such countries, due to poor infrastructure, lack of local data and lack of qualified researchers (126).

Another key concern is the difficulty of generalizing or transferring results of economic evaluations based in developed countries to other settings. Babar and Scahill (2010) (127) published an opinion piece asking whether there is a role for pharmacoeconomics in developing countries. This article discussed the use and understanding of pharmacoeconomics in developing countries, provided examples from Asia and the Middle East, and suggested that a conceptual model addressing the perceived need and benefits of using pharmacoeconomics in formulary development in a given developing country would be of use.

A summary of literature on HTA in developing countries, focusing solely on the use of economic evaluation and development of HTA in these settings, is provided in Table ES6.2 below.

9.10.6 Implementation requirements

- Introduction of legislation that mandates use of HTA for reimbursement and price of pharmaceuticals.
- Establishment of a regulatory system.

- A system and resources to consider HTA evidence, including staff to assess or compile clinical and economic data.
- Ability to assess or conduct statistical analyses of data, as well as to assess or construct economic models.
- Determination of decision-making criteria, how analyses will be conducted or evaluated, how results are communicated, and whether fees will be charged.

9.10.7 Feasibility

There remain numerous uncertainties regarding the use of HTA, particularly in LMICs. A common theme across the literature is that HTA is best used after other price control interventions.

9.10.8 Gaps, research needs, and comments

- Quantitative assessment of the benefits of HTA, preferably compared with other price control measures.
- Assessment and agreement on standards for HTA, with particular consideration of whether such standards would be applicable across settings.

Table ES6.1: Summary of systematic reviews and other literature relevant to HTA

Author (year)	Review aim and number/type of studies included	Outcomes
Anis & Gagnon (2000) (118)	<ul style="list-style-type: none"> • Assess compliance of pharmacoeconomic studies submitted to Pharmacoeconomic Initiative of British Columbia, Canada. • Assess methodological quality of individual submissions. • Demonstrate importance of submitting guidelines-compliant analyses. • 88 submissions reviewed. 	<ul style="list-style-type: none"> • 25 cost-comparison analyses, 14 cost-effectiveness, 11 cost-minimization, 9 cost-utility, and 29 budget impact analyses. • 65 of 88 (74%) of submissions failed to comply with the guidelines. • 80% of non-compliant analyses were cost-comparison or budget impact analyses. • 74% of all submissions were not recommended for listing as a provincial drug plan benefit. • 80% of non-compliant submissions were not recommended. • 13 of 64 (20%) of non-compliant analyses were recommended for coverage while 10 of 24 (42%) of compliant analyses received a positive recommendation. • An association between type of analysis and type of recommendation was found ($p = 0.03$). Cost-comparison and budget impact analyses were less likely to be recommended
Drummond et al (2011) (116)	<ul style="list-style-type: none"> • Compare the use of reference pricing and HTA for pricing and reimbursement status of drugs in Germany, the Netherlands, Sweden, and the UK • Number/type of studies: not applicable. 	<ul style="list-style-type: none"> • The impact of reference pricing is only substantial when there are large differences in the prices of drugs in a given group or cluster. • Once one of the drugs in a group/cluster becomes generic, reference pricing can have a major impact. • No clear pattern of the impact of HTA on prices could be determined. • The focus of reference pricing is setting the reimbursement level for the cluster; however, in the absence of a generic, it is unclear how this level is set. In contrast, with HTA reimbursement can be conditional or limited to certain indications of the drug or certain patient subgroups. • The authors concluded that reference pricing alone does not represent a viable policy for obtaining value for money from pharmaceuticals, and HTA represents a much better approach, given the reward for innovation and value for money. A dual policy, in which the primary policy for obtaining value for money from new drugs is based on HTA, supported by reference pricing or another approach, may be emerging.
Lee et al (2005) (119)	<ul style="list-style-type: none"> • Review published economic evaluations of health-care technologies in the Republic of Korea. • Assess whether these evaluations were done according to international standards, and whether the results are useful for decision-making. • 45 economic evaluations included. 	<ul style="list-style-type: none"> • 14 (31%) cost-effectiveness analyses; 14 (31%) cost-benefit analyses; 5 (11%) cost-utility analyses; and 12 (27%) other analyses, including cost-of-illness and cost-comparison studies. • 20 evaluations (44%) used discounting and 20 (44%) performed sensitivity analyses. • 52% of studies used a time horizon of less than one year and 11% of studies did not clearly specify the time period. • 64% of evaluations stated a societal perspective was used, but this perspective was not always taken consistently, completely, or appropriately. • There were misunderstandings of what type of analysis was actually performed, i.e. some analyses were presented as cost-effectiveness analyses when they were in fact cost analyses or cost comparisons.

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Author (year)	Review aim and number/type of studies included	Outcomes
		<ul style="list-style-type: none"> • The authors concluded that many studies did not meet international standards.
Mason & Mason (2006) (123)	<ul style="list-style-type: none"> • Update of 1997 review of generalizability of pharmacoeconomic studies. • Number/type of studies: not provided. 	<ul style="list-style-type: none"> • Generalizability is comprised of three aspects – technical merit, applicability, and transferability. • Technical elements of best practice are uncontroversial, and these include choosing relevant alternatives, transparent reporting of methods and findings, accessing and using the best-quality evidence, using the best methods to synthesize data, using deterministic sensitivity analysis to explore systematic bias, and probabilistic sensitivity analysis to explore influence of random error at the whole model level. • Applicability of economic evaluation findings within original policy context can be determined assuming best practice guidelines for economic modelling are followed. • Transferability of results from one policy setting to another requires consideration of changes in resource implications, unit prices, and outcomes. • Limitations remain for economic analyses because of opaqueness of method, failure to reflect opportunity cost of decisions, and lack of societal mandate. • The authors conclude that making health economic findings accessible to patients, clinicians, and society in the form of relevant narratives will expose the assumptions underlying economic analysis to broader critical inspection.
Neumann et al (2009) (125)	<ul style="list-style-type: none"> • Review and critical evaluation of published cost-utility analysis pertaining to pharmaceuticals over the past 30 years. • 640 cost-utility analyses relating to pharmaceuticals sourced from cost-effectiveness analysis registry in the USA included. 	<ul style="list-style-type: none"> • 51.2% of cost-utility analyses had a US perspective (although economic evaluation is generally not required for formulary submissions or health technology assessments in the USA), 15.6% a UK perspective, and 6.9% a Canadian perspective. • 41.4% of the cost-utility analyses were industry funded, 33.0% were non-industry funded, and 25.6% did not disclose funding source. • There has been an improvement in adherence to recommended methods over time (clearly stated perspective, discounted costs and QALYs, time horizon stated, year of currency stated, incremental analyses conducted correctly), with 90% of cost-utility analyses in 2005–2006 adhering to the five criteria stated above compared with 60–85% adherence during 1976–1998. • ICERs from industry-sponsored studies are more favourable than other ratios.
Sculpher et al (2004) (124)	<ul style="list-style-type: none"> • Three systematic reviews and a series of case studies to review and develop the methods used to assess and increase the generalizability of economic evaluation studies. • Review of methods literature on generalizability to identify factors causing variability in cost-effectiveness between locations and over time. • Review of literature on available methods to assess variability between locations and over time. 	<ul style="list-style-type: none"> • Unit costs were the factor most frequently cited as generating variability in economic results between locations. • No studies were that which considered factors causing variability in results over time. • Evidence of variation between locations in volume and cost of resource use and in cost-effectiveness. • Regression analytic methods have indicated that some components of resource use are exchangeable across locations while others are not. • Both cost and effectiveness aspects of decision analytic models may need to be adapted between locations.

Author (year)	Review aim and number/type of studies included	Outcomes
	<ul style="list-style-type: none"> • Review of applied economic evaluation studies done in parallel with multilocation trials to describe how studies have assessed and reported generalizability and variability in results between locations. • Case studies to explore use of multilevel modelling to assess variability in cost-effectiveness between locations. • Review of economic evaluations based on decision analytic models in osteoporosis to describe how studies have made analyses relevant to decision-makers. • Case study of decision analytic model to illustrate methods to estimate cost-effectiveness for UK National Health Service using data collected in non-UK locations. • 109 studies included. 	<ul style="list-style-type: none"> • Weaknesses in some aspects of the reporting of cost-effectiveness analyses may limit decision-makers' ability to judge relevance of a study for their location. • Multilevel modelling can facilitate correct estimates of uncertainty in cost-effectiveness results and also provide a means of estimating location-specific cost-effectiveness. • Few studies were explicit about their target decision-makers/jurisdictions. • Generally more effort is made to ensure cost inputs are specific to their jurisdiction than effectiveness parameters.
Teerawattanon et al (2007) (120)	<ul style="list-style-type: none"> • Assessment of trends in the literature on economic evaluation of health technology in Thailand to identify quantity- and quality-related information gaps and determine whether studies target the country's major health problems. • 41 economic evaluation publications included. 	<ul style="list-style-type: none"> • 2 (5%) partial economic evaluations, 5 (12%) cost-minimization analyses, 27 (66%) cost-effectiveness analyses, 2 (5%) cost-utility analyses, 5 (12%) cost-benefit analyses • application of recommended guidelines was low, with less than half reporting an ICER (41%) and a third conducting sensitivity analyses (32%) or using discounting (31%) • Lack of publication of economic evaluations on 15 of 20 leading causes of disease burden.
Williams et al (2008) (122)	<ul style="list-style-type: none"> • Assessment of use (or lack of use) of research evidence relating to economic analyses in health-care decision-making in the UK. • To what extent, and in what ways, is health economic information used in health policy decision-making in the UK? • What factors are associated with use, or non-use, of such research findings? • Five case studies of four local committees and one national committee included. 	<ul style="list-style-type: none"> • At the local level it was an exception for economic evaluation to inform technology coverage decisions. Main sources of cost-effectiveness information were manufacturers of the product and NICE guidance. Local respondents were receptive to making greater use of health economic information, but levels of understanding and expertise in the subject were low. • At the national level the use of economic analysis is highly integrated into the decision-making process of NICE's technology appraisal programme. Attitudes towards economic evaluation varied among committee members and there was significant disagreement between members about economic evaluations. • The authors conclude that the most fundamental challenges relate to the overall design of the health system and structure of health care organizations, beyond attempts to make cost-effectiveness studies easier to obtain and understand.
Yothasamut et al (2009) (121)	<ul style="list-style-type: none"> • Assessment of the potential uses of economic evaluation and the barriers that could prohibit the use or diminish the usefulness of economic evaluation in Asian settings. • Review does not indicate number 	<ul style="list-style-type: none"> • Potential uses of economic evaluation include development of public reimbursement lists, price negotiation, development of clinical practice guidelines, and communicating with health professionals. • Two types of potential barriers are defined. (1) Barriers relating to production of economic evaluation data include generalizability of results and ability to

Author (year)	Review aim and number/type of studies included	Outcomes
	of papers included but reference list indicates that 32 papers were used.	<p>conduct evaluations in a particular setting; study bias due to poor quality of evidence used and deficient reporting; time frame; lack of focus on key health concerns; and lack of guidelines. (2) Barriers related to decision context include lack of understanding of economic evaluation among potential users; social expectation; politics, social institutional barriers; and philosophical and ethical considerations.</p> <ul style="list-style-type: none"> • Suggested solutions include the development of national guidelines; development of an economic evaluation database; use of economic evaluation in a systematic manner; prioritization of topics for assessment; educating users and the public; and making the process transparent and participatory.

ICER = incremental cost-effectiveness ratio, NHS = National Health Service, NICE = National Institute of Clinical Excellence

Table ES6.2: Summary of literature relevant to use of HTA in developing countries

Author	Summary
Augustovski et al (2009) (128)	<ul style="list-style-type: none"> • Systematic review to determine to what extent health economic evaluations conducted in industrialized economies are generalizable to the Latin American and Caribbean region (LAC) and to other LAC countries. • Identified and included 72 studies that involved patient- and model-based health economic evaluations in at least one LAC country. • More than one-third of the studies did not specifically report the type of economic analysis used; 78% were cost-effectiveness and cost-consequence analyses. • Authors state that overall reporting in the studies was poor and there was evidence of unfamiliarity with international guidelines. Reporting problems included issues related to sample representativeness, data collection, and data analysis. • Economic evaluation methodology was usually weak and less developed than the analysis of clinical data. • There were problems with the interpretation of studies that precluded an assessment of generalizability and transferability. Most studies had either general or specific criteria that could not be assessed or were inadequately described to allow an assessment of generalizability.
Bae & Lee (2009) (129)	<ul style="list-style-type: none"> • Discussion of the process and content of pharmacoeconomic guidelines in the Republic of Korea. • Lack of local data and limited availability of human resources identified as barriers for economic evaluation in the Republic of Korea.
Chaikledkaew et al (2009) (130)	<ul style="list-style-type: none"> • Study aimed to (i) explore decision-makers' knowledge, experience, and attitudes towards the use of economic evaluation at the subnational level in Thailand and (ii) assess current capacity and gaps in economic evaluation among decision-makers and Thai scholars. • 2575 postal questionnaires were distributed to members of the management committees of Provincial Health Offices and researchers. The questionnaires gathered sociodemographic information, and had eight questions relating to respondents' knowledge and experience of economic evaluation and their attitudes towards its use in making health resource allocations. Further questions assessed potential barriers in conducting or applying economic evaluations in practice for policy decisions. Respondents were also asked to rank the top five health problems where economic evaluation could play a role in identifying mitigating interventions. • 758 (29.4%) of questionnaires were completed and returned. The highest response rate came from researchers in the public sector; the lowest response rate was among faculty members at academic institutions. • The majority of researchers and decision-makers were not familiar with technical terms commonly used in health economic evaluations, e.g. incremental cost-effectiveness ratio, discounting, sensitivity analysis. • 50% of researchers and 71% of decision-makers had not been trained in economic evaluation. Only 20% of researchers and 7% of decision-makers had ever been involved in economic evaluations. More than 80% indicated an interest in training. • The main barriers to use of economic evaluation identified by researchers were lack of methodological skills, inadequate human resources, lack of local information regarding costs and effectiveness, no clear government policy on use of economic evaluations, inadequate financial support, lack of time, and lack of support from their own organizations. Decision-makers indicated the main barriers were lack of an explicit ceiling threshold for QALY or DALY gained, lack of economic evaluation studies on particular topics of interest, potential bias because of industry sponsorship, lack of confidence in use and interpretation of results, no clear government policy on use of economic evaluation, and political barriers. • Both researchers and decision-makers agreed that economic evaluation studies should focus on HIV/AIDS, road traffic accidents, diabetes, and homicide.
Jirawattanapisal et al (2009) (120)	<ul style="list-style-type: none"> • Review of the use of evidence in the market approval process, reimbursement, and price control mechanisms for medicines and medical devices in Taiwan, China; the Republic of Korea; and Thailand.

Author	Summary
	<ul style="list-style-type: none"> • Only Thailand used an explicit benchmark on cost-effectiveness for inclusion in the reimbursement list. • All have established mechanisms and processes for price negotiation.
Lee et al (2005) (131)	<ul style="list-style-type: none"> • Review of published economic evaluations of health-care technologies in the Republic of Korea. • Assessment of whether these evaluations were done according to international standards, and whether the results are useful for decision-making. • 14 (31%) cost-effectiveness analyses; 14 (31%) cost-benefit analyses; 5 (11%) cost-utility analyses; and 12 (27%) other analyses, including cost-of-illness and cost-comparison studies. • 20 evaluations (44%) used discounting and 20 (44%) performed sensitivity analyses. • 52% of studies used a time horizon of less than one year and 11% of studies did not clearly specify the time period. • 64% of evaluations stated a societal perspective was used, but this perspective was not always taken consistently, completely, or appropriately. • There were misunderstandings of what type of analysis was actually performed, i.e. some analyses were presented as cost-effectiveness analyses but were in fact cost analyses or cost comparisons. • The authors concluded that many studies did not meet international standards.
Shih et al (2009) (132)	<ul style="list-style-type: none"> • Assessment of the use of data from an electronic health information system in Taiwan, China, to assess cost-effectiveness of chemotherapy use among patients with breast cancer. • A cohort of patients in the National Health Insurance Research Database who had been diagnosed with breast cancer and received chemotherapy following surgical tumour removal were identified and their data were used to conduct a cost-effectiveness analysis that compared two different chemotherapy regimens. • Analyses indicated that cyclophosphamide, epirubicin, fluorouracil (CEF) was not cost-effective compared with cyclophosphamide, methotrexate, fluorouracil (CMF), with CEF more costly and less effective than CMF. Sensitivity analyses indicated that CEF could have been more cost-effective than CMF had the optimal dosage level for CEF been established for breast cancer patients in Taiwan, China. • The authors concluded that a population-based, fully integrated health information system provides useful data to assess the cost-effectiveness of competing treatments and interventions in clinical practice and that such information may potentially inform policy-makers of modifications that can be instituted to improve cost-effectiveness of a new therapy.
Shillcutt et al (2009) (121)	<ul style="list-style-type: none"> • Editorial discussing the advent of pharmacoeconomics in South Africa. • Discussion of pharmaceutical expenditure in South Africa and means of controlling expenditure, with the indication that the implementation of pharmacoeconomic analysis will take 2 to 5 years. • Editorial indicates that there would have to be sufficient capacity before pharmacoeconomic analysis could be implemented, which would require capacity building for both the Department of Health and industry.
Spencer Jones (2006) (129)	<ul style="list-style-type: none"> • Editorial describing the expected implementation of pharmacoeconomics in South Africa. It was anticipated that pharmacoeconomics would be introduced once the initial phases of price regulation were fully implemented.
Tantivess et al (2009) (130)	<ul style="list-style-type: none"> • Description of the establishment and characteristics of the Health Intervention and Technology Assessment Program (HITAP) in Thailand. • Paper provides contextual background information about the development of HITAP and provides information about its structure, finance, staffing, and management and the contribution of cost-effectiveness analysis to policy. • As there were only 2 years of HITAP data when the paper was published, the role of HITAP's research and associated recommendations in policy decisions was unclear. • The authors hoped that information based on the creation of HITAP, as well as information on its strategies and management structure, would be helpful for other resource-constrained countries when considering how to strengthen their capacity for conducting economic appraisals.

Author	Summary
Teerawattananon et al (2007) (120)	<ul style="list-style-type: none"> • Assessment of trends in the literature on economic evaluation of health technology in Thailand to identify quantity- and quality-related information gaps and determine whether studies target the country's major health problems. • 2 (5%) partial economic evaluations; 5 (12%) cost-minimization analyses; 27 (66%) cost-effectiveness analyses; 2 (5%) cost-utility analyses; and 5 (12%) cost-benefit analyses were identified. • Application of recommended guidelines was low, with less than half reporting an incremental cost-effectiveness ratio (41%) and one-third conducting sensitivity analyses (32%) or using discounting (31%). • There was a lack of publications on economic evaluations for 15 of the 20 leading causes of disease burden.
Thatte et al (2009) (131)	<ul style="list-style-type: none"> • Paper describes programmes used in India, Malaysia, Pakistan, and the Philippines for approval, pricing, reimbursement, and financing of medicines, diagnostics, and medical devices. • The Ministries of Health are responsible for drug, medical device, and diagnostics approval in all four countries. • The price control mechanism in India is the National Pharmaceutical Pricing Authority, while in the Philippines the Essential Drug Price Monitoring System monitors the prices of essential drugs monthly. In Pakistan and Malaysia, the pricing of new drugs is negotiated by the government with the vendor. • Only the Philippines has a reimbursement system in which cost-effectiveness is considered. The 'reimbursement' systems described for the other three countries deal only with insurance plans and reimbursement of medical claims by the government. • In India and the Philippines, the bulk of health expenditure is out-of-pocket with government paying 20% and 28%, respectively. In Malaysia, public health care services are subsidized by the government with minimum fees paid by the public. In Pakistan, free medicines are supplied to patients at public health facilities. • The authors conclude that all countries would benefit from human resource development to facilitate evidence-based assessment of health technologies.
van Hulst et al (2010) (132)	<ul style="list-style-type: none"> • Literature review of cost-effectiveness in blood product safety in sub-Saharan Africa. • 7 relevant studies were found; all considered the cost-effectiveness of HIV-antibody screening. • Results of all studies indicated that HIV-antibody screening provides health gains and saves costs. • The authors recommend that all peer-reviewed journals should prompt authors to publish their economic models with technical appendices online, in order to promote transparency.
Yothasamut et al (2009) (121)	<ul style="list-style-type: none"> • Assessment of the potential uses of economic evaluation and the barriers that could prohibit the use or diminish the usefulness of economic evaluation in Asian settings. • Potential uses of economic evaluation include development of public reimbursement lists, price negotiation, development of clinical practice guidelines, and communicating with health professionals. • Two types of potential barriers are defined. (1) Barriers relating to production of economic evaluation data include generalizability of results and ability to conduct evaluations in a particular setting; study bias due to poor quality of evidence used and deficient reporting; time frame; lack of focus on key health concerns; and lack of guidelines. (2) Barriers related to decision context include lack of understanding of economic evaluation among potential users; social expectation; politics, social institutional barriers; and philosophical and ethical considerations. • Suggested solutions include the development of national guidelines; development of an economic evaluation database; use of economic evaluation in a systematic manner; prioritization of topics for assessment; educating users and the public; and making the process transparent and participatory.

QALY = quality-adjusted life year, DALY = disability-adjusted life year

9.11 Annex K: References

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