WHO Guideline on Country Pharmaceutical Pricing Policies

Contents

Acknowledgements:

The contents of this guideline reflect the dedicated efforts of many experts who contributed their time and expertise.

Overall coordination

Clive Ondari, Department of Essential Medicines and Health Products, Medicines Access and Rationale Use, WHO.

This draft was written by Alexandra Cameron, Suzanne Hill, Patti Whyte and finalized by Sarah Ramsey and Lisa Hedman.

Copy editing was done by Sarah Ramsey.

This document is available in English.

Funding and declarations of interest

The development of these guidelines was supported by a grant of the Bill and Melinda Gates Foundation.

Declarations of interest were collected from every member of the expert panel. The WHO Secretariat assessed all declared interests and determined that they should not preclude the experts on the panel from participating in the development of the guidelines.

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
Regulation of mark-ups in the pharmaceutical supply and distribution chain	➢ 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.
Tax exemptions/reductions for pharmaceutical products	➢ Countries should consider exempting essential medicines from taxation. ➢ Countries should ensure any tax reductions or exemptions result in lowered prices to the patient/purchaser.
Application of cost-plus pricing formulae for pharmaceutical price setting	➢ 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.
Use of external reference pricing	➢ 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.
Promotion of use of generic medicines	➢ 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.

POLICY INTERVENTION	RECOMMENDATIONS
Use of health technology assessment	➢ 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

- 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 polices 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 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 frees 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 lead 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	• 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	• Medicine prices; sales data.
Infrastructure	• Legislation setting up parameters for use. • Structures for consultation with concerned stakeholders. • A mechanism for monitoring medicine prices, use, and sales.
Methodological considerations	• 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	• Assessment of the impact of taxation, or absence thereof, on medicine prices as well as the amount of revenue generated by taxes.
Infrastructure	• Legislation specific to medicine taxation. • Mechanism for monitoring medicine prices.
Methodological considerations	• 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	• Cost accounting. • Knowledge of manufacturing practices. • Market analysis.
Data required	• Prices of active pharmaceutical ingredients, excipients, packaging materials, wastages, cost of conversion, and profits and mark-ups in supply chain.
Infrastructure	• 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	• 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	• Database management, data analysis.
Data required	• True negotiated prices rather than shadow prices.
Infrastructure	• 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	• 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 takes 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	• 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	• 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.	• Procedures on how to apply IRP. • Procedures on how IRP feeds into decision-making process, possibly supported by legislation.	• 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/dispensers	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	• 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	• Clinical data on efficacy and safety of drugs. • Cost data. • Data used in economic modelling.
Infrastructure	• Legislation mandating use of HTA for reimbursement and price of pharmaceuticals. • System and resources to consider HTA evidence.
Methodological considerations	• 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	• organization with private actors publicly funded • organization with private actors privately funded • public organization and funding of health care system
Primary 'payer'	• social health insurance • public sector • consumers/private households (i.e. direct payment) • private actuarial insurance • government (via finance or taxation) • enterprises
Regulatory agency	• no regulatory agency • regulatory agency with limited capacity • stringent regulatory authority
Pharmaceutical sector	• unregulated with little scope for regulation within political environment • unregulated but regulation feasible within the political environment • regulated

Type of system	Characteristics
Pharmaceutical market	• 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	• number and nature of suppliers, wholesalers, and retailers
Legal enforcement	• limited capacity to enforce regulations • capacity to enforce regulations
Target for policy intervention	**Characteristics**
Type of product	• on-patent versus off-patent • single-source versus multisource • high-cost • reimbursed • essential versus non-essential • prescription versus over-the-counter
Sector	• public • private • other • all
Patient contribution	• 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 polices 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.

8. References

i Cameron A et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*, 2009, 373(9659):240–249.

ii MDG Gap Task Force. *Delivering on the global partnership for achieving the Millennium Development Goals*. New York, NY, United Nations, 2008.

iii Niëns LM et al. Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. *PLoS Medicine*, 2010, 7(8):e1000333.

iv Cameron A et al. *The world medicines situation 2011*. Geneva, World Health Organization, 2011.

v Espin J, Rovira J, Olry de Labry, A. Working paper 1: External reference pricing – review series on pharmaceutical pricing policies and interventions. Geneva, World Health Organization and Health Action International, 2011.

vi 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.

vii 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.

viii Saif A. *Cost-plus price setting – WHO/HAI review series on pharmaceutical pricing policies and interventions*. Unpublished.

ix 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.

x Pillay T. *Value based price determination – pharmacoeconomics – WHO/HAI review series on pharmaceutical pricing policies and interventions*. Unpublished.

xi See http://www.haiweb.org/medicineprices/

xii Patouillard E et al. Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. *Malaria Journal*, 2010, 9:50.

xiii *Measuring medicine prices, availability, affordability, and price components: survey reports [online database]. Geneva, World Health Organization and Health Action International.* (http://www.haiweb.org/medicineprices/surveys.php, accessed October 2012).

[xiv] OECD. *Pharmaceutical pricing policies in a global market*. Geneva, Organisation for Economic Co-operation and Development, 2008.

[xv] Goldman DP et al. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *Journal of the American Medical Association*, 2007, 298(1):61–69.

[xvi] *Estonian health insurance fund annual report*. Tallinn, Estonian Health Insurance Fund, 2011.

[xvii] See http://www.inahta.net/

[xviii] Drummond M et al. Reimbursement of pharmaceuticals: reference pricing versus health technology assessment. *European Journal of Health Economics*, 2011, 12(3):263-271.

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