



ACCESS TO MEDICINES
AND HEALTH PRODUCTS

WHO guideline on country pharmaceutical pricing policies

WHO guideline on country pharmaceutical pricing policies



WHO guideline on country pharmaceutical pricing policies, second edition

ISBN 978-92-4-001187-8 (electronic version)

ISBN 978-92-4-001188-5 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. WHO guideline on country pharmaceutical pricing policies, second edition. Geneva: World Health Organization; 2020. Licence: [CC BY-NC-SA 3.0 IGO](https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Contents

Annexes	iv
Abbreviations	v
Foreword	vi
Acknowledgements	vii
Executive summary and recommendations.....	viii
1. Pharmaceutical pricing policies and this guideline	1
1.1 Pharmaceutical pricing policies and their purpose	1
1.2 WHO mandates.....	1
1.3 Objective of this guideline.....	2
1.4 Using this guideline	2
1.5 Target audience.....	3
1.6 Scope of content.....	3
1.7 Method of guideline development.....	4
1.8 Dissemination plan.....	6
1.9 Updating and user feedback	6
2. Principles for formulating and implementing pharmaceutical pricing policies	7
3. Evidence and recommendations.....	8
3.1 External reference pricing	8
3.2 Internal reference pricing.....	11
3.3 Value-based pricing	14
3.4 Mark-up regulation across the pharmaceutical supply and distribution chain	18
3.5 Promoting price transparency.....	21
3.6 Tendering and negotiation	25
3.7 Promoting the use of quality-assured generic and biosimilar medicines	28
3.8 Pooled procurement.....	32
3.9 Cost-plus pricing for setting the price of pharmaceutical products	35
3.10 Tax exemptions or tax reductions for pharmaceutical products	37
4. Considerations towards research needs	39
References.....	41

Annexes

Annex 1: Persons involved in development of the guideline I

Annex 2: Declaration of interests of GDG members V

Web Annex A: Tordrup D, van den Ham R, Leopold C, Joosse I, Glanville J, Kotas E, Mantel-Teeuwisse A. Systematic reviews for the update of the WHO Guideline on country pharmaceutical pricing policies. Utrecht: Utrecht University, 2020.

Web Annex B: Evidence-to-Decision tables.

Abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	health technology assessment
R&D	research and development
SDG	Sustainable Development Goal
TRIPS	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WTO	World Trade Organization

Foreword

Universal health coverage hinges on the right of everyone to access safe, quality-assured, effective and affordable medicines.

Unaffordable prices for medicines have become one of the most pressing concerns for patients and health-care systems in high-, middle- and low-income countries alike. WHO constantly hears from governments struggling with rising pharmaceutical prices when trying to provide population-wide access to life-saving health products for people in need, especially for people living with chronic diseases.

In 2019, the World Health Assembly expressed its serious concerns “about high prices for some health products, and inequitable access to such products within and among Member States, as well as the financial hardships associated with high prices which impede progress towards achieving universal health coverage”. Every year, out-of-pocket expenditures for medicines force approximately 100 million people into poverty. Worst of all, many people simply do not have access to potentially life-saving products many years after the discovery of these products. Such a situation is clearly not acceptable because medical innovation has little value to our society if people cannot access its benefits.

Strong country pharmaceutical pricing policies can improve the affordability of pharmaceutical products when carefully planned, carried out, and regularly checked and revised according to changing conditions. Over the years, the World Health Organization (WHO) has supported countries in the development of pharmaceutical pricing policies, including working with experts to formulate policy recommendations such as those presented in this publication.

This guideline has been revised to reflect the years of country experiences and the existing evidence on pricing policies. It contains recommendations for ten pricing policies commonly considered in countries to manage medicine prices, as well as pragmatic considerations for what is required to implement these policies according to the objectives and context of individual health systems. WHO will continue to work with countries in the coming years to develop sound pharmaceutical pricing policies, including by running workshops with country stakeholders and enabling information sharing through the Fair Pricing Forum.

As I write this Foreword, the world is grappling with the COVID-19 pandemic. The pandemic is a constant reminder that in a globalized crisis, we will only find solutions through global cooperation. Similarly, for an issue that is now affecting all countries, achieving affordable access to pharmaceutical products requires a collective effort from the global community to ensure that people in need of these products can achieve good health and exercise their human rights and fundamental freedoms. Those principles are clear – they are enshrined in United Nations conventions, they are reflected in the WHO constitution, in the agendas of the Millennium Development Goals and Sustainable Development Goals and they are, I believe, what the vast majority of national constitutions uphold. So, let us be guided by those principles to ensure that everyone has a right to access quality-assured pharmaceutical products.

Mariângela Simão,
Assistant Director General, Medicines and Health Products
World Health Organization

Acknowledgements

The World Health Organization (WHO) is grateful for the contributions from many individuals and organizations towards the development of this guideline.

This guideline was developed under the overall direction of Mariângela Simão (WHO Division of Access to Medicines and Health Products) and Clive Ondari (Department of Health Product Standards and Policy). Kiu Tay-Teo coordinated the work and processes for the development of this guideline with contributions from other WHO staff members (in alphabetical order): Adi al-Nuseirat, Melanie Bertram, Bernadette Cappello, Tania Cernushchi, Allison Colbert, Socorro Escalante, Johanna Fihman, Sarah Garner, Suzanne Hill, André Ilbawi, Swathi Iyengar, Houda Langer, Jean-Baptiste Nikiema, Dorina Pargari, Analía Porras, Andrew Rintoul, Aissatou Sougou, Klara Tisocki. .

The Secretariat gratefully acknowledges the technical guidance and inputs provided by all members of the following groups of contributors (in alphabetical order):

- **Guideline development group:** Lisa Bero, YingYao Chen, Amadou Moctar Dièye, Andrew Hill, Tanya Potashnik, Shadi Saleh, Vânia Cristina Canuto Santos, Sakthivel Selvaraj, Netnapis Suchonwanich, Fatima Suleman, Sabine Vogler, Jo Watson, Rasha Ziada.
- **Systematic review:** Mick Arber, Zaheer-Ud-Din Babar, Chris Bartlett, Ross Birtles, Kalipso Chalkidou, Jaime Espín, Julie Glanville, Iris Joosse, Eleanor Kotas, Christine Leopold, James Mahon, Aukje Mantel-Teeuwisse, Deborah Toppenberg-Pejcic, David Tordrup, Rianne van den Ham.
- **External reviewers:** Mohamed Amine, Sónia Caldeira, Maulik Chokshi, Jonathan Cushing, Asita de Silva, Helga Festøy, Claudia Furtado, Andrew Gray, Ana Holt, International Generic and Biosimilar Medicines Association (coordinated by Suzette Kox), International Federation of Pharmaceutical Manufacturers & Associations (coordinated by Fumie Griego), Saad Jaddoua, Erki Laidmäe, Siana Mapunjo, Faridah Aryani binti Md. Yusof, Suerie Moon, Yannis Natsis, Gergely Németh, Andrew Rintoul, Jonathan Rodrigues, Bettina Ryll, Cha-ongcin Sooksriwong.

Special thanks to Lisa Bero, Fatima Suleman and Sabine Vogler, who served as the Chairs of the guideline development group, for their commitment and expert guidance. We also thank the members of the systematic review team from Utrecht University and York Health Economics Consortium for their meticulous work under the overall guidance of Lisa Bero as the guideline methodologist.

The Secretariat is thankful to Rebekah Thomas, Susan Norris, Tomas Allen and the broader WHO Guideline Review Committee for their guidance on the processes for developing this guideline. Thanks also to Alma Alic for her guidance on ethics. Copy-editing was undertaken by Further Consulting (Kai Lashley).

This work was funded by the United Kingdom Department for International Development (DFID). DFID was not involved in the formulation of the guideline. The content of this guideline does not necessarily reflect the views of DFID.

Executive summary and recommendations

Affordable access to safe and efficacious pharmaceutical products is at the core of global efforts towards achieving universal health coverage. When attentively formulated and properly implemented, pharmaceutical pricing policies could contribute to improving patient access to essential medicines and other health products. Accordingly, the World Health Organization (WHO) has been given the mandates to support countries through guidance on the development of pricing policies for pharmaceutical products.

This guideline replaces the 2015 *WHO guideline on country pharmaceutical pricing policies*, revised to reflect the growing body of literature since the last evidence review in 2010. This update also recognizes country experiences in managing the prices of pharmaceutical products, including the increasing challenges of unaffordable prices for some health products widely experienced in many countries¹.

Using this guideline

This guideline defines pharmaceutical pricing policies as a set of written principles or requirements for managing the prices of pharmaceutical products, agreed or adopted by a public institution (e.g. a government authority), a group of purchasing organizations, or individual health services.

The **primary audience** for this guideline is policy-makers and decision-makers responsible for introducing and revising price-management policies to improve access to pharmaceutical products in countries of all income levels. Managers and personnel involved in the operational planning of procurement, distribution, and reimbursement of pharmaceutical products may also find this guideline useful.

This guideline recommends that countries apply **eight overarching principles** when formulating and implementing pricing policies for pharmaceutical products (Section 2). This guideline makes **specific recommendations** regarding ten pricing policies **countries may choose and adapt** according to the objectives, architecture and contexts of their respective health systems. This guideline also suggests a suite of **implementation considerations** countries should follow when operationalizing the recommendations.

How this guideline was developed

The development of this guideline followed the processes and requirements described in the second edition of the *WHO handbook for guideline development*. The recommendations were formulated by the guideline development group (GDG) that consisted of international experts with experiences in research and implementation of pharmaceutical pricing policies in countries. In developing the recommendations, the GDG considered the evidence appraised and synthesized in a systematic review commissioned by WHO. The GDG also considered additional qualitative evidence and information pertaining to the following factors: policy importance, evidence on desirable and undesirable effects, certainty of the evidence, overall balance of effects, generalizability, equity, acceptability, resources required, feasibility and long-term financial sustainability. The evidence was concisely summarized to inform judgements about overall advantages and

¹ As stated in resolution WHA72.8 adopted in 2019, the Seventy-second World Health Assembly was “[s]eriously concerned about high prices for some health products, and inequitable access to such products within and among Member States, as well as the financial hardships associated with high prices which impede progress towards achieving universal health coverage”.

disadvantages of each policy. Other contributors included a WHO steering group and external reviewers (Annex 1).

Summary of recommendations

Readers should refer to the definition, design and policy rationale; overview of evidence; and implementation considerations for each policy presented in individual sections of this guideline.

1. External reference pricing

Section 3.1

Conditional² recommendations for the policy

1.A. WHO suggests the use of external reference pricing under the following conditions:

- External reference pricing is used in conjunction with other pricing policies, including price negotiation;
- Adequate resources and skilled personnel are available to implement external reference pricing;
- Selection of reference countries or jurisdictions is based on a set of explicitly stated factors;
- Reference prices are obtained from verifiable data sources;
- Reference prices have accounted for all forms of discounts, rebates and taxes with a high degree of confidence; and
- Methods for determining prices follow a transparent and consistent process.

1.B. WHO suggests that countries undertake regular price revisions at pre-specified frequency when using external reference pricing.

1.C. WHO suggests that countries monitor the impacts of implementing external reference pricing on price, affordability and access to medicines.

2. Internal reference pricing

Section 3.2

Conditional recommendation for the policy

2.A. WHO suggests the use of internal reference pricing for generic and biosimilar medicines according to the principles of generic reference pricing³, under the following conditions:

- Internal reference pricing is used in conjunction with policies to promote the use of quality-assured generic or biosimilar medicines.
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria for pricing of generic and biosimilar medicines are explicitly evaluated and stated based on an established methodology.

² With a conditional recommendation, the guideline communicates the message that the effects of adhering to this recommendation (both desirable and undesirable) are subject to the conditions specified, and could be modified by a greater range of context-specific factors. This means that there is a need for involving relevant stakeholders to understand these conditions and factors before this recommendation can be adopted or adapted as policy.

³ Equivalence for the purpose of pricing set through the Anatomical Therapeutic Chemical Classification System 5th Level, with consideration to factors such as dose and pack size.

2.B. WHO suggests the use of internal reference pricing for medicines according to the principles of therapeutic reference pricing⁴, under the following conditions:

- Internal reference pricing is used in conjunction with other pricing policies.
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria, including therapeutic or dose equivalence, are explicitly evaluated and stated based on an established methodology.

3. Value-based pricing

Section 3.3

Conditional recommendation for the policy

3.A. WHO suggests the use of value-based pricing for medicines to support price setting, and reimbursement decision-making where appropriate, under the following conditions:

- Value-based pricing is used in conjunction with other pricing policies, such as price negotiation, internal and external reference pricing, and policies to promote the use of quality-assured generic and biosimilar medicines;
- Adequate resources and skilled personnel are available to implement value-based pricing;
- Value-based pricing using health technology assessment (HTA) must include an analysis on budget impact and affordability from the perspective of the payer and the patient;
- A well-established governance structure for value-based pricing using HTA is in place to ensure processes are transparent, and assessment reports and decisions are disseminated publicly;
- The method and perspective for determining value are explicit;
- Decisions and evidence should be periodically reviewed and re-assessed.

4. Mark-up regulation across the pharmaceutical supply and distribution chain

Section 3.4

Conditional recommendation for the policy

4.A. WHO suggests the use of mark-up regulation across the supply and distribution chain for medicines under the following conditions:

- Mark-up regulation should be used in conjunction with other pricing policies;
- Mark-up structure should be regressive, where mark-up rate decreases as the price increases (rather than a fixed percentage mark-up for all prices).

4.B. WHO suggests that countries consider using remuneration and mark-up regulation as incentives for supplying specific medicines (e.g. generic medicines, low volume medicines, reimbursable medicines) or to protect medicine access for specific patients or population groups (e.g. vulnerable groups, populations living in remote areas).

4.C. WHO suggests that countries ensure transparency of prices and methods when setting up mark-ups along the supply and distribution chain, including disclosure of any rebates and discounts.

4.D. WHO suggests regular review of mark-up regulation to protect patients from out-of-pocket expenditures.

⁴ Equivalence for the purpose of pricing set through Anatomical Therapeutic Chemical Classification System 4th Level based on clinical trial evidence of non-inferiority.

5. Promoting price transparency

Section 3.5

Conditional recommendation for the policy

5.A. WHO suggests that countries improve the transparency of pricing and prices through the following mechanisms:

- Sharing the net transaction prices of pharmaceutical products to relevant stakeholders, within and external to the country;
- Disclosing prices along the supply and distribution chain;
- Reporting publicly research and development (R&D) contributions from all sources;
- Communicating pricing and reimbursement decisions to the public.

5.B. WHO suggests that countries improve the transparency of pricing and prices through clear description of pricing approaches and their technical requirements.

6. Tendering and negotiation

Section 3.6

Conditional recommendation for the policy

6.A. WHO suggests that countries use tendering for pharmaceutical products under the following conditions:

- Price level should be considered alongside other criteria, including product quality, product characteristics, availability, supply security, supply reliability and charges along the supply chain;
- Tendering should be used in conjunction with other pricing policies to improve affordability and availability.

6.B. WHO suggests that countries use price negotiation to complement tendering as well as other pricing policies.

7. Promoting the use of quality-assured generic and biosimilar medicines

Section 3.7

Strong⁵ recommendations for the policy

7.A. WHO recommends that countries enable early market entry of generic and biosimilar medicines through legislative and administrative measures, with a view to encouraging early submission of regulatory applications, allowing for prompt and effective review, and ensuring these products are safe, efficacious and quality-assured.

7.B. WHO recommends that countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are informed by the cost of production⁶. These policies may include: internal reference pricing, mark-up regulation, direct price controls, tendering, promoting price transparency and lower patient co-payments.

⁵ With a strong recommendation, the guideline communicates the message that the desirable effects of adherence to this recommendation outweigh any potential undesirable effects. This means that in most situations the recommendation can be adopted as policy.

⁶ For the purpose of this guideline, costs of production include manufacturing costs, costs associated with research and development, regulatory processes and compliance, overheads and other business operation expenses.

7.C. To maximize uptake of generic and biosimilar medicines, WHO recommends that countries should implement, and enforce as appropriate, a suite of policies, including:

- Legislation to allow generic substitution by dispensers and, where applicable, biosimilar substitution;
- Legislative structure and incentives for prescribers to prescribe by International Nonproprietary Name;
- Dispensing fees that encourage use of low-price generic and biosimilar medicines;
- Regressive mark-up structure where lower rates of mark-ups are applied for higher-priced products, and appropriate financial and non-financial incentives for dispensers; and
- Education programmes for consumers and professionals regarding the quality, safety, efficacy and price of generic and biosimilar medicines.

8. Pooled procurement

Section 3.8

Conditional recommendation for the policy

8.A. WHO suggests the use of pooled procurement of medicines under the following conditions:

- Pooled procurement should be used in conjunction with other pricing policies, such as tendering and negotiation.
- Procurement processes are transparent and accompanied with high standard of governance.
- Financing for pooled procurement must be sustainable, predictable and timely with dedicated resources mobilized for a capitalization fund to stabilize initial regional pooled procurement efforts.

8.B. WHO suggests that countries consider initiation of pooled procurement of medicines under the following conditions:

- Pooled procurement is initiated with a clear understanding of the price and non-price benefits to be achieved (e.g. quality; availability; administrative efficiencies; bargaining power; improved capacity to forecast; collective technical expertise).
- Pooled procurement is initiated with a clear understanding of the regulatory policies, quality assurance, patent laws and relevant patent information, and financing processes in participating jurisdictions.

9. Cost-plus pricing for setting the price of pharmaceutical products

Section 3.9

Conditional recommendation against the policy

9.A. WHO suggests against countries using cost-plus pricing as a primary policy for setting the price of pharmaceutical products, given the current lack of transparency and the lack of an agreed framework among stakeholders regarding the inputs for price determination.

Conditional recommendation for the policy

- 10.A. WHO suggests that countries consider exempting essential medicines and active pharmaceutical ingredients from taxation.
- 10.B. WHO suggests that countries consider any tax reductions or exemptions, with measures to ensure that the policy results in lower prices of medicines to patients and purchasers.

Future update

An update to this guideline is planned in 2025, or earlier if a substantive body of evidence has accumulated, particularly on policies implemented in lower-income countries or where this guideline noted the certainty of evidence as low or very low. The GDG is mindful of several emerging pricing approaches and arrangements being explored or implemented in specific contexts. These approaches might be considered in future updates as the evidence evolves.

1. Pharmaceutical pricing policies and this guideline

1.1 Pharmaceutical pricing policies and their purpose

Pharmaceutical pricing policies are a set of written principles or requirements for managing the prices of pharmaceutical products, agreed or adopted by a public institution (e.g. a government), a group of purchasing organizations or individual health services. The overall objectives of pricing policies should explicitly focus on achieving affordable and equitable access to quality-assured pharmaceutical products for consumers and health systems, which should ensure value-for-money based on improved health outcomes at the population level, as well as maintaining supply security of high-quality products.

The importance of attaining affordable access to pharmaceutical products in the global efforts towards universal health coverage has long been recognized. Most recently, the United Nations Sustainable Development Goals (SDGs) has set SDG Target 3.8 as “financial risk protection, access to quality essential health-care services and access to safe, effective, quality and *affordable* essential medicines and vaccines for all” (emphasis added) (1). By extension, achieving this SDG is the responsibility of all levels of governments of Member States and the global community.

The commitment to ensure affordable access to essential pharmaceutical products globally is encouraging. Despite this commitment, however, high prices of pharmaceutical products continue to pose significant challenges in high- and low-income countries alike. It is well documented that high prices of pharmaceutical products have impaired the ability of many health-care systems to provide population-wide access. In the absence of insurance coverage, patients and their families often experience significant, if not catastrophic, financial hardship when in need of pharmaceutical products. Patients without any financial means could be denied access to beneficial pharmaceutical treatments altogether. Conversely, low prices could result in profit margins deemed insufficient for meeting commercial participants’ expectations for maintaining the scale and scope of business operation. This could potentially cause unavailability, supply interruptions or shortages of certain medicines, disrupt health service operations and lead to negative patient health outcomes.

Sound policies on the pricing of pharmaceutical products, in conjunction with other broader system-strengthening policies, could put health systems in good stead for improving access to affordable pharmaceutical products while ensuring continuity of supply.

1.2 WHO mandates

The World Health Organization (WHO) is mandated to support Member States through policy guidance on pricing of pharmaceutical products, notably in the following ways.

- World Health Assembly resolutions WHA61.21 and WHA62.16 on *Global strategy and plan of action on public health, innovation and intellectual property*, which requested actions on “promoting competition to improve availability and affordability of health products consistent with public health policies and needs”.

- World Health Assembly resolution WHA71(8) *Addressing the global shortage of, and access to, medicines and vaccines*, which requested a road map report that outlines the programming of WHO's work on access to medicines and vaccines for the period 2019–2023. Guidance on pricing policy is one of the key milestones specified in this road map: “policy guidance for more effective pricing policies to improve the affordability of essential health products to health systems and individuals”.
- World Health Assembly resolution WHA72(8) *Improving the transparency of markets for medicines, vaccines, and other health products*, which requested the Director-General, inter alia, “to continue supporting Member States, especially LMICs⁷, in developing and implementing their national policies relevant to the transparency of markets for health products”.
- Reports from WHO regional committees, resolutions and decisions relating to access to medicines, which have noted the importance of having robust policies on the pricing of health products (e.g. (2–7)).

1.3 Objective of this guideline

This document presents evidence-informed recommendations to guide countries on formulating and implementing policies relating to price management of, and access to, pharmaceutical products. This version of the guideline replaces the 2015 *WHO Guideline on country pharmaceutical pricing policies (8)*. It revises the recommendations of the previous guideline based on critical appraisal of the current body of evidence according to the standards and procedures for guideline development at WHO (see Section 1.7).

1.4 Using this guideline

This guideline encourages readers to interpret the evidence and consider its recommendations in light of the objectives, architecture and contexts of their respective health systems. Readers should also consider the applicability of this guideline to relevant subnational jurisdictions and authorities.

This guideline advises readers to consider all policy options that could affect the pricing, affordability and accessibility of pharmaceutical products, including policy options beyond the scope of this guideline. Examples include policies pertaining to selection of pharmaceutical products and intellectual property management. Coherence and consistency among related policies and their interlocking elements are needed to ensure that they are mutually reinforcing, and could prevent inefficiencies and unintended consequences.

This guideline encourages countries to adhere to the eight overarching principles described in Section 2 commonly applicable to the planning and implementing of all pricing policies for pharmaceutical products.

In line with the aspirations of the SDGs, this guideline urges users of this guideline, particularly those from government authorities, to take concerted and concrete actions through robust pricing policy towards achieving affordable access to pharmaceutical and other health products of established quality, efficacy and safety.

⁷ Low- and middle-income countries

1.5 Target audience

The primary audience for this guideline is policy-makers and decision-makers responsible for the introduction and revision of price-management policies to improve access to pharmaceutical products. Managers and personnel involved in the operational planning of procurement, distribution and reimbursement of pharmaceutical products may also find this guideline useful. This guideline may be beneficial for donors, development partners and other stakeholders assisting countries in development of the pharmaceutical sector and supply of pharmaceutical products.

This guideline is intended for use in countries of all income levels. References to low- and middle-income countries are intended to highlight the specific implementation needs of these settings where pricing regulations may require stronger support, but not to preclude its appropriateness for high-income settings.

1.6 Scope of content

This guideline focuses on two questions pertinent to the pricing of pharmaceutical products:

- I. Which pharmaceutical pricing policy or policies are effective in managing the prices of pharmaceutical products, with consideration given to their impacts on the volume, availability and affordability of these products?
- II. What contextual factors and implementation strategies may influence the effects of a specific pricing policy?

The guideline covers ten pricing policies that could be applied for setting, managing or influencing prices of pharmaceutical products, listed below. The definitions of individual policy interventions are presented under each section in Chapter 3.

1	External reference pricing
2	Internal reference pricing
3	Value-based pricing
4	Mark-up regulation across the pharmaceutical supply and distribution chain
5	Promoting price transparency
6	Tendering and negotiation
7	Promoting the use of quality-assured generic and biosimilar medicines
8	Pooled procurement
9	Cost-plus pricing for setting the price of pharmaceutical products
10	Tax exemptions or tax reductions for pharmaceutical products

This set of policies was identified based on the 2015 guideline and through consultations with experts on pharmaceutical pricing policies internal and external to WHO. Recommendations on four additional policies are included in this revised guideline: internal reference pricing; promoting price transparency; tendering and negotiation; and pooled procurement. This revised guideline has expanded the scope of the policy on

promoting the use of quality-assured generic medicines to also include biosimilar medicines. It has reframed the policy on “use of health technology assessment” as “value-based pricing” (using health technology assessment) because health technology assessment could be used for purposes other than pricing. The recommendations for pricing policies included in the 2015 guideline have been re-worded in the revised guideline for clarity and consistency, but the revised recommendations on these policies are broadly in line those in the 2015 guideline.

A pharmaceutical product is defined as “any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings” (9). It is commonly referred interchangeably with the terms drug, medicine or pharmaceutical. For the purpose of this guideline, the scope includes medicines (both small molecules and biological products) and vaccines for human use.

1.7 Method of guideline development

The development of this guideline followed the processes and requirements described in the second edition of the *WHO handbook for guideline development* (10).

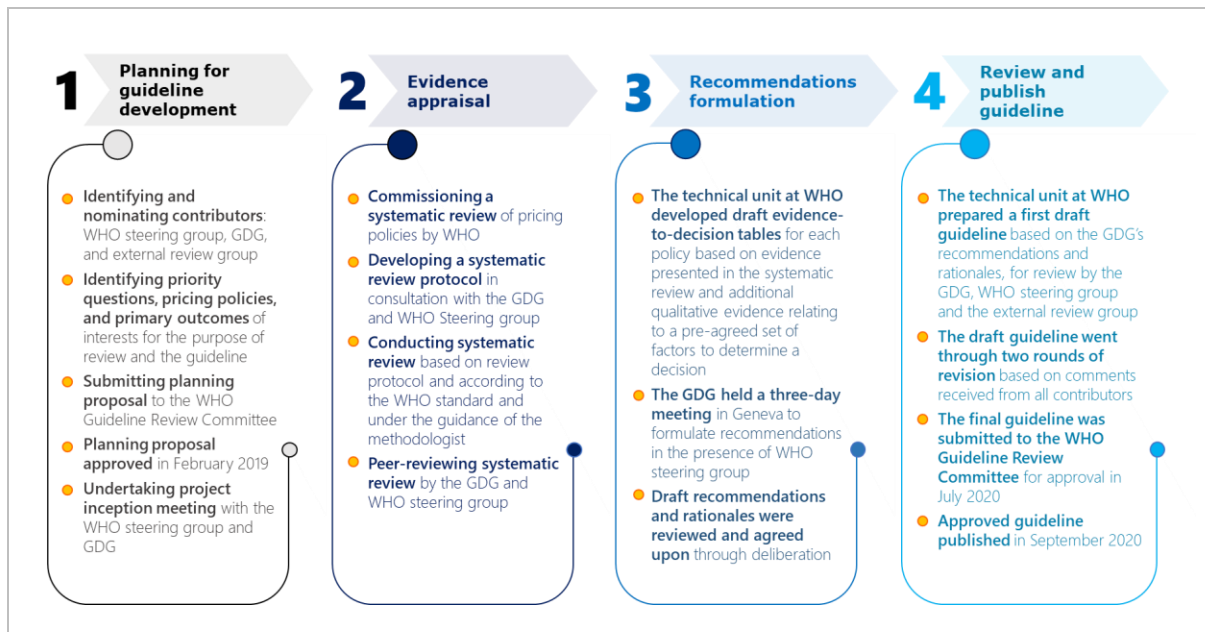
The process comprised four broad steps: (i) planning for guideline development; (ii) evidence appraisal; (iii) recommendations development; and (iv) reviewing and publication of the guideline document. These steps were undertaken between January 2019 and September 2020, explained below and illustrated in Fig. 1.1 (p.5).

- i. **Planning for guideline development:** The technical unit at WHO headquarters Department of Health Products Policy and Standards worked with personnel at WHO regional offices and experts to identify three groups of contributors required for guideline development: WHO steering group, guideline development group (GDG) and external review group. Members of these groups are content experts, methodologists and representatives of potential stakeholders (see Annex 1). The GDG and WHO steering group were involved in identifying priority questions and outcomes. A planning proposal outlining the priority questions, outcomes and processes was submitted and approved by the WHO Guideline Review Committee. The technical unit conducted a project inception meeting with the GDG and WHO steering group to confirm the scope and details of guideline development.
- ii. **Evidence appraisal:** WHO issued a Request for Proposal and commissioned a team of researchers to undertake systematic literature search and critical appraisal of the evidence pertaining to the scope of this guideline. The proposal from the Utrecht Centre for Pharmaceutical Policy and Regulation at Utrecht University, in collaboration with York Health Economics Consortium at the University of York, was selected. The systematic review team developed a review protocol in consultation with the GDG and WHO steering group. Systematic review was conducted under the guidance of the methodologist and in accordance with applicable WHO standards. This includes applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology when appraising evidence for the preparation of the evidence profiles related to each pricing policy option.
- iii. **Recommendations development:** The GDG held a three-day meeting in Geneva in February 2020 to formulate the recommendations on each of the policy options. In preparation for this meeting, the

technical unit sent the evidence report prepared by the systematic review team [Web Annex A] with the evidence-to-decision tables [Web Annex B]. These tables summarize information pertaining to the following factors: policy importance; evidence on desirable and undesirable effects; certainty of the evidence (based on GRADE); overall balance of effects; generalizability; equity; acceptability to government authorities, patients and community; resources required; feasibility; and long-term financial sustainability. The evidence-to-decision tables provide concise and structured summaries of the best available research evidence and additional qualitative information to inform the GDG's judgements about the overall advantages and disadvantages of each policy. All recommendations were made by consensus.

- iv. **Reviewing and publication of guideline:** Based on the GDG's recommendations and rationales, the technical unit prepared a draft of the guideline document, subsequently reviewed by the GDG, WHO Guideline steering group and external reviewers. Following two rounds of revision, the technical unit made a formal submission to the WHO Guideline Review Committee for approval. The guideline document was approved in August 2020.

Fig. 1.1: Guideline development process



1.7.1 Management of conflicts of interest

Declarations of interest were collected from every member of the GDG, and members of the external review group if their comments do not represent an institution. The technical unit assessed all declared interests, sought advice from the WHO Compliance, Risk Management and Ethics Office, to determine if an expert should be recused from participating in the development of the guideline to avoid any actual or perceived conflict of interest. A complete review of this process is found in Annex 2.

1.7.2 Funding

This work was funded by the United Kingdom Department for International Development (DFID). DFID was not involved in the formulation of the guideline. The content of this guideline does not necessarily reflect the views of DFID.

1.8 Dissemination plan

The guideline will be disseminated as an electronic publication on the WHO website dedicated to pharmaceutical pricing, availability and affordability. Plain language summaries will be developed from this guideline to reach a broader audience. Furthermore, a companion publication that describes and illustrates specific country pharmaceutical pricing policies will be developed to facilitate sharing of country experiences in implementing different policies. The guideline and its derivative products are developed in English. In collaboration with WHO regional offices and as necessary, these resources will be translated into other WHO official languages for wider dissemination.

Through WHO regional and country offices, the technical unit at headquarters will notify relevant government authorities about the guideline and its derivative products. Dissemination will also be encouraged through WHO collaboration with international organizations and associations. In coordination with the WHO Communications Department, the media will be notified of the new guideline through a press release.

Countries will be supported to implement the guideline recommendations through capacity-building activities, including webinars and workshops at key conferences (e.g. the WHO Fair Pricing Forum).

1.9 Updating and user feedback

The technical unit will continue to monitor research and policy trends relating to the pricing of pharmaceutical products globally, including priority research areas specified in Chapter 4. An update would be performed in 2025 or earlier if a substantive body of evidence has accumulated, particularly on policies implemented in lower-income countries or where this guideline noted the certainty of evidence as low or very low.

Future updates to the guideline would also benefit from an evaluation of the clarity of its recommendations and ability for users to translate the information into implementation. The technical unit will undertake an update prior to 2025 if there is substantive feedback on the usability of the guideline.

2. Principles for formulating and implementing pharmaceutical pricing policies

WHO recommends that countries adhere to eight overarching principles when formulating and implementing pricing policies for pharmaceutical products.

i. Clear purpose

The overall objectives of pricing policies should explicitly focus on achieving affordable and equitable access to quality-assured pharmaceutical products for consumers and health systems, which should ensure value-for-money based on improved health outcomes at the population level, as well as maintaining supply security of high-quality products.

ii. Specificity to context

Pricing policies should be selected with specific consideration given to the contextual factors of the local health system, including its structure, as well as the supply and demand of pharmaceutical products.

iii. Policy coherence

Pricing policies should be used in combination with a coherent set of technical specifications for managing prices along the supply and distribution chain, and at different time points of a product life cycle. Since a country's pharmaceutical sector interacts with the health sector among others, wider principles need to be identified and considered when choosing between policy options.

iv. Integrated framework

Pricing policies should be integrated with the legislative framework of health and other related sectors, administrative structures and technical capacity, with a view to achieving a supportive environment for policy implementation.

v. Transparency

The processes, technical methods, decisions and outcomes of implementing pricing policies should be transparently communicated to relevant stakeholders, including suppliers and consumers.

vi. Policy relevance through monitoring and review

The relevance of pricing policies must be maintained through regular monitoring and reviews of the extent to which the policies have achieved the objectives, not only on prices but also their effect on other outcomes such as out-of-pocket expenditures and availability of essential medicines. Where required, amendments to the pricing policies must be informed by data and experiences.

vii. Compliance and enforcement

Where pricing regulations are enacted or policy guidance is issued, compliance should be encouraged through appropriate incentives, monitored through routine data and information gathering and enforced through proportional penalties to create deterrence for policy breaches.

viii. Collaboration

The effectiveness of country pricing policies is strengthened through collaboration with health systems in other countries and stakeholders, including information exchange and skill transfers about policies, the pharmaceutical market and impacts on price and access.

3. Evidence and recommendations

3.1 External reference pricing

Definition, design and policy rationale

What is the policy? External reference pricing (also known as international reference pricing) refers to the practice of using the price of a pharmaceutical product in one or several jurisdictions to derive a benchmark or reference price. Note that jurisdictions refer to countries, regions or other organized purchasing authorities.

Why is the policy implemented? The purpose of external reference pricing is to assess the appropriateness of prices of pharmaceutical products based on the selected benchmark prices, with a view to setting or negotiating the price of the product in a given jurisdiction. Both single-source or multisource supply products could be subject to external reference pricing, but external reference pricing has been used particularly for the pricing of single-source on-patent medicines. Depending on the design of the policy, external reference pricing tries to ensure that the jurisdiction does not pay more than other comparable jurisdictions, or pay less when the jurisdiction has lower income. Prices derived from external reference pricing may not be affordable to a jurisdiction.

How is the policy implemented? Selection of appropriate and comparable country benchmarks is one of the main steps of implementing external reference pricing. Criteria for selection may include geographical proximity, country income, availability of medicines, country of origin and market size. Prices would be compared at common points along the distribution chain, such as ex-manufacturer price. Calculation methods for converting benchmark prices into the final price vary among countries using external reference pricing. These include lowest price, average price, average of the lowest prices, and price adjusted for market factors such as market size and purchasing power parity. External reference pricing may be applied to single-source products, or less commonly, multisource supply products.

How commonly is the policy used? External reference pricing is a policy widely adopted in many European countries (11), as well as in high- and middle-income countries of other regions (e.g. Brazil, Egypt, Saudi Arabia, Thailand, Turkey, the United Arab Emirates) (12, 13). Other countries are also considering the implementation of external reference pricing (14, 15).

Conditional recommendations⁸ for external reference pricing

1.A. WHO suggests the use of external reference pricing under the following conditions.

- External reference pricing is used in conjunction with other pricing policies, including price negotiation.
- Adequate resources and skilled personnel are available to implement external reference pricing.
- Selection of reference countries or jurisdictions is based on a set of explicitly stated factors.
- Reference prices are obtained from verifiable data sources.

⁸ With a conditional recommendation, the guideline communicates the message that the effects of adhering to this recommendation (both desirable and undesirable) are subject to the conditions specified, and could be modified by a greater range of context-specific factors. This means that there is a need for involving relevant stakeholders to understand these conditions and factors before this recommendation can be adopted or adapted as policy.

- Reference prices have accounted for all forms of discounts, rebates and taxes with a high degree of confidence.
 - Methods for determining prices follow a transparent and consistent process.
- 1.B. WHO suggests that countries undertake regular price revisions at pre-specified frequency when using external reference pricing.
- 1.C. WHO suggests that countries monitor the impacts of implementing external reference pricing on price, affordability and access to medicines.

Justifications

- The GDG recognized the extensive experiences in using external reference pricing across jurisdictions with different health system settings. It also acknowledged a lack of evidence from comparative studies conducted to the standards of the WHO-commissioned systematic review. Considering the totality of evidence and information, however, the GDG reached a consensus that the balance of effects of external reference pricing was in favour of implementing the policy.
- Despite the relative conceptual simplicity of external reference pricing, the GDG recognized the complexity of implementing so-called best-practice external reference pricing, particularly when prices of medicines are often not transparent and their reporting not harmonized. For this reason, the GDG emphasized the importance of having adequate resources and skilled personnel to implement external reference pricing, especially in low- and middle-income countries.

Overview of evidence

Balance of effects

No controlled studies were identified in the systematic review.

Other reviews (16–18) that included uncontrolled studies, simulation modelling and descriptive studies suggested potentially substantial savings for public payers through lower prices at least in the short term. Effect size was dependent on policy design: reference jurisdictions, calculation method, update frequency and availability of price information accurately reflecting the net transaction price.

Qualitative evidence suggests potential launch delays and product withdrawals in countries expected to list such products at lower prices, to avoid prices being referenced to these countries and potential parallel exports to higher-priced countries (19). However, the evidence did not consider whether products would be launched in various countries at different prices at the same time in the absence of external reference pricing. Some commentators also suggest that external reference pricing might result in price convergence internationally due to interlinking of prices (16, 20). However, the evidence of this was limited and indirect.

On balance, existing evidence suggests that external reference pricing is likely to deliver more desirable than undesirable effects, as indicated by: some (un-appraised) evidence on price reduction at least in the short term (albeit limited in the quantity and quality of evidence); a lack of robust evidence attributing undesirable effects to external reference pricing, including launch delays or product withdrawals in lower-income countries by the manufacturers to avoid prices being referenced; and wide adoption or consideration of external reference pricing as one part of the overall pricing policy.

Generalizability	Evidence from uncontrolled studies, simulation modelling and descriptive studies was based on data and information from high- and upper-middle-income countries. There is no evidence from lower-middle-income and low-income countries.
Equity	Some commentators suggest that higher-income countries might refer to the lower prices in lower-income countries, potentially “nurtur[ing] inequalities among countries, as wealth differences between referrer and referenced country proliferate” (19). However, there is no empirical evidence to suggest the presence of such practice.
Acceptability	Wide adoption of external reference pricing suggests it is acceptable to government authorities.
Resource use	Implementation of external reference pricing requires skilled personnel for data collection and management of the policy. These include developing a methodology, standardizing price information from reference jurisdictions, and revising prices regularly to reflect changes in the reference prices in other markets.
Feasibility	The feasibility of implementation in lower-income countries is highly dependent on the availability and reliability of price information, which could be hampered by confidential pricing agreements implemented in many countries, timing of product launches and wide price variability (12).
Sustainability	Only short-term impacts on price and expenditure were described in the literature. Long-term financial sustainability is unclear.

Implementation considerations

- Effective operation of external reference pricing policy should consider the following factors:
 - a. sufficient technical capacity, database management, monitoring and evaluation;
 - b. a governance structure supported by transparent legislation and appeals process;
 - c. an international collaborative network that promotes price sharing and skill transfers;
 - d. overall system readiness, including gaining political support.
- Methodology of external reference pricing should consider the following factors:
 - a. comparability of price types along the supply and distribution chain (i.e. ex-manufacturer, ex-wholesaler, pharmacy and consumers);
 - b. number of jurisdictions included to obtain reference prices;
 - c. comparability of referenced jurisdictions, such as market sizes, national income, purchasing power;
 - d. legislative measures and operational procedures for methodologically challenging situations, such as availability of data only from non-comparable jurisdictions, missing data and currency fluctuations; and
 - e. use for products lacking sufficient competition (to which external reference pricing is most often applied), with prices determined through external reference pricing being used as the point of reference for further price negotiation.

3.2 Internal reference pricing

Definition, design and policy rationale

What is the policy? Internal reference pricing refers to the practice of using the prices of a set of pharmaceutical products that are therapeutically comparable and interchangeable, to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement rate of a product. Therapeutic comparability and interchangeability are determined by chemical entity and pharmacological class according to the Anatomical Therapeutic Chemical Classification System (ATC)⁹ or by therapeutic indication.

Why is the policy implemented? The purpose of internal reference pricing is to harmonize prices of products with the same or similar therapeutic effects, with a view to reducing price variability among comparable products. It may also encourage competition among products with the same or similar therapeutic effects.

How is the policy implemented? A main step of implementing internal reference pricing is selecting groups of therapeutically comparable and interchangeable products so that prices could be benchmarked. Reference price could be set through ATC 5th Level where the active pharmaceutical ingredients of different products have the same chemical substance, with consideration to factors such as dose and pack size. For therapeutic equivalence at ATC 4th Level for the purpose of setting the reference price¹⁰, assessment of clinical trial evidence of non-inferiority and therapeutically-equivalent dose could be considered, with consideration given to factors such as frequency of dose administration. Prices of these products would be compared and set according to evidence of equivalence and at common points along the distribution chain.

How commonly is the policy used? Many countries have employed internal reference pricing for linking the prices of (closely) substitutable medicines i.e. generic, biosimilar, or therapeutically equivalent or closely-substitutable products (21, 22). In addition to setting prices, internal reference pricing has also been used to set the reimbursement rates of closely substitutable products, in health-care systems with public pharmaceutical insurance, or where reimbursements from private insurers are regulated. For example, patients preferring a branded product would incur the price difference between the branded and reference generic or lowest priced product.

Conditional recommendations for internal reference pricing

2.A. WHO suggests the use of internal reference pricing for generic and biosimilar medicines using the principles of generic reference pricing¹¹, under the following conditions.

- Internal reference pricing is used in conjunction with policies to promote the use of quality-assured generic or biosimilar medicines (Section 3.7).
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria for pricing of generic and biosimilar medicines are explicitly evaluated and stated based on an established methodology.

⁹ In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are grouped at five different levels according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

¹⁰ The active pharmaceutical ingredients of different products have the same chemical, pharmacological or therapeutic effect.

¹¹ Equivalence for the purpose of pricing set through ATC 5th Level, with consideration to factors such as dose and pack size.

2.B. WHO suggests the use of internal reference pricing for medicines according to the principles of therapeutic reference pricing¹², under the following conditions.

- Internal reference pricing is used in conjunction with other pricing policies.
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria, including therapeutic or dose equivalence, are explicitly evaluated and stated based on an established methodology.

Justifications

- The GDG considered the body of literature on internal reference pricing assessed in the WHO-commissioned systematic review; the evidence suggests moderate to large reductions in price of medicines when used in conjunction with generic substitution policies and increased utilization of lower cost or fully reimbursed generic medicines. The GDG reached a consensus that the overall balance of effects favours the policy, particularly with consideration of acceptability and financial sustainability to government authorities, patients and the community.
- Despite a lack of evidence relating to the pricing of biosimilar medicines, the GDG considered the policy principles of internal reference pricing as applicable to biosimilar medicines. The GDG envisaged the importance of the future market for biosimilar medicines, and anticipated that policies on interchangeability, switching and substitution will be resolved.

Overview of evidence

Balance of effects	<p>Twenty-six studies were included in the systematic review: 11 on generic reference pricing (i.e. ATC 5th level) (23, 24, 33, 25–32); 5 on related policies where prices of generic products were set at a proportion of the price of the originator product according to the sequence of market entry (34–38); 8 on therapeutic reference pricing (i.e. ATC 4th Level) (39–46); and 2 on a mix of generic and therapeutic reference pricing (47, 48).</p> <p>On balance, generic reference pricing and therapeutic reference pricing are likely to deliver more desirable than undesirable effects, as indicated by evidence of price reduction and improved expenditure efficiency (through seemingly higher volume) at least in the short term, but could be longer term (up to 10 years of observation); a lack of robust evidence to attribute generic reference pricing and therapeutic reference pricing to undesirable effects, including switching to therapeutically similar on-patent products not subject to price regulations; and wide adoption or consideration of generic reference pricing and therapeutic reference pricing as one part of the overall pricing policy.</p>
Generalizability	<p>Evidence from uncontrolled studies was based on data and information from high- and middle-income countries from many regions globally. There is no evidence from low-income countries.</p>
Equity	<p>There is no formal evidence examining the impact of generic reference pricing or therapeutic reference pricing on equity, however, lower costs of treatments arising from generic reference pricing and therapeutic reference pricing could enhance equity because of better affordability and broader access.</p>

¹² Equivalence for the purpose of pricing set through ATC 4th Level based on clinical trial evidence of non-inferiority.

Acceptability	Acceptable to government authorities as suggested by wide adoption of the policy. It is likely to be acceptable to patients and community if internal reference pricing is accompanied by rules that retain the rights of the patients to choose between lower-priced generic or therapeutic-equivalent products.
Resource use	Implementation of therapeutic reference pricing requires technical expertise in determining therapeutic equivalence; it also requires maintenance of a price database to ensure regular revision of prices in accordance with changes in market prices arising from price competition.
Feasibility	Feasibility of implementing generic reference pricing or therapeutic reference pricing is dependent on low- and middle-income countries' capacity to implement generic substitution policies, or substitution policies for medicines belonging to the same therapeutic group, which have been noted as an important co-intervention that effects price impacts of internal reference pricing.
Sustainability	Existing evidence suggests that both generic reference pricing and therapeutic reference pricing could have longer-term (2–10 years) impacts on price, although observed impacts were less substantial over time (26, 47).

Implementation considerations

- Effective operation of internal reference pricing policy requires:
 - a. strong national regulatory authorities to assure quality of generic and biosimilar medicines, including established post-market surveillance;
 - b. concurrent implementation of policies to promote the use of quality-assured generic and biosimilar medicines, including but not limited to policy options presented in Section 3.7;
 - c. public health campaigns for patients and providers with respect to use of generic medicines, with a view to building trust and acceptance;
 - d. a clear understanding of the incentives in the supply chain, including financial incentives to service providers, that may moderate or enhance the overall effects of internal reference pricing;
 - e. forward-looking policy design in anticipation of growing demand for biosimilar medicines with market characteristics likely to mirror that of generic medicines.
- Internal reference pricing methodology and processes should consider the following factors.
 - a. For therapeutic reference pricing, therapeutic equivalence is determined through established scientific methods (e.g. supporting evidence from pharmacokinetic and pharmacodynamic studies).
 - b. Where applicable (e.g. health-care systems with reimbursement), methodology, policy and legislative processes for specific circumstances should be clearly defined (e.g. when considering the delisting of a product that does not comply with internal reference pricing or when authorizing the use of products priced higher than the internally referenced price because of specific patient clinical needs).
 - c. Prices of generic medicines could be cross-checked with the prices of raw materials, with a view to informing the pricing by the cost of production (See recommendations under Section 3.7).

3.3 Value-based pricing

Definition, design and policy rationale

What is the policy? Value-based pricing is an approach that aims to set prices for pharmaceutical products based on the measured and quantified “value”¹³ or worth that patients and health systems attribute to pharmaceutical products.

Why is the policy implemented? Theoretical arguments suggest that value-based pricing might encourage profit-maximizing companies to innovate and produce medicines with attributes that society and governments value most. It is, however, important to note that a range of public investments and incentives (e.g. research and development (R&D) infrastructure and workforce investments, tax credits or reductions, regulatory flexibilities) have been implemented to stimulate innovation.

How is the policy implemented? Value assessment may be performed through health technology assessment (HTA), which refers to the systematic evaluation of properties, effects, and/or impacts of health technology through a multidisciplinary process evaluating the social, economic, organizational and ethical issues of a health intervention or health technology, with a view to informing policy decision-making (49). In determining the price, the technical methodology often constrains the “value”, and by extension the price, by a willingness-to-pay threshold or budget that is explicit (e.g. the United Kingdom) or implicit (e.g. Australia), or a frontier for efficiency optimization (e.g. Germany). HTA-informed value-based pricing is most commonly used for informing the pricing of on-patent or single-sourced medicines and is often used in conjunction with other pricing policies in countries, including negotiation and reference pricing. It is worth noting that HTA has been applied for broader purposes¹⁴ other than setting the price of medicines (50). HTAs are also not limited to economic evaluation of health technology (i.e. cost–effectiveness analysis); they often encompass budget impact analysis to better inform the full opportunity costs of funding decisions (i.e. “value” from a system perspective). HTAs have been used as a tool to inform broad health system reform and divestment decisions.

How commonly is the policy used? Many countries globally, in collaboration with professional organizations or networks, have initiated or established formal or informal processes or dedicated agencies for undertaking HTAs, with a view to informing coverage of health technologies, including their prices and amounts of reimbursement according to the health technologies’ value. However, value-based pricing informed by HTA is applied systematically and formally linked to coverage decisions only in several high-income countries (e.g. Australia, the United Kingdom, the Republic of Korea), and a very limited number of

¹³ The measurement of “value” involves the so-called “preference elicitation methods”, quantified using summary metrics such as quality-adjusted life years (QALYs) or disability-adjusted life-years (DALYs).

¹⁴ HTA may be applied to support decision-makers in numerous instances, among which: (i) implementing broad public health programmes; (ii) priority setting in health care; (iii) including a new medicine into a reimbursement scheme; (iv) identifying health interventions that produce the greatest health gain and offer value for money; (v) setting prices for medicines and other technologies based on their cost–effectiveness; (vi) formulating clinical guidelines; (vii) advising on the organizational systems within which health care is provided; (viii) supporting decisions on diagnostics and medical equipment; (ix) improving resource allocation and distribution particularly for high-cost technologies; (x) helping managers of hospital health-care networks and other health-care organizations; (xi) making decisions regarding technology acquisition or adoption; and (xii) informing clinicians, providers, and patients about the proper use of health-care interventions for particular health problems.

middle-income countries (e.g. Thailand). This reflects the considerable human and financial resources required for its implementation.

Conditional recommendations for value-based pricing

3.A. WHO suggests the use of value-based pricing for medicines to support price setting, and reimbursement decision-making where appropriate, under the following conditions.

- Value-based pricing is used in conjunction with other pricing policies – such as price negotiation, internal and external reference pricing – and policies to promote the use of quality-assured generic and biosimilar medicines.
- Adequate resources and skilled personnel are available to implement value-based pricing;
- Value-based pricing using health technology assessment must include an analysis of budget impact and affordability from the perspective of the payer and the patient.
- A well-established governance structure for value-based pricing using health technology assessment is in place to ensure processes are transparent, and assessment reports and decisions are disseminated publicly.
- The method and perspective for determining value are explicit.
- Decisions and evidence should be periodically reviewed and re-assessed.

Justifications

- The GDG acknowledged the very limited evidence from comparative studies conducted to the standards of the WHO-commissioned systematic review. While considering overall balance of effects in favour of value-based pricing, the GDG emphasized that the effects are likely to be highly variable depending on the robustness of value assessment using HTA. In particular, the GDG underscored the necessity for assessing budget impacts and affordability for health systems and patients to better inform the full opportunity costs of funding decisions (i.e. “value” from a system perspective). The GDG cautioned that unconstrained value-based pricing could lead to unaffordable prices detrimental to the sustainability of health systems.
- The GDG recognized that implementing best-practice value-based pricing using HTA poses significant feasibility challenges, particularly in health systems not having the necessary financial and human resources for managing the governance and technical complexity of this policy option. The GDG acknowledged the progress made in recent years in establishing institutions for undertaking HTA, and evidence-informed decision-making more broadly, in line with World Health Assembly resolution WHA67.23 *Health intervention and technology assessment in support of universal health coverage (51)*. The GDG believed such efforts in establishing HTA should continue, but the extent to which value-based pricing should be implemented as a pharmaceutical pricing policy must be aligned with the maturity of the HTA system, particularly in considering value domains other than cost–effectiveness (e.g. quality, social, ethical).

Overview of evidence

Balance of effects	Three studies on value-based pricing met the inclusion criteria of the systematic review (47, 52, 53). Pricing or decision-making processes based on value, as determined through HTA, is likely to deliver more desirable than undesirable effects, as indicated by: well accepted theoretical rationale of the approach; a lack of robust evidence to attribute undesirable effects to value-based pricing/HTA, including launch delays due to technical and process complexities; wide adoption of value-based pricing/HTA as the main pricing policy or a supporting pricing policy. However, desirable effects are likely to be dependent on the capacity of the health systems to manage the technical and process complexities of value-based pricing and HTA.
Generalizability	Evidence included in the systematic literature review was exclusively from high-income countries, often based on a small subset of medicines and with significant methodological shortcomings. The generalizability of the findings is therefore unclear.
Equity	HTA often uses composite metrics such as quality- or disability-adjusted life years (i.e. QALYs or DALYs) as the measures for quantifying comparative value of a health technology. Numerous commentaries and individual cases in published literature (e.g. (54–56)) have highlighted that the application of these measures have the potential or actual negative impacts on health equity (e.g. discrimination on age and severe illness).
Acceptability	The concept and approach of value-based pricing and HTA seem to have received attention and some acceptance among governments, particularly in higher-income countries. However, the significant human and financial resources required for institutionalizing HTA and formalizing value-based pricing could be strong barriers to acceptance (57). Patients and the community may object to pricing or reimbursement decisions that fail to fully capture social values or judgements on social values.
Resource use	Value-based pricing informed by HTA requires considerable human and financial resources to manage the technical, administrative and governance aspects of implementation. It is data intensive, requiring robust IT infrastructure and reliable data.
Feasibility	Variable depending on existing capacity, including data availability, to undertake value assessment through HTA. An increasing number of new medicines do not have well-established evidence to inform their clinical and economic values at the time when they are being considered for regulatory and reimbursement approvals, posing significant challenges in applying value-based pricing even in the countries with well-established HTA authorities.
Sustainability	Existing health-care systems featuring the use of value-based pricing through HTA in high-income countries suggest that once established and with timely reform, such institutions and processes are sustainable. However, it is unclear what the financial implications of such an approach are, compared to possible policy alternatives.

Implementation considerations

- Effective operation of value-based pricing using HTA should consider the following factors.
 - a. Value-based pricing using HTA should be implemented in the context of maximizing health outcomes (cf. other conceptualizations of “value” such as innovativeness, industry development, public expectation).
 - b. Countries should consider value-based pricing and HTA approaches suitable for local decision-making structures and technical capacity.
 - c. Countries should collaborate to promote exchange of information, and if appropriate, develop common requirements for value-based pricing using HTA.
 - d. Countries could take a stepwise approach to develop legislative and technical capacity to take full advantage of the potential utility of value-based pricing using HTA in pharmaceutical price setting.
 - e. The legislative and administrative framework for undertaking value-based pricing using HTA should clearly define the roles and responsibilities of decision-makers and other stakeholders, as well as the process of decision-making.
 - f. Horizon scanning may be performed in anticipation of future medicines and technologies, particularly those likely to have significant public health impacts.
- Value-based pricing using HTA may consider the following approaches and methodology:
 - a. reviewing the applicability of reports from other countries with similar health system settings and adapting the methodology and findings only if relevant to the health system settings under consideration;
 - b. reviewing reports on value-based pricing using HTA submitted by companies with consideration to applicability to the local context;
 - c. evaluating the availability and completeness of the evidence on the new medicine and any companion technology at the time of value assessment; and
 - d. undertaking value-based pricing using HTA based on local information (e.g. clinical service and financing models) and data (e.g. demographic structure, costs).

3.4 Mark-up regulation across the pharmaceutical supply and distribution chain

Definition, design and policy rationale

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

Why is the policy implemented? Mark-up regulation is intended to reduce the variability of prices along the supply and distribution chain through clear pricing rules. This could enhance price transparency for consumers and health systems and provide greater predictability for expenditure management. Well-structured mark-up regulations might enhance efficiency and incentivize the supply of certain products (e.g. low-volume products) if the mark-up levels closely correlate with the costs and profit expectation.

How is the policy implemented? A fixed or percentage mark-up could be specified at any point along the supply chain (e.g. mark-up at ex-factory price level; and incorporating fee-for-service remuneration into the mark-up, such as fees for dispensing or meeting a pre-specified service quality standard). Other types of price regulation, such as direct price controls, could be set at any point along the supply chain, with a view to specifying the maximum prices, also referred to as price caps or price ceilings.

How commonly is the policy used? Many health-care systems have regulated prices of pharmaceutical products by setting price and mark-up thresholds across the pharmaceutical supply and distribution chain. These include policies that specify zero mark-up for medicines supplied at public facilities (e.g. China, Kuwait), setting maximum mark-up for medicines supplied at privately-owned retail pharmacies (e.g. Kuwait, Oman), fixed or percentage mark-up for most stages of distribution (e.g. Australia, Brazil, Jordan, Lebanon, Mozambique, Syrian Arab Republic and Tunisia), fixed or maximum fees or prices, or a combination policy (e.g. South Africa's combination of regulations that comprise a single exit price at the ex-factory level with annual adjustment, a ban on volume discounts or bonuses, and a maximum dispensing fee based on regressive margins for pharmacists and a separate maximum dispensing fee for non-pharmacist licensed dispensing practitioners (58–60).

Conditional recommendations for mark-up regulation

4.A. WHO suggests the use of mark-up regulation across the supply and distribution chain for medicines under the following conditions.

- Mark-up regulation should be used in conjunction with other pricing policies.
- Mark-up structure should be regressive, where mark-up rate decreases as the price increases (rather than a fixed percentage mark-up for all prices).

4.B. WHO suggests that countries consider using remuneration and mark-up regulation as incentives for supplying specific medicines (e.g. generic medicines, low volume medicines, reimbursable medicines) or to protect medicine access for specific patients or population groups (e.g. vulnerable groups, populations living in remote areas).

4.C. WHO suggests that countries ensure transparency of prices and methods when setting up mark-ups along the supply and distribution chain, including disclosure of any rebates and discounts.

4.D. WHO suggests regular review of mark-up regulation to protect patients from out-of-pocket expenditures.

Justifications

- The GDG considered the body of literature and extensive country experiences of implementing mark-up regulations across the pharmaceutical supply and distribution chain. The GDG noted the considerable variations in the structures of mark-ups and remuneration and recognized that the scope and design of mark-up regulation, if not well-designed, might result in undesirable effects, such as potential price convergence towards maximum regulated prices that are higher than prices that could have been achieved through greater competition, as well as potential supplier-induced demand for products with higher mark-up margins. Nonetheless, on balance, the GDG reached a consensus favouring the policy because of evidence of positive effects, and that potential undesirable effects could be mitigated through well-designed regulation (e.g. by avoiding fixed percentage mark-ups).
- The GDG recognized that the feasibility of implementing mark-up regulations across the pharmaceutical supply and distribution chain depends greatly on the complexity of policy design, as well as the complexity and visibility of the supply and distribution chain. The GDG emphasized that consistent and clearly specified mark-up regulation is a prerequisite for achieving price transparency. Through regular review, this in turn could inform better policy design to enhance affordability for health systems and patients.

Overview of evidence

Balance of effects	<p>The systematic review included 12 studies for full appraisal: 7 on mark-up regulation (32, 47, 61–65) and 5 on setting maximum retail or reimbursement prices (32, 46, 66–68).</p> <p>Mark-up regulation across the pharmaceutical supply and distribution chain is likely to deliver more desirable than undesirable effects, as indicated by observed statistically significant reduction in price; and stable or growing demand for the medicines within price regulation. However, consideration must be given to the scope of regulation and the policy design for the mark-up levels and structure, with a view to minimizing possible undesirable effects documented in the literature, such as price convergence (66) or supplier-induced demand for products with higher mark-up margins (61, 62, 68).</p>
Generalizability	<p>The generalizability of the findings is unclear. Evidence included in the systematic literature review was from upper-middle-income and high-income countries, often with context-specific co-interventions that could influence the effects of mark-up regulations (e.g. government subsidy to minimize the effects of lost revenue from medicines). Some studies also included only a selective set of medicines.</p>

Equity	If well-structured and implemented, mark-up regulation could enhance equity through incentivizing supply of medicines important for specific patient or population groups, where the market conditions might not otherwise be as preferable compared to other more profitable medicines (e.g. lower price, lower volume, stricter dispensing requirements such as sterile dispensing). A regressive mark-up structure, where higher-priced medicines are subject to a lower level of mark-ups, could incentivize broader access to lower-priced medicines (e.g. generic medicines). Equity could also be enhanced through promoting consistency and transparency of prices across the health-care system and for patients and consumers.
Acceptability	Likely to be acceptable to both government authorities and patients.
Resource use	Resource requirements are dependent on the complexity of the policy, the design, planning, implementation and enforcement of mark-up regulations.
Feasibility	The feasibility of implementing mark-up regulations would be dependent on various system factors, including existing health-care system context, complexity of the policy, and the level of stakeholder engagement required (e.g. with insurers, manufacturers and suppliers, and service providers).
Sustainability	If well structured and implemented, mark-up regulation would probably enhance the long-term financial sustainability of a health-care system by improving the government's ability to manage expenditure.

Implementation considerations

- Effective operation of mark-up regulations along the supply and distribution chain requires the following:
 - a. adequate expertise to manage the operation, including statistical expertise to collect and analyse price data, clinical expertise to assess the effects on rational use of medicines, and economic expertise to ensure policy design balances the incentives in the supply chain and maintains overall financial sustainability;
 - b. a mechanism for monitoring medicine prices, use, and sales, supported by adequate information technology infrastructure, and arrangements for seeking inputs from concerned stakeholders;
 - c. consideration of potential effects on non-regulated products; and
 - d. consideration of potential negative and positive effects on the operational revenue of health services following changes to mark-up regulations.
- Methodology of mark-up regulations along the supply and distribution chain should consider the following factors:
 - a. point or points along the supply and distribution chain (e.g. ex-factory, ex-wholesaler, ex-pharmacy) at which mark-ups should be applied;
 - b. magnitude of mark-ups at each point on the supply and distribution chain, price level, product type and facility type, where appropriate;
 - c. design of the regressive mark-up structure, defined by percentage or fixed mark-ups;
 - d. methods for data collection and determining mark-up levels (e.g. financial impact modelling); and
 - e. non price-related measures, such as specifying dispensing fee and performance incentives.

3.5 Promoting price transparency

Definition, design and policy rationale

What is the policy? Price transparency refers to the sharing, disclosure and dissemination of information related to prices of pharmaceutical products to relevant parties and the general public to ensure accountability. Full price transparency includes the publication of prices at all price types (e.g. ex-factory prices, pharmacy retail prices), the disclosure of the net transaction prices between the suppliers (e.g. manufacturers, service providers) and the payers/purchasers (governments, consumers). Transparency of pricing policies involves sharing and publication of the pricing methodology, including description of rationale and magnitude of reimbursement rates, and price components where relevant (e.g. production costs, R&D costs, added therapeutic value, profit margin). It also involves sharing and publication of the contents of pricing arrangements such as managed-entry agreements, patent status and licensing arrangements.

Why is the policy implemented? Price and pricing transparency are essential for the design and implementation of pricing policies. Non-transparent medicine prices can conflict with the principles of good governance and confidential agreements can compromise clear lines of accountability. In 2019, the Seventy-second World Health Assembly adopted resolution WHA72.8 on *Improving the transparency of markets for medicines, vaccines, and other health products* (69). This resolution urges Member States, inter alia, to take appropriate measures to publicly share information on the net prices of health products.

How is the policy implemented? Some countries have, to various extents, shared pricing and price information of pharmaceutical products through regular voluntary or mandatory arrangements. In the European Union, the Transparency Directive (70) mandates the publication of the list prices of all reimbursable medicines. When sharing to the public, the information is most often published on websites or gazettes, but the information often relates to list prices that have not accounted for discounts and rebates (e.g. Australia, Denmark). In other countries, the information is only shared with authorities of individual jurisdictions without public disclosure. In countries where medicines are not provided through a national publicly-funded or publicly-regulated scheme (i.e. unregulated private sector), there is a considerable lack of market transparency.

How commonly is the policy used? Several countries have implemented measures to promote price transparency. Notable examples include mandatory publication of purchasing prices of medical supplies in federally-funded hospitals in Brazil (71); and the implementation of the Single Exit Price policy in South Africa, which mandates the disclosure of the weighted average of all net sales prices for each medicine on a government website, with a view to clarifying to logistics service providers or medicine dispensers at which price a manufacturer may sell a pharmaceutical product (72, 73). In Australia, the Price Disclosure policy mandates manufacturers to disclose to the government authority, the sales revenue and the volume sold in units of brand (including any discounts, rebates and bonus stocks), for multiple brand products as these products were sold to pharmacists and wholesalers by manufacturers. This policy aims to ensure that the government prices for products sold under multiple brand names, and therefore the reimbursements for the supply of these products, are in line with market prices (74). However, a general lack of price transparency has been widely noted. Furthermore, there is a proliferation of confidential agreements on rebates and discounts aiming to facilitate faster access to high-cost medicines with uncertain clinical benefits (75). These agreements have masked market transparency, including the level of price competition.

Conditional recommendation for promoting price transparency

5.A. WHO suggests that countries improve the transparency of pricing and prices through the following mechanisms.

- Share the net transaction prices of pharmaceutical products with relevant stakeholders, within and external to the country.
- Disclose prices along the supply and distribution chain.
- Report publicly the R&D contributions from all sources.
- Communicate pricing and reimbursement decisions to the public.

5.B. WHO suggests that countries improve the transparency of pricing and prices through a clear description of pricing approaches and their technical requirements.

Justifications

- The GDG acknowledged the very limited evidence on promoting the transparency of prices and pricing of pharmaceutical products from comparative studies conducted to the standards of the WHO-commissioned systematic review. The GDG considered the overall balance of effects in favour of the policy because disclosure of price and pricing information is essential for safeguarding accountability, informing the design and implementation of effective pricing regulations (particularly on ex-manufacturer price).
- The GDG recognized that improving transparency may require measures to address non-disclosure requirements stemming from the use of confidentiality agreements, including, where needed, legal or policy or regulatory changes. In line with the World Health Assembly resolution WHA72.8 *Improving the transparency of markets for medicines, vaccines, and other health products*, the GDG urged stakeholders to take the necessary steps towards achieving greater transparency of the factors influencing the supply and demand of pharmaceutical products, particularly on medicine prices.
- The GDG considered disclosed prices and pricing information could serve multiple purposes for improving pricing policies, including citizen engagement, external reference pricing, public sector negotiations, monitoring and evaluation of pricing policies and impacts.

Overview of evidence

Balance of effects	Two studies from three publications were included in the systematic review (72, 73, 76). The evidence presented in the systematic review suggests that mandatory disclosure of the weighted average of all sales prices after considering all discounts and off-invoice rebates, as per the Single Exit Price programme in South Africa, might deliver lower prices for the health-care system (72, 73). Disclosure of price information to prescribers does not seem likely to produce sustained effects (72).
Generalizability	The generalizability of the findings is unclear. Evidence from the Single Exit Price programme might be generalizable in low- and lower-middle-income countries, provided the programme is suitable for national legal requirements and contexts.

Equity	Some commentators have expressed opposition to price transparency for on-patent medicines, arguing that “the effect will be to slow the diffusion of innovative products to low-income countries” because “differential pricing is important and can best be achieved in the current environment via confidential discounts” (77). If proven to be true, this would have negative equity impacts on patient access to innovative medicines in lower-income countries. However, such risk remains theoretical and seems comparatively minimal considering the significant disparity of access to on-patent medicines even in the presence of non-transparent prices. Indeed, another commentator has argued that increased transparency would enable more evidence-based policy-making, and therefore could enhance equity by improving access (78).
Acceptability	Likely to be acceptable to government authorities given the adoption of resolution WHA72.8 (69) by Member States. Patient groups and non-profit-making organizations have also expressed support for the resolution.
Resource use	The resource requirements would be dependent on the level of transparency and scope of data collection and reporting.
Feasibility	The feasibility would be dependent on the level and design of transparent reporting, including (i) voluntary or mandatory; (ii) number of points along the supply and distribution chain for which price data need to be collected or reported; and (iii) local, regional, national or international management of database and analytics. The legal systems in many countries, specific trade agreements or contractual arrangements may prohibit the disclosure of prices. Further analysis is needed to understand the extent to which trade secrets legislation may or may not interfere with transparency policies.
Sustainability	Sustainability would depend on the design and maturity of the data infrastructure in the country. Political commitment together with an ethos for transparent governance could also enhance the sustainability of this policy.

Implementation considerations

- Effective operation of policies to promote transparency of prices and pricing at the **national level** should consider the following factors.
 - a. Development and implementation of national policies relevant to the transparency of markets for health products, including disclosure of prices along the supply and distribution chain, and reimbursement rates/amounts, where relevant.
 - b. Harmonization of decision-making and communication frameworks across government agencies to facilitate reporting.
 - c. Collaboration to improve the reporting of information by suppliers of registered health products, such as reports on sales revenues, prices, units sold, marketing costs, and subsidies and incentives.
 - d. Use of financial-based managed-entry agreements (e.g. flat discounts, price-volume agreements, capping) and performance-based managed-entry agreements (e.g. risk-sharing agreement, coverage with evidence development) only if such arrangements:
 - facilitate early access to new medicines at affordable prices;
 - address uncertainty about performance of the product (e.g. clinical efficacy and cost-effectiveness), maximize the product use in the population most likely to benefit, or place a limit on budget;

Promoting price transparency

- o are operationally manageable without having to dedicate a disproportionate amount of resources for complex monitoring and contract management; and
 - o are on non-confidential terms.
- e. Clarification of the extent of disclosure that is required or permitted according to national legal frameworks, including existing confidentiality agreements.
- f. Enactment of legislation, regulations or rules to mandate transparent pricing and reporting of prices, where appropriate.
- Operation of policies to promote transparency of prices and pricing at the **international level** should consider the following factors.
 - a. Availability of international data platforms (e.g. database) and forums for sharing of information on prices and pricing approaches.
 - b. Development of data standards for pricing information to enhance data interoperability across jurisdictions, with consideration of existing frameworks (e.g. International Commercial Terms (Incoterms) and the data interoperability guide by the United Nations Statistical Commission) as well as potential linkage with data on other related metrics (e.g. Product Quality Review).
 - c. Clarification of the extent of disclosure that is required or permitted according to international legal frameworks, including existing confidentiality agreements.

3.6 Tendering and negotiation

Definition, design and policy rationale

What are the policies? Two policies with a shared principle of managing pharmaceutical prices through encouraging competitive mechanisms are jointly presented in this section. Tendering is any formal and competitive procurement procedure through which tenders (offers) are requested, received and evaluated for the procurement of medicines and vaccines, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous. Negotiation refers to discussions aimed at reaching an agreement with potential suppliers. In addition to acceptable general terms and conditions, the outcome of tendering and negotiation might include specific price reductions through discounts and rebates.

Why is the policy implemented? The purpose of tendering is to encourage competition among potential tenderers through a formal process, with the contract awarded to the favourable tenders selected based on objective predetermined criteria such as price, product quality, and value for money. Negotiation is usually used to establish the terms and conditions on various aspects of procurement (e.g. price, quality, risk, payment schedule) between the negotiating parties or facilitate resolution of any remaining disagreements over the terms and conditions of an offer.

How is the policy implemented? The general steps in undertaking formal tendering are well-documented in the literature (e.g. (79)), which involve: setting relevant legislation, defining the scope by selecting pharmaceutical products within the tender, preparing and publishing tender documents to invite offers from potential tenderers, collating offers and adjudicating supplier selection in preparation for awarding the contract, monitoring the performance of suppliers, and enforcing contract terms if necessary. The format of negotiation is generally less structured and is dependent on factors including size and complexity of the contract, number of parties involved, existing relationship, and other health care, regulatory, legal and commercial requirements. Depending on the context, tendering and negotiation have been done individually, jointly, or implemented to complement other pricing policies.

How commonly is the policy used? Tendering and negotiation have been one of the core methods of procurement commonly used in many countries, particularly in lower-income countries or international agencies procuring on behalf of lower-income countries. In higher-income countries, tendering has been used primarily in hospital settings and public services, such as pandemic plans (80) and human papillomavirus vaccines (81).

Conditional recommendations for tendering and negotiation

6.A. WHO suggests that countries use tendering for pharmaceutical products under the following conditions.

- Price level should be considered alongside other criteria including product quality, product characteristics, availability, supply security, supply reliability and charges along the supply chain.
- Tendering should be used in conjunction with other pricing policies to improve affordability and availability.

6.B. WHO suggests that countries use price negotiation to complement tendering as well as other pricing policies.

Justifications

- The GDG considered broad country experiences in using tendering and negotiation, as well as the feasibility and acceptability of the policy. Despite limited evidence from the systematic review, the GDG considered that the overall balance of effects favoured the policy.

Overview of evidence

Balance of effects	<p>The systematic review included one controlled study that examined the introduction of a new commission with a mandate for negotiating prices to achieve discounts on patented medicines (antiretroviral medicines) (82).</p> <p>Despite very limited comparative evidence to ascertain the effects of tendering and negotiation on price, volume, availability and affordability, if well-implemented through clear processes and requirements, tendering and negotiation could result in effects in favour of the policy, as indicated by (i) long standing implementation of the policy in many countries and international agencies, including when used with pooled procurement; and (ii) commentaries on the beneficial effects observed in several jurisdictions where tendering and negotiation have been the primary method of procurement for pharmaceutical products as documented in the literature (e.g. South Africa (83), New Zealand (84), Chile (85)).</p>
Generalizability	<p>There is insufficient information to inform the generalizability of the single study identified in the systematic review. However, tendering and negotiation are commonly used in many contexts and seem to have been largely effective in meeting the needs of procurement authorities.</p>
Equity	<p>No information.</p>
Acceptability	<p>This policy is likely to be acceptable to government authorities, patients and the community. However, patients and community might express dissatisfaction when the duration of the tendering and negotiation affects the timeliness of access.</p>
Resource use	<p>Resource requirements are likely to be dependent on the complexity of the contract and process design.</p>
Feasibility	<p>Tendering and negotiation are commonly used in high- and low-income countries, although the scope and processes might differ (e.g. open tenders, restricted tenders, or competitive negotiation, product specific, market specific, etc.). Feasibility and effectiveness of implementation would also depend on the governance structure (e.g. roles of different ministries in managing tendering and financing) and the size of the market (e.g. countries with smaller markets may not solicit sufficient tenders for certain products).</p>
Sustainability	<p>Wide adoption suggests that tendering and negotiation is probably likely to increase long-term financial sustainability of health-care systems.</p>

Implementation considerations

WHO suggests readers of this guideline refer to the principles described in *Operational principles for good pharmaceutical procurement (86)*, reproduced thematically below with additional considerations raised by the GDG.

- Effective operation of procurement through tendering and negotiation should consider the following factors.
 - a. Different procurement functions and responsibilities (selection, quantification, product specification, pre-selection of suppliers and adjudication of tenders) should be divided among different offices, committees and individuals, each with the appropriate expertise and resources for the specific function.
 - b. Procurement procedures should be transparent, following formal written procedures throughout the process and use explicit criteria to award contracts.
 - c. Procurement should be planned properly, and procurement performance should be monitored regularly; monitoring should include an annual external audit and be able to inform potential supply disruptions.
 - d. Mechanisms should be put in place to ensure reliable financing for procurement. Good financial management procedures should be followed to maximize the use of financial resources.
 - e. Procurement procedures and systems should include all assurances that the drugs purchased are quality-assured. This should involve close collaboration between procurement agencies and national regulatory authorities.
 - f. Members of the purchasing groups should purchase all contracted items from the supplier(s) which hold(s) the contract.
 - g. Prospective suppliers should be pre-qualified, and selected suppliers should be monitored through a process which considers product quality, service reliability, delivery time and financial viability.
 - h. Purchasing groups should develop and enhance negotiation capacity and skills.
- Methodology of procurement through tendering and negotiation should consider the following factors.
 - a. Public sector procurement should be limited to an essential drugs list or national/local formulary list.
 - b. Procurement and tender documents should list medicines by International Nonproprietary Name, or generic name.
 - c. Order quantities should be based on a reliable estimate of actual need.
 - d. Procurement should be effected in the largest possible quantities to achieve economies of scale; this applies to both centralized and decentralized systems.
 - e. Options for structuring the tender should be explored with a view to fully exploiting market size, purchasing power and ensuring supply security (e.g. single vs split tender).
 - f. Duration of agreements are linked to the frequency of calls for tender.
 - g. Minimum set of information required for initiating tendering is clearly specified.
 - h. Patent status and the number of supply sources should be assessed, with a view to informing the relative merits of tendering and negotiation.
 - i. Clearly defined rules should be enforced to deter and penalize unethical or illegal conduct, including intentional failure to supply products, or intentional provision of products that are of substandard quality.

3.7 Promoting the use of quality-assured generic and biosimilar medicines

Definition, design and policy rationale

What is the policy? This policy refers to strategies directed at patients, prescribers or pharmacists to encourage the use of quality-assured generic medicines¹⁵ or similar biological medicines (i.e. biosimilar medicines).

Why is the policy implemented? Although not having a direct role in regulating pricing of pharmaceutical products, increasing the use of quality-assured generic and biosimilar medicines would influence the price of these medicines not only because these medicines are priced lower than the originator product prior to loss of market exclusivity but also through enhanced price competition.

How is the policy implemented? Governments have implemented a suite of supply- and demand-side measures. Supply-side measures include removing regulatory barriers; using voluntary licence agreements or applying World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities for patented medicines where appropriate; specific pricing and purchasing policies for generic medicines, such as internal reference pricing. Governments have also implemented other policies to influence demand, such as preferential co-payment plans for generic medicines, mandatory substitutions or education campaigns to raise awareness about the efficacy and safety of generic medicines (87). Similar policies have been used to promote the use of biosimilar medicines, albeit to a lesser extent (88).

How commonly is the policy used? Promoting the use of quality-assured generic medicines has been an important public health policy globally since the 1990s. Policies for promoting the use of biosimilar medicines have been implemented to a lesser extent and largely in higher-income countries in Europe. There have been efforts towards greater harmonization of regulatory requirements for biosimilar medicines, with a view to enhancing market entry of biosimilar medicines (e.g. (89)).

Strong recommendations¹⁶ for promoting the use of quality-assured generic and biosimilar medicines

7.A. WHO recommends that countries enable early market entry of generic and biosimilar medicines through legislative and administrative measures, with a view to encouraging early submission of regulatory applications, allowing for prompt and effective review, and ensuring these products are safe, efficacious and quality-assured.

¹⁵ Generic products, also known as multisource pharmaceutical products, are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable. Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. Branded generics are generic products, as defined above, marketed with a brand name by their manufacturers.

¹⁶ A strong recommendation of this guideline indicates that the desirable effects of adherence to this recommendation outweigh any potential undesirable effects. This means that in most situations the recommendation can be adopted as policy.

7.B. WHO recommends that countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are informed by the cost of production¹⁷. These policies may include: internal reference pricing, mark-up regulation, tendering and lower patient co-payments.

7.C. To maximize uptake of generic and biosimilar medicines WHO recommends that countries implement, and enforce as appropriate, a suite of policies, including:

- legislation to allow generic substitution by dispensers and, where applicable, biosimilar substitution;
- legislative structure and incentives for prescribers to prescribe by International Nonproprietary Name;
- dispensing fees that encourage use of low-price generic and biosimilar medicines;
- regressive mark-up structure where lower rates of mark-ups are applied for higher-priced products, and appropriate financial and non-financial incentives are applied for dispensers (See Section 3.4); and
- education programmes for consumers and professionals regarding the quality, safety, efficacy and price of generic and biosimilar medicines.

Justifications

- The GDG considered the body of literature reviewed, which indicates the benefits of promoting the use of quality-assured generic medicines outweigh any undesirable consequences – including the effects on price, expenditure, equity and financial sustainability of health systems. The GDG also had a favourable view of the long standing and extensive country experiences in implementing a suite of effective policies promoting the use of quality-assured generic medicines, including for managing their affordability and accessibility.
- The GDG recognized the ongoing development of regulatory policies regarding the substitutability and interchangeability of biosimilar medicines. The GDG envisaged the importance of the future market for biosimilar medicines, and anticipated that policies on interchangeability, switching and substitution will be resolved. On this basis, the GDG believed that the recommendations applicable to generic medicines are also applicable to biosimilar medicines.

Overview of evidence

Balance of effects

The systematic review included 16 studies¹⁸: 6 on generic dispensing policy (30, 31, 34, 47, 90, 91); 4 on preferential reimbursement policies (46, 92–94); 4 on policies designed to incentivize or mandate generic prescribing (32, 95–97); 1 on mixed regulatory and reimbursement policies for generic medicines (98); and 1 on regulatory bioequivalence requirements (99). Overall, the evidence reviewed indicated effects on price and expenditure favour the use of quality-assured generic and biosimilar medicines – if the overall policy design encompasses a combination of strategies reflecting the context and goals of health-care systems.

¹⁷ For the purpose of this guideline, costs of production include manufacturing costs, costs associated with R&D, regulatory processes and compliance, overhead and other operating expenses of the business.

¹⁸ There is literature documenting the benefits of policies related to generic medicines more broadly; this was not included in the systematic review because the scope of the review was on pricing policy.

Generalizability	The generalizability of the evidence appraised is variable because most studies were conducted in high-income countries in Europe and the United States. Many studies only assessed impacts on specific medicine groups, with potential confounding from context-specific factors such as co-intervention. There is also a lack of research on the use of biosimilar medicines.
Equity	If well-structured and implemented, strategies to promote the use of quality-assured generic and biosimilar medicines could enhance equity through directly increasing access to lower cost generic and biosimilar medicines.
Acceptability	This policy is likely to be acceptable to government authorities given broad adoption of policies to promote the use of generic medicines, and to a much lesser extent (but with growing interest) for biosimilar medicines. While there is increasing acceptance of generic medicines in higher-income countries, a significant proportion of patients (and clinical service providers) in lower-income countries may have misperceptions about the efficacy or safety of generic medicines (100, 101), or unsatisfactory past experiences with using these medicines. Clinicians' knowledge, particularly on biosimilar medicines, may also have an impact on overall acceptability of these products (e.g. (102)).
Resource use	Resource requirements are likely to be dependent on the existing policies and the complexity of policy design. National regulatory authorities in lower-income countries may need to rely on third-party quality control laboratories to ensure the quality of generic and biosimilar medicines.
Feasibility	Policies to promote the use of biosimilar medicines might consider some lessons learned from those on generic medicines, with recognition of the differences in regulatory complexity.
Sustainability	The evidence, albeit with some limitations, suggests that promotion of the use of generic and biosimilar medicines is probably likely to increase long-term financial sustainability of health-care systems.

Implementation considerations

- Effective operation of policies to promote the use of quality-assured generic and biosimilar medicines should consider the following factors.
 - a. Legislation to allow substitution by dispenser, including clearly defined criteria for mandatory substitution, if relevant.
 - b. Elaboration of a national guideline on the substitution of generic and biosimilar medicines.
 - c. Education of clinicians and pharmacy personnel in appropriate substitution.
 - d. Development of a monitoring and process plan for specific circumstances, such as occurrences of products that do not meet quality standards and anticompetitive behaviours in the market.
 - e. Implementation of other policies to enhance price competition, including using voluntary licence agreements or applying WTO TRIPS flexibilities for patented medicines where appropriate, as well as other supply-side measures such as supporting local productions, if appropriate.
 - f. Countries with lower regulatory capacity may consider using information from the WHO prequalification programme or information from other well-established regulatory authorities.

- Methodology of policies to promote the use of quality-assured generic and biosimilar medicines should consider the following factors.
 - a. Clear definition of evidence is required to demonstrate bioequivalence and therapeutic equivalence to facilitate market entry of generic and biosimilar medicines, with consideration of the following guidelines (103–105):
 - *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*: Annex 7.
 - *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)*: Annex 2.
 - *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology*: Annex 4.
 - b. Clear technical specifications are available for quality assurance.
 - c. Application of internal reference pricing policies (Section 3.2) to harmonize the prices of generic and biosimilar medicines (branded or not), except in specific pre-specified circumstances (e.g. specific clinical needs, product characteristics).
 - d. Ensuring that generic and biosimilar medicines enter the market at an acceptably low price (e.g. where possible, informed by the differences between generic ex-manufacturer prices and the estimated cost of production).

3.8 Pooled procurement

Definition, design and policy rationale

What is the policy? Pooled procurement refers to the formal arrangement where financial and non-financial resources are combined across various purchasing authorities to create a single entity for purchasing health products (e.g. medicines) on behalf of individual purchasing authorities.

Why is the policy implemented? Pooled procurement has been implemented to create greater purchasing power through economies of scale and scope, as well as greater efficiency through sharing of human resources (i.e. expertise and workload) and possible streamlining of procurement processes.

How is the policy implemented? There are in principle four models of pooled procurement that reflect different levels of collaboration and integration: informed buying through sharing of price and supplier information; coordinated informed buying through joint market research; group contracting through joint negotiation; and central contracting and procurement through an established procurement agent.

How commonly is the policy used? Pooled procurement has been commonly used at different levels of administrative jurisdiction. At the national and subnational level, examples include centralized procurement systems for public hospitals implemented in Denmark and Norway for medicines used in hospitals; specialized national programmes (e.g. for tuberculosis, vector-borne diseases and HIV/AIDS) in India; regional central purchasing bodies in Italy, and the “high-cost medicines E2 access program” for medicines for rare diseases and complex conditions in Thailand, to name a few. At the international level, examples of initiatives include Pharmaceutical Procurement Services of the Organization of Eastern Caribbean States; pooled procurement services for member states of the Southern African Development Community; joint HTA/reimbursement and pricing negotiations through the Beneluxa Initiative; pilot projects among signatories of the Valletta Declaration; and the group purchasing programme of Gulf Cooperation Council. Pooled procurement has also been managed through third-party funds such as the United Nations Children’s Fund (UNICEF) Supply Division; the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund); Stop TB Partnership Global Drug Facility; and the Pan American Health Organization (PAHO) Regional Revolving Fund for Strategic Public Health Supplies.

Conditional recommendations for pooled procurement

8.A. WHO suggests the use of pooled procurement of medicines under the following conditions.

- Pooled procurement should be used in conjunction with other pricing policies, such as tendering and negotiation.
- Procurement processes are transparent and accompanied by a high standard of governance.
- Financing for pooled procurement must be sustainable, predictable and timely with dedicated resources mobilized for a capitalization fund to stabilize initial regional pooled procurement efforts.

8.B. WHO suggests that countries consider initiation of pooled procurement of medicines under the following conditions.

- Pooled procurement is initiated with a clear understanding of the price and non-price benefits to be achieved (e.g. quality, availability, administrative efficiencies, bargaining power, improved capacity to forecast and collective technical expertise).

- Pooled procurement is initiated with a clear understanding of the regulatory policies, quality assurance, patent laws and relevant patent information, and financing processes in participating jurisdictions.

Justifications

- The GDG considered the evidence presented in the literature review and various country experiences in using pooled procurement at different levels of collaboration and integration, especially at the subnational, national and international levels. The GDG recognized the growing interest in using pooled procurement to mitigate low purchasing power (e.g. in countries with small populations or insufficient volume for maintaining the supply of low-price generic products), and unaffordability of low-volume high-price products (e.g. for rare diseases).
- The GDG acknowledged the positive experience associated with pooled procurement through the Revolving Fund of the Pan American Health Organization, and recognized the importance of political commitment, alignment of legal, regulatory and policy requirements and processes and ability to address local needs.

Overview of evidence

Balance of effects	The systematic review included 6 studies: 3 at the regional (subnational) level (106–108) and 1 study each at the national (109), international (110) and responsible agency (111) levels. On balance, pooled procurement is likely to deliver more desirable than undesirable effects, as indicated by evidence of reduced prices of health products under a pooled procurement arrangement. However, the effects are likely to be dependent on the characteristics of market and health system, including level of competition, collective credit risk and institutional quality.
Generalizability	The effects on reduced price of pooled procurement due to economies of scale are likely to be generalizable. However, the contexts of different health-care systems, such as language of legislative frameworks, may influence the overall effectiveness of this policy.
Equity	Various pooled procurement initiatives have been successful in enhancing equity by meeting the needs of vulnerable populations with HIV, tuberculosis and malaria in lower-income countries.
Acceptability	This policy seems to be acceptable to government authorities given broad adoption of policies at different levels of administrative jurisdiction. However, when implementing pooled procurement, the overall acceptability depends on significant political commitment to have a common understanding or agreement on legal, regulatory, policy and administrative requirements and processes, including product registration, quality assurance, patent, price, volume and finance.
Resource use	Resource requirements would highly depend on the level of integration and cooperation. Upfront resource requirements to set up a pooled procurement mechanism would likely be significant.

Feasibility Feasibility would highly depend on the level of integration and cooperation. It would be contingent upon harmonization or clear arrangements on issues pertaining to legal, regulatory, policy and administrative requirements and processes.

Sustainability Long standing pooled procurement mechanisms suggests that such arrangement could be sustainable financially in the long term. The sustainability of initial regional pooled procurement efforts is dependent on predictable and timely financing, as well as the ability to mobilize resources for capitalization for the eventual procurement (112).

Implementation considerations

- Preparation and operation of pooled procurement should consider the following factors.
 - a. Conditions of procurement under international arrangements must be established from the outset, including common values, compatible legislation, administrative structures and shared timeline and milestones.
 - b. The sharing of information and experiences through cross-training, study tours or twinning to disseminate lessons learned is considered beneficial to both experienced and emerging groups. Such collaboration should be facilitated at political and technical levels.
 - c. Development of databases on issues such as price, patent status, prequalification of suppliers, and medicines registration can be useful and, in some cases, necessary for regional pooled procurement.
 - d. Capacity building based on best practice should be undertaken at country and regional levels, with consideration for the specific needs of member countries.
 - e. Local manufacturing can be supported by regional pooled procurement through the principles of fair competition (as defined in competition laws) and establishing good manufacturing practices.
 - f. A third party could be considered to help countries harmonize points for pooled procurement, such as legislation, regulations, economic factors and administrative processes – particularly for international pooled procurement.
- Methodology of pooled procurement should consider the following factors.
 - a. Pooled procurement may be initiated with a limited list of products (e.g. high cost medicines).
 - b. Multi-year contracts in pooled procurement show buying commitment, and should be considered to ensure stable sources of supply and facilitate favourable prices from manufacturers.
 - c. Factors specific to the types of pharmaceutical products should be considered in the final arrangement (e.g. storage and supply requirements for vaccines and volume forecast for medicines for rare diseases).

3.9 Cost-plus pricing for setting the price of pharmaceutical products

Definition, design and policy rationale

What is the policy? Cost-plus pricing refers to the pricing practice for setting the price¹⁹ of pharmaceutical products that considers the manufacturing costs, costs of R&D, costs associated with regulatory processes and compliance, overhead and other operational expenses, and a profit to determine a price.

Why is the policy implemented? Cost-plus pricing has been noted for its conceptual simplicity, with clear and justifiable pricing rules that provide some level of certainty for budgetary planning and profits for the suppliers.

How is the policy implemented? A few countries have noted cost-plus pricing as part of national pharmaceutical pricing policies (Australia's "cost-plus method" (113), and the "cost accounting system" in Japan for products with no comparable products (114) are two examples). However, the extent of use in practice and the practical details are not widely known. Many countries (e.g. in Europe) only use costs as one of the criteria for price negotiation. This is likely to be due to the practical challenges in obtaining reliable information from suppliers regarding direct material costs, direct labour costs, overhead costs associated with R&D, manufacturing, regulatory processes and compliance and other costs of business operation. It could also be challenging to determine the final price, for which the suppliers and the pricing authority would need to come to an agreement on profit margin additional to the estimated costs, based on a mutually-acceptable level and structure (i.e. percentage or a fixed amount) (12).

How commonly is the policy used? Cost-plus pricing has not been widely used for setting medicine prices at the ex-manufacturer or ex-wholesaler levels.

Conditional²⁰ recommendations against the policy

9.A. WHO suggests against countries using cost-plus pricing as a primary policy for setting the price of pharmaceutical products, given the current lack of transparency and the lack of an agreed framework among stakeholders regarding the inputs for price determination.

Justifications

- The GDG considered the lack of evidence and country experience in using cost-plus pricing as a primary policy for setting the price of pharmaceutical products. The GDG recognized the significant problems associated with the feasibility and reliability of implementing cost-plus pricing because of a lack of transparency and accessibility to R&D costs and other cost information needed for setting prices.
- The GDG is mindful of the increasing policy interests and current technical work by various stakeholders in developing a validated framework for setting pharmaceutical prices based on cost inputs. While

¹⁹ Mark-up regulation along the supply and distribution chain is covered in Section 3.4 of this guideline.

²⁰ A conditional recommendation indicates that the effects of adhering to this recommendation (both desirable and undesirable) are subject to the conditions specified, and could be modified by a greater range of context-specific factors. This means that there is a need for involving relevant stakeholders to understand these conditions and factors before this recommendation can be adopted or adapted as policy.

recommending against cost-plus pricing, the GDG considered exploring the possibility of using a refined cost-plus pricing policy for pharmaceutical products as a supplementary policy or criterion to inform pricing, if a policy and methodology framework could be agreed to ensure the transparency and reliability of information, including the attribution of joint costs for R&D.

Overview of evidence

Balance of effects	No study met the inclusion criteria of the systematic review. Commentators have suggested that cost-plus pricing would disincentivize competition and create various potential undesirable effects, such as shortages, inefficient R&D and production. However, to what extent such undesirable effects would occur, if any, is subject to debate.
Generalizability	No information
Equity	No information
Acceptability	There is renewed interest to understand R&D costs (69), particularly the public contribution to R&D (e.g. France (115)).
Resource use	Application of cost-plus pricing to medicines requires significant technical and human resources, particularly in obtaining and validating reliable estimates of component costs.
Feasibility	Cost-plus pricing is unlikely to be feasible unless transparent reporting of cost components is mandated. Feasibility would also depend on standardized methods for allocating joint costs to a specific medicine, with consideration of the global nature of pharmaceutical companies and the complexity of their cost structures. There is also no agreement on the methodology for determining and reporting costs related to R&D.
Sustainability	No information

Implementation considerations

- Countries which currently use a cost-plus pricing as a primary policy for setting the price of pharmaceutical products and wish to change their policy should consider replacing or complementing the cost-plus approach with other policies, including policies covered in this guideline, such as using cost of production to inform the pricing of generic and biosimilar medicines (See recommendations under Section 3.7).
- Country policy-makers considering cost-plus pricing (in the context of price transparency) must recognize the limitations of price information submitted by manufacturers and develop a framework for verifying the information accordingly.

3.10 Tax exemptions or tax reductions for pharmaceutical products

Definition, design and policy rationale

What is the policy? Tax is a compulsory transfer of money from private individuals, institutions or groups to the government. There are two main categories of tax: direct taxes, 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 or value-added taxes.

Why is the policy implemented? Tariffs and taxes could present trade barriers, thereby potentially hindering access and market competition. Tax burden (i.e. tax incidence) could also potentially fall disproportionately on the patients, resulting in reduced affordability.

How is the policy implemented? Typically, the policy is managed by the Ministry of Finance or Treasury through integration into the overall taxation regime.

How commonly is the policy used? Many countries, particularly high-income countries, have eliminated customs duties for pharmaceutical products. These include signatories to the World Trade Organization's 1995 reciprocal Pharmaceutical Tariff Elimination Agreement also known as the Zero-for-Zero initiative (116). However, many lower-income countries continue to apply import tariffs as high as 10% for pharmaceutical products. Value-added tax has been more widely applied on pharmaceutical products in countries, up to 25% (60). Nonetheless, some countries apply a reduced rate for all pharmaceutical products or specific medicines (e.g. reimbursed medicines) compared to the standard tax rates.

Conditional recommendations for the policy

- 10.A. WHO suggests that countries consider exempting essential medicines and active pharmaceutical ingredients from taxation.
- 10.B. WHO suggests that countries consider any tax reductions or exemptions, with measures to ensure that the policy results in lower prices of medicines to patients and purchasers.

Justifications

- The GDG considered broad country experiences in exempting or reducing the taxes for pharmaceutical products, with wide acceptability among stakeholders and proven feasibility for implementation.
- The GDG recognized that tax exemption or reduction for pharmaceutical products might reduce patient out-of-pocket expenditures without having a significant impact on overall government revenue.
- The GDG also acknowledged that, in health systems with high levels of public funding for medicines, tax exemption or reduction for pharmaceutical products would have a limited impact on overall government revenue and patient out-of-pocket expenditures.

Overview of evidence

Balance of effects	No study met the inclusion criteria of the systematic review.
Generalizability	No information.
Equity	Consistent application of tax exemption would enhance equity through greater affordability to patients. In contrast, inconsistent application of tax exemption, or savings from tax reduction or exemption not being directly transferred to service providers or patients could create inequity.
Acceptability	Some governments might consider the lost revenue due to reduction or removal of taxes for pharmaceutical products as unacceptable. However, evidence suggests that value-added tax does not substantially contribute to revenue goals (e.g. $\approx 1\%$ of public revenue) but can make medicines unaffordable for patients (117, 118).
Resource use	Resources would be required for the initiation of tax exemption. Additional resources over the longer term would be minimal because of integration into the overall taxation regime.
Feasibility	The policy is likely to be feasible because the policy relates to removal or amendment of an existing policy. Furthermore, countries generally have experience managing much more complex tax regimens.
Sustainability	Tax exemptions or tax reductions for pharmaceutical products are likely to have a neutral impact on the long-term sustainability of health-care systems. However, they would be likely to enhance patient affordability in the long term.

Implementation considerations

- Tax exemption or reduction could be implemented in conjunction with mark-up regulations.
- Tax exemption or reduction could be implemented for subsets of medicines or active pharmaceutical ingredients, such as medicines included in special patient access programmes or active pharmaceutical ingredients for local production. However, selective application of tax policies would need to consider potential impacts on equity, implementation feasibility and administration costs.

4. Considerations towards research needs

In developing the recommendations, the GDG noted that the completeness and quality of research and evidence in relation to the impacts of pharmaceutical policy implementation is low. In particular, there is a lack of comparative studies on different approaches to allow a better understanding of what policies should be chosen and how they should be implemented, particularly in the settings of lower-income countries. Where conducted, the studies have significant methodological shortcomings.

The GDG identified the following research topics by policy, with a view to informing future updates of this guideline.

External reference pricing

- Study the impact of external reference pricing on price, availability and affordability, with a focus on specific settings (e.g. low- and middle-income countries) and longer-term impacts.
- Assess the effects of external reference pricing on timing of product launch, with the study design, (i) accounting for factors such as market size, price and dates for dossier submission for product registration and reimbursement; (ii) setting a clear null hypothesis (e.g. external reference pricing has no effect on the timing of product launch between jurisdictions expected to have both high and low prices); and (iii) specifying and including a counterfactual (e.g. jurisdictions not using external reference pricing).

Internal reference pricing

- Monitor and evaluate the impacts of internal reference pricing on the price, availability and affordability of medicines (particularly for biosimilar medicines), and over the longer term (particularly for therapeutic reference pricing).

Value-based pricing

- Study the impact of value-based pricing using HTA on affordability, expenditure, and access to medicines.
- Assess the societal implications of value-based pricing using HTA, including resource allocations for medicines intended for people with conditions that limit the magnitude of their capacity to benefit (e.g. people living with disability, elderly), or medicines intended for people living with rare diseases.
- Assess the extent and nature of innovation potentially induced by the policy of value-based pricing using HTA.
- Determine data and develop a methodology to support value-based pricing using HTA pertinent to local contexts.
- Incorporate findings from evaluation of post-marketing performance (i.e. real-world evidence) into the policy framework of value-based pricing.

Mark-up regulations across the pharmaceutical supply and distribution chain

- Review the relationship between mark-up structures, incentives and access to medicines.
- Monitor and evaluate the impacts of mark-up regulation across the pharmaceutical supply and distribution chain on the price, availability and affordability of medicines.

Promoting price transparency

- Study the intended and unintended impacts of price transparency on affordability and availability of products.
- Review frameworks and information needed to enable comparisons across jurisdictions.
- Assess the technical and governance components required for achieving transparency of prices and pricing within countries, including the feasibility and benefits of common web-based tools for sharing information.

Tendering and negotiations

- Monitor and evaluate the implementation and impacts of tendering and negotiation on the price, availability and affordability of medicines.

Promoting the use of generic and biosimilar medicines

- Assess the feasibility of a database that includes evaluation dossiers for generic and biosimilar medicines from well-established regulatory authorities to support national regulatory authorities from low- and middle-income countries.
- Study the impact of technical guidance, or lack thereof, on interchangeability and substitutability for biosimilar medicines.
- Assess the impact of measures to facilitate market entry of biosimilar medicines.
- Assess the impact on affordability and accessibility of biological products in countries with long standing policies that promote the use of biosimilar medicines.
- Assess the impact of marketing strategies on prices and uptake of branded and non-branded generic and biosimilar medicines.
- Review governance issues relating to promoting pharmaceutical products more broadly.

Pooled procurement

- Review frameworks on the components needed for the effective functioning of pooled procurement at different levels of collaboration and integration, and levels of jurisdictions.
- Assess the impact of the levels of collaboration and integration on price, affordability and access to medicines.

Cost-plus pricing for setting the price of pharmaceutical products

- Develop methods for calculating costs, with consideration to R&D costs by private companies, public contribution to drug discovery and development, manufacturing requirements (e.g. for biological products), allocation of shared costs and fair profits.
- Develop an implementation framework for collection, calculation and revision and reporting of prices based on cost-plus pricing.
- Study the feasibility of applying cost-plus pricing for determining the prices of advanced therapeutic medical products based on genes, tissues or cells, and medicines for rare diseases.
- Determine the intended and unintended consequences of applying cost-plus pricing.

Tax exemptions or tax reductions for pharmaceutical products

- Study the impact of tax exemptions and reductions on affordability and availability of medicines to patients and health systems.
- Determine the best practices for implementing policy related to tax exemptions or reductions.

The GDG is mindful of several emerging pricing approaches and arrangements being explored or implemented in specific contexts. Forthcoming evidence will be included in future updates of this guideline.

References

1. Sustainable Development Goals 2015 – 2030 - Goal 3. Ensure Healthy Lives and Promote Well Being for All at All Ages [website]. New York (NY): United Nations; 2015 (<http://www.un.org/sustainabledevelopment/health/>, accessed 7 April 2018).
2. Regional Committee for the Americas. Access and rational use of strategic and high-cost medicines and other health technologies (Resolution CD55R12). Washington (DC): WHO Regional Office for the Americas; 2016.
3. Regional Committee for Africa. Final report for the sixty-eighth session of the WHO Regional Committee for Africa. Brazzaville: WHO Regional Office for Africa; 2018 (AFR/RC68/17).
4. Ministerial roundtable: improving access to essential medical products in the Region and beyond. New Delhi: WHO Regional Office for South-East Asia; 2018 (SEA/RC71/3; <http://apps.who.int/iris/handle/10665/273935%0Ahttp://apps.who.int/iris/bitstream/10665/273935/1/sea-rc71-3.pdf>).
5. Regional Committee for Europe. Decision on strengthening Member State collaboration on improving access to medicines in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2017 (EUR/RC67(1)).
6. Regional Committee for the Western Pacific. Final report of the regional committee. Sixty-eighth session. Manila: WHO Regional Office for the Western Pacific; 2018. [Crosscheck title is correct vis-à-vis the title in reference 3]
7. Regional Committee for the Eastern Mediterranean. Medicine prices and access to medicines in the Eastern Mediterranean Region. Resolution EM/RC54/R8. [add city]: WHO Regional Office for the Eastern Mediterranean; 2007.
8. WHO guideline on country pharmaceutical pricing policies. Geneva: World Health Organization; 2015.
9. Glossary. In: Essential medicines and health products: prequalification of medicines [website]. Geneva: World Health Organization; 2020 (<https://extranet.who.int/prequal/content/glossary>, accessed 29 August 2020).
10. WHO handbook for guideline development. Geneva: World Health Organization; 2012.
11. Vogler S, Haasis MA, Dedet G, Lam J, Pedersen HB. Medicines reimbursement policies in Europe. Copenhagen: WHO Regional Office for Europe; 2018 (http://www.euro.who.int/__data/assets/pdf_file/0011/376625/pharmaceutical-reimbursement-eng.pdf?ua=1, accessed 29 August 2020).
12. Pricing of cancer medicines and its impacts. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1>, accessed 29 August 2020).
13. Holtorf AP, Gialama F, Wijaya KE, Kaló Z. External reference pricing for pharmaceuticals—A survey and literature review to describe best practices for countries with expanding healthcare coverage. *Value Heal Reg Issues*. 2019; 19(122–31).
14. Drug price controls in Malaysia: implications and considerations. Policy Brief. Kuala Lumpur: Galen Centre for Health and Social Policy; 2019.
15. Medicare Program; International Pricing Index Model for Medicare Part B Drugs. Federal Registry. Washington (DC): US Department of Health and Human Services; 2018;83(210):54546–61.

16. Fontrier AM, Gill J, Kanavos P. International impact of external reference pricing: should national policy-makers care? *Eur J Heal Econ.* 2019; 20(8):1147–64 (<https://doi.org/10.1007/s10198-019-01083-w>, accessed 29 August 2020).
17. Vogler S, Lepuschütz L, Schneider P, Stühlinger V. Study on enhanced cross-country coordination in the area of pharmaceutical product pricing - Final report. Brussels: European Commission; 2015 (http://ec.europa.eu/health/systems_performance_assessment/docs/pharmaproductpricing_frep_en.pdf, accessed 29 August 2020).
18. Espin J, Rovira J, Labry AO. Pharmaceutical pricing policies and interventions. In: *Medicine prices, availability, affordability & price components* [website]. Geneva: Health Action International/World Health Organization; 2011 (<http://www.haiweb.org/medicineprices/articles/>, accessed 24 August 2020).
19. Kanavos P, Fontrier AM, Gill J, Efthymiadou O. Does external reference pricing deliver what it promises? Evidence on its impact at national level. *Eur J Heal Econ.* 2020;21(1):129–151 (<https://doi.org/10.1007/s10198-019-01116-4>, accessed 29 August 2020).
20. Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, et al. Impact of external price referencing on medicine prices - A price comparison among 14 European countries. *South Med Rev.* 2012; 5(2):34–41.
21. Maniadakis N, Kourlaba G, Shen J, Holtorf A. Comprehensive taxonomy and worldwide trends in pharmaceutical policies in relation to country income status. *BMC Health Serv Res.* 2017; 17(1):1–17.
22. Hasan SS, Kow CS, Dawoud D, Mohamed O, Baines D, Babar ZUD. Pharmaceutical policy reforms to regulate drug prices in Asia Pacific Region: the case of Australia, China, India, Malaysia, New Zealand, and South Korea. *Value Heal Reg Issues.* 2019; 18:18–23 (<http://dx.doi.org/10.1016/j.vhri.2018.08.007>, accessed 29 August 2020).
23. Adriaen M, De Witte K, Simoens S. Pricing strategies of originator and generic medicines following patent expiry in Belgium. *J Generic Med.* 2008; 5(3):175–87.
24. Brekke KR, Grasdal AL, Holmås TH. Regulation and pricing of pharmaceuticals: reference pricing or price cap regulation? *Eur Econ Rev.* 2009; 53(2):170–85.
25. Brekke KR, Canta C, Straume OR. Does reference pricing drive out generic competition in pharmaceutical markets? Evidence from a policy reform. NHH Dept. of Economics Discussion Paper No. 11/2015. Bergen: Norwegian School of Economics; 2015 (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2617267, accessed 4 September 2020).
26. Ghislandi S, Armeni P, Jommi C. The impact of generic reference pricing in Italy, a decade on. *Eur J Heal Econ.* 2013; 14(6):959–69.
27. Grootendorst P, Stewart D. A re-examination of the impact of reference pricing on anti-hypertensive drug expenditures in British Columbia. *Health Econ.* 2006; 15(7):735–42.
28. Hsiao FY, Tsai YW, Huang WF. Price regulation, new entry, and information shock on pharmaceutical market in Taiwan: a nationwide data-based study from 2001 to 2004. *BMC Health Serv Res.* 2010; 10:218.
29. Kaiser U, Mendez SJ, Rønne T, Ullrich H. Regulation of pharmaceutical prices: evidence from a reference price reform in Denmark. *J Health Econ.* 2014; 36(1):174–87 (<http://dx.doi.org/10.1016/j.jhealeco.2014.04.003>, accessed 29 August 2020).
30. Koskinen H, Ahola E, Saastamoinen LK, Mikkola H, Martikainen JE. The impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic medication in Finland. *Health Econ Rev.* 2014; 4(1):1–10.

31. Koskinen H, Mikkola H, Saastamoinen LK, Ahola E, Martikainen JE. Time series analysis on the impact of generic substitution and reference pricing on antipsychotic costs in Finland. *Value Heal.* 2015; 18(8):1105–12 (<http://dx.doi.org/10.1016/j.jval.2015.08.014>, accessed 29 August 2020).
32. Moreno-Torres I, Puig-Junoy J, Raya JM. The impact of repeated cost containment policies on pharmaceutical expenditure: experience in Spain. *Eur J Heal Econ.* 2011; 12(6):563–73.
33. Puig-Junoy J. The impact of generic reference pricing interventions in the statin market. *Health Policy.* 2007; 84(1):14–29.
34. Bergman MA, Granlund D, Rudholm N. Reforming the Swedish pharmaceuticals market: consequences for costs per defined daily dose. *Int J Heal Econ Manag.* 2016; 16(3):201–14.
35. Kwon HY, Bae S, Choi S, Park S, Lee EK, Park SM, et al. Easy cuts, easy rebound: drug expenditures with massive price cuts in Korea. *Health Policy (New York).* 2019; 123(4):388–92 (<https://doi.org/10.1016/j.healthpol.2018.11.002>, accessed 29 August 2020).
36. Lee IH, Bloor K, Hewitt C, Maynard A. The effects of new pricing and copayment schemes for pharmaceuticals in South Korea. *Health Policy.* 2012;104(1):40–9. Available from: <http://dx.doi.org/10.1016/j.healthpol.2011.09.003>, accessed 29 August 2020).
37. Suh HS, Kim JA, Lee IH. Effects of a price cut reform on the cost and utilization of antidiabetic drugs in Korea: a national health insurance database study. *BMC Health Serv Res.* 2018; 18(1):1–10.
38. Yoo KB, Lee SG, Park S, Kim TH, Ahn J, Cho MH, et al. Effects of drug price reduction and prescribing restrictions on expenditures and utilisation of antihypertensive drugs in Korea. *BMJ Open.* 2015; 5(7).
39. Johnson JT, Neill KK, Davis DA. Five-year examination of utilization and drug cost outcomes associated with benefit design changes including reference pricing for proton pump inhibitors in a state employee health plan. *J Manag Care Pharm.* 2011; 17(3):200–12 (<http://www.jmcp.org/doi/10.18553/jmcp.2011.17.3.200>, accessed 29 August 2020).
40. Stargardt T, Schreyögg J, Busse R. Arzneimittelfestbeträge: Gruppenbildung, preisberechnung mittels regressionsverfahren und wirkungen [Fixed drug prices: group formation, price calculation using regression methods and effects]. *Gesundheitswesen.* 2005; 67(7):468–77 (in German).
41. Marđetko N, Kos M. Introduction of therapeutic reference pricing in Slovenia and its economic consequences. *Eur J Heal Econ.* 2018; 19(4):571–84.
42. Stargardt T. The impact of reference pricing on switching behaviour and healthcare utilisation: The case of statins in Germany. *Eur J Heal Econ.* 2010; 11(3):167–77.
43. Armeni P, Jommi C, Otto M. The simultaneous effects of pharmaceutical policies from payers' and patients' perspectives: Italy as a case study. *Eur J Heal Econ.* 2016; 17(8):963–77.
44. Schneeweiss S, Dormuth C, Grootendorst P, Soumerai SB, Maclure M. Net health plan savings from reference pricing for angiotensin-converting enzyme inhibitors in elderly British Columbia residents. *Med Care.* 2004; 42(7):653–60.
45. Andersson K, Petzold MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986-2002. *Health Policy.* 2006; 79(2–3):231–43.
46. Leopold C, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, et al. Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: interrupted time series analyses. *Int J Equity Health.* 2014; 13(1):1–9.

47. von der Schulenburg F, Vondoros S, Kanavos P. The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors. *Health Econ Rev.* 2011; 1(1):1–8 (<http://www.healtheconomicsreview.com/content/1/1/18>, accessed 29 August 2020).
48. Grootendorst PV, Marshall JK, Holbrook AM, Dolovich LR, O'Brien BJ, Levy AR. The impact of reference pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. *Health Serv Res.* 2005; 40(5 1):1297–317.
49. HTA definitions. In: Health technology assessment [website]. Geneva: World Health Organization; 2020 (<https://www.who.int/health-technology-assessment/about/Defining/en/>, accessed 29 August 2020).
50. Why use HTA?. In: Health technology assessment [website]. Geneva: World Health Organization; 2020 (<https://www.who.int/health-technology-assessment/about/WHY/en/>, accessed 29 August 2020).
51. 2015 Global Survey on Health Technology Assessment by National Authorities. Geneva: World Health Organization; 2015 (https://www.who.int/health-technology-assessment/MD_HTA_oct2015_final_web2.pdf, accessed 24 August 2020)
52. Ben-Aharon O, Shavit O, Magnezi R. Does drug price-regulation affect healthcare expenditures? *Eur J Heal Econ.* 2017; 18(7):859–67.
53. Kwon HY, Hong JM, Godman B, Yang BM. Price cuts and drug spending in South Korea: the case of antihyperlipidemic agents. *Health Policy (New York).* 2013; 112(3):217–26 (<http://dx.doi.org/10.1016/j.healthpol.2013.08.011>, accessed 29 August 2020).
54. Harris J. It's not NICE to discriminate. *Journal of Medical Ethics.* 2005; 31:373–5.
55. Nord E, Daniels N, Kamlet M. QALYs: some challenges. *Value Heal.* 2009; 12(Suppl. 1):S10–15 (<http://dx.doi.org/10.1111/j.1524-4733.2009.00516.x>, accessed 29 August 2020).
56. Caro JJ, Brazier JE, Karnon J, Kolominsky-Rabas P, McGuire AJ, Nord E, et al. Determining value in health technology assessment: stay the course or tack away? *Pharmacoeconomics.* 2019; 37(3):293–9 (<https://doi.org/10.1007/s40273-018-0742-2>, accessed 29 August 2020).
57. Rajan A, Gutierrez-Ibarluzea I, Moharra M. Addressing issues in health technology assessment promotion: motives, enablers, and barriers. *Int J Technol Assess Health Care.* 2011; 27(1):55–63.
58. Abdel Rida N, Mohamed Ibrahim MI, Babar ZUD, Owusu Y. A systematic review of pharmaceutical pricing policies in developing countries. *J Pharm Heal Serv Res.* 2017; 8(4):213–26.
59. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Pharmaceutical Pricing and Reimbursement Information, Gensundheit Österreich. Country poster book. 3rd International PPRI Conference -- Pharmaceutical pricing and reimbursement policies: challenges beyond the financial crisis. Vienna: Gesundheit Österreich GmbH; 2015.
60. Vogler S, Zimmermann N, Haasis AM. PPRI report 2018: pharmaceutical pricing and reimbursement policies in 47 PPRI network member countries. Vienna: WHO Collaborating Centre for Pricing and Reimbursement Policies, Gesundheit Österreich GmbH (GÖG/Austrian National Public Health Institute); 2019 (https://ppri.goeg.at/sites/ppri.goeg.at/files/inline-files/PPRI%20Report2018_final.pdf, accessed 19 August 2020).
61. Cheng W, Fang Y, Fan D, Sun J, Shi X, Li J. Study on the effect of "zero mark-up" policy on medicines in Beijing community health facilities. *Pharm Policy Law.* 2012; 14(2–4):177–86.
62. Fu H, Li L, Yip W. Intended and unintended impacts of price changes for drugs and medical services: evidence from China. *Soc Sci Med.* 2018; 211(January):114–22 (<https://doi.org/10.1016/j.socscimed.2018.06.007>, accessed 29 August 2020).

63. Yang C, Shen Q, Cai W, Zhu W, Li Z, Wu L, et al. Impact of the zero-markup drug policy on hospitalisation expenditure in western rural China: an interrupted time series analysis. *Trop Med Int Heal*. 2017; 22(2):180–6.
64. Zhou Z, Su Y, Campbell B, Zhou Z, Gao J, Yu Q, et al. The financial impact of the “Zero-Markup Policy for Essential Drugs” on patients in county hospitals in western rural China. *PLoS One*. 2015; 10(3):1–17.
65. Li L, Chen Y, Yao L, Li Y. 成都市试点社区卫生服务机构实施药品“零差率”政策的效果评价 [Evaluation of the effects of implementing the “Zero-Markup” policy to drugs sold in community health service institutions of Chengdu]. *Chinese J New Drugs*. 2008; 17(21):1820–2 (in Chinese).
66. Bhaskarabhatla A, Chatterjee C, Anurag P, Pennings E. Mitigating regulatory impact: the case of partial price controls on metformin in India. *Health Policy Plan*. 2017; 32(2):194–204.
67. Lu CY, Ross-Degnan D, Stephens P, Liu B, Wagner AK. Changes in use of antidiabetic medications following price regulations in China (1999–2009). *J Pharm Heal Serv Res*. 2013; 4(1):3–11.
68. Chu HL, Liu SZ, Romeis JC. Assessing the effects of drug price reduction policies on older people in Taiwan. *Heal Serv Manag Res*. 2011; 24(1):1–7.
69. Resolution WHA72.8. Improving the transparency of markets for medicines, vaccines, and other health products. In: Seventy-second World Health Assembly, Geneva, 20–28 May 2019. Resolutions and decisions, annexes. Geneva: World Health Organization; 2019:2 (WHA72/2019/REC/1; https://apps.who.int/gb/or/e/e_wha72r1.html, accessed 29 August 2020).
70. The Council of the European Communities. Council directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems. *Official Journal of the European Communities*. 1989; 32(22):8–12 (<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31989L0105&from=EN>, accessed 19 August 2020).
71. Kohler JC, Mitsakakis N, Saadat F, Byng D, Martinez MG. Does pharmaceutical pricing transparency matter? Examining Brazil’s public procurement system. *Global Health*. 2015; 1–13 (<http://dx.doi.org/10.1186/s12992-015-0118-8>, accessed 29 August 2020).
72. Moodley R, Suleman F. Evaluating the impact of the single exit price policy on a basket of originator medicines in South Africa from 1999 to 2014 using a time series analysis. *BMC Health Serv Res*. 2019;19(1):1–18.
73. Moodley R, Suleman F. The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014. *PLoS One*. 2019; 14(7):1–18 (<http://dx.doi.org/10.1371/journal.pone.0219690>, accessed 29 August 2020).
74. Pharmaceutical benefits scheme price disclosure arrangements procedural and operational guidelines. Canberra: Australian Government Department of Health; 2016.
75. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed entry agreements for oncology drugs: lessons from the European experience to inform the future. *Front Pharmacol*. 2017; 8(April):1–8.
76. Langley T, Lacey J, Johnson A, Newman C, Subramanian D, Khare M, et al. An evaluation of a price transparency intervention for two commonly prescribed medications on total institutional expenditure: a prospective study. *Future Healthc J*. 2018; 5(3):198–202.
77. Berdud M, Chalkidou K, Dean E, Ferraro J, Garrison L, Nemzoff C, et al. The future of global health procurement: issues around pricing transparency. Vol. 507. Washington (DC): Center for Global Development Working Paper; 2019 (www.cgdev.org, accessed 29 August 2020).

78. Moon S. Removing the blindfold on medicines pricing. *Br Med J.* 2018; 360:k840 (<https://doi.org/10.1136/bmj.k840>, accessed 29 August 2020).
79. Clark M, Heltzer N, Rankin J. Managing the tender process. In: Embrey MA, editor. *MDS-3 Managing access to medicines and technologies*. Arlington (VA): Management Sciences for Health; 2012:21.10 21.28.
80. Maniadakis N, Holtorf AP, Otávio Corrêa J, Gialama F, Wijaya K. Shaping pharmaceutical tenders for effectiveness and sustainability in countries with expanding healthcare coverage. *Appl Health Econ Health Policy.* 2018; 16(5):591–607 (<https://doi.org/10.1007/s40258-018-0405-7>, accessed 29 August 2020).
81. Garattini L, Van de Vooren K, Freemantle N. Tendering and value-based pricing: lessons from Italy on human papilloma virus vaccines. *J R Soc Med.* 2014; 107(1):4–5.
82. Adesina A, Wirtz VJ, Dratler S. Reforming antiretroviral price negotiations and public procurement: the Mexican experience. *Health Policy Plan.* 2013; 28(1):1–10.
83. Wouters OJ, Sandberg DM, Pillay A, Kanavos PG. The impact of pharmaceutical tendering on prices and market concentration in South Africa over a 14-year period. *Soc Sci Med.* 2019; 220:362–70 (<https://doi.org/10.1016/j.socscimed.2018.11.029>, accessed 29 August 2020).
84. Managing medicine supply [website]. PHARMAC: New Zealand Pharmaceutical Management Agency; 2016 (<https://www.pharmac.govt.nz/about/your-guide-to-pharmac/factsheet-07-managing-medicine-supply/>, accessed 24 August 2020).
85. Raventós P, Zolezzi S. Electronic tendering of pharmaceuticals and medical devices in Chile. *J Bus Res.* 2015; 68(12):2569–78 (<http://dx.doi.org/10.1016/j.jbusres.2015.06.024>, accessed 29 August 2020).
86. Operational principles for good pharmaceutical procurement. Geneva: World Health Organization; 1999 (<https://www.who.int/3by5/en/who-edm-par-99-5.pdf>, accessed 29 August 2020).
87. Kaplan W, Wirtz V, Nguyen A, Ewen M, Vogler S, Laing R. Policy options for promoting the use of generic medicines in low- and middle-income countries. Amsterdam: Health Action International; 2016 (http://haiweb.org/wp-content/uploads/2017/02/HAI_Review_generics_policies_final.pdf, accessed 19 August 2020).
88. Rémuzat C, Kapuśniak A, Caban A, Ionescu D, Radière G, Mendoza C, et al. Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. *J Mark Access Heal Policy.* 2017; 5(1):1307315 (<https://www.tandfonline.com/doi/full/10.1080/20016689.2017.1307315>, accessed 29 August 2020).
89. Center for Drug Evaluation and Research. Clinical immunogenicity considerations for biosimilar and interchangeable insulin products guidance for industry DRAFT GUIDANCE. Silver Spring (MD): United States Food and Drug Administration; 2019 (<https://www.fda.gov/media/133014/download>, accessed 29 August 2020).
90. Buzzelli C, Kangasharju A, Linnosmaa I, Valtonen H. Impact of generic substitution on pharmaceutical prices and expenditures in OECD countries. *J Pharm Financ Econ Policy.* 2006; 15(1):41–63.
91. Andersson K, Bergström G, Petzold MG, Carlsten A. Impact of a generic substitution reform on patients' and society's expenditure for pharmaceuticals. *Health Policy (New York).* 2007; 81(2–3):376–84.
92. Clark B, DuChane J, Hou J, Rubinstein E, McMurray J, Duncan I. Evaluation of increased adherence and cost savings of an employer value-based benefits program targeting generic antihyperlipidemic and antidiabetic medications. *J Manag Care Pharm.* 2014; 20(2):141–50.

93. Fraeyman J, Verbelen M, Hens N, Van Hal G, De Loof H, Beutels P. Evolutions in both co-payment and generic market share for common medication in the Belgian reference pricing system. *Appl Health Econ Health Policy*. 2013; 11(5):543–52.
94. Chen CL, Chen L, Yang WC. The influences of Taiwan's generic grouping price policy on drug prices and expenditures: Evidence from analysing the consumption of the three most-used classes of cardiovascular drugs. *BMC Public Health*. 2008; 8:1–13.
95. Godman B, Wettermark B, Miranda J, Bennie M, Martin A, Malmström RE. Influence of multiple initiatives in Sweden to enhance ARB prescribing efficiency following generic losartan; findings and implications for other countries. *Int J Clin Pract*. 2013; 67(9):853–62.
96. Lee B, Garay OU, Goldhaber-Fiebert J, Tang J, Lightwood J, Wilson LS. Argentina's generic drug law: was it successful? *Value Heal*. 2013; 16(7):A672.
97. Bhargava V, Greg ME, Shields MC. Addition of generic medication vouchers to a pharmacist academic detailing program: effects on the generic dispensing ratio in a physician-hospital organization. *J Manag Care Pharm*. 2010; 16(6):384–92.
98. Danzon PM, Furukawa M. Cross-national evidence on generic pharmaceuticals: pharmacy vs. physician-driven markets. NBER Working Paper. Report No.: 17226. Cambridge (MA): National Bureau of Economic Research; 2011 (www.nber.org/papers/w17226, accessed 19 August 2020).
99. Balmaceda C, Espinoza MA, Diaz J. Impacto de una Política de Equivalencia Terapéutica en el Precio de Medicamentos en Chile [Impact of a policy of therapeutic equivalence on the price of medicines in Chile]. *Value Heal Reg Issues*. 2015; 8:43–8 (in Spanish) (<http://dx.doi.org/10.1016/j.vhri.2015.04.003>, accessed 29 August 2020).
100. Colgan S, Faasse K, Martin LR, Stephens MH, Grey A, Petrie KJ. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. *BMJ Open*. 2015; 5(12).
101. Gebresillassie BM, Belachew SA, Tefera YG, Abebe TB, Mekuria AB, Haile KT, et al. Evaluating patients', physicians' and pharmacy professionals' perception and concern regarding generic medicines in Gondar town, northwest Ethiopia: a multi-stakeholder, cross-sectional survey. *PLoS One*. 2018; 13(11):1–13.
102. Jacobs I, Singh E, Sewell KL, Al-Sabbagh A, Shane LG. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient Prefer Adherence*. 2016; 10:937–48.
103. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. WHO Technical Report Series. Geneva: World Health Organization; 2015: Annex 7 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf?ua=1, accessed 21 August 2020).
104. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization. Sixty-seventh report. WHO Technical Report Series. Geneva: World Health Organization; 2017: Annex 2 (https://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1, accessed 21 August 2020).
105. Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology replacement. In: WHO Expert Committee on Biological Standardization. Sixty-fourth report. WHO Technical Report Series. Geneva: World Health Organization; 2014: Annex 4 (https://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf, accessed 21 August 2020).

106. Ferraresi M, Gucciardi G, Rizzo L. Does purchase centralization reduce public expenditure? Evidence from the Italian healthcare system. *Soc Ital di Econ pubblica*. 2017; (732).
107. Toulemon L. The effect of group purchasing on prices hospitals pay for medicines. *Heal Econ (United Kingdom)*. 2018; 27(9):1380–93.
108. Baldi S, Vannoni D. The impact of centralization on pharmaceutical procurement prices: the role of institutional quality and corruption. *Reg Stud*. 2017; 51(3):426–38.
109. Dubois P, Lefouili Y, Straub S. Pooled procurement of drugs in low and middle income countries. Toulouse: Toulouse School of Economics; 2020 (https://www.tse-fr.eu/sites/default/files/TSE/documents/doc/wp/2019/wp_tse_999.pdf, accessed 21 August 2020).
110. Kim SW, Skordis-Worrall J. Can voluntary pooled procurement reduce the price of antiretroviral drugs? A case study of Efavirenz. *Health Policy Plan*. 2017; 32(4):516–26.
111. Barbosa K de S, Fiuza E. Demand aggregation and credit risk effects in pooled procurement: evidence from the Brazilian public purchases of pharmaceuticals and medical supplies. C-Micro Working Paper Series. Report No. 299. São Paulo: Escola de Economia de São Paulo, Fundação Getulio Vargas; 2011.
112. Multi-country regional pooled procurement of medicines. Geneva: World Health Organization; 2007 (<https://www.who.int/medicines/publications/PooledProcurement.pdf>, accessed 21 August 2020).
113. Setting an approved ex-manufacturer price for new or extended listings. Fact sheet. Canberra: Australian Government Department of Health; 2017. (<https://www.pbs.gov.au/info/industry/pricing/pbs-items/fact-sheet-setting-an-approved-ex-manufacturer-price>, accessed 29 August 2020).
114. Mamiya H. Update of drug pricing system in Japan. Tokyo: Ministry of Health, Labour and Welfare; 2018 (<https://www.mhlw.go.jp/content/11123000/000335166.pdf>, accessed 29 August 2020).
115. V éran M. Amendement N°474. Paris: L'Assemblée Nationale; 2019 (<http://www.assemblee-nationale.fr/dyn/15/amendements/2416/AN/474>, accessed 29 August 2020) (in French).
116. Trade in Pharmaceutical Products. Geneva: World Trade Organization; 1994 (https://www.wto.org/gatt_docs/English/SULPDF/91770009.pdf, accessed 21 August 2020).
117. Bauer M. The compounding effect of tariffs on medicines: estimating the real cost of emerging markets' protectionism. *Eur Cent Int Polit Econ*. 2017; 1(1):1–45 (<http://ecipe.org/app/uploads/2017/09/Tariffs-on-medicines-final.pdf>, accessed 29 August 2020).
118. Creese A. Working paper 5: Sales taxes on medicines. Geneva: World Health Organization/Health Action International; 2011 (<http://www.haiweb.org/medicineprices/24072012/CompetitionFinalMay2011.pdf>, accessed 29 August 2020).

Annex 1: Persons involved in development of the guideline

Members of the GDG

Lisa Bero

Chair, Medicines Use and Health Outcomes
The University of Sydney School of Pharmacy,
Sydney, Australia

Amadou Moctar Dièye

Director
Ministère de la Santé et de l'Action sociale
Dakar, Senegal

Tanya Potashnik

Director of Policy and Economic Analysis
Patented Medicine Prices Review Board
Government of Canada, Ottawa, Canada

Vânia Cristina Canuto Santos

Director, Health Technology Incorporation
Department (DGITS)
Ministry of Health, Brasília, Brazil

Netnapis Suchonwanich

Advisor, Health Intervention and Technology
Assessment Program (HiTAP)
Ministry of Public Health,
Mueang Nonthaburi, Thailand

Sabine Vogler

Head of the Pharmacoeconomic Department
Austrian National Public Health Institute
Vienna, Austria

Rasha Ziada

Head of Central Administration of Pharmaceutical
Affairs
Egyptian Drug Authority, Cairo, Egypt

YingYao Chen

Director, Key Lab of Health Technology Assessment
Fudan University
The People's Republic of China

Andrew Hill

Senior Visiting Research Fellow
Department of Pharmacology and Therapeutics
The University of Liverpool, the United Kingdom

Shadi Saleh

Founding Director Global Health Institute
American University of Beirut
Beirut, Lebanon

Sakthivel Selvaraj

Director, Health Economics, Financing and Policy
Public Health Foundation of India
New Delhi, India

Fatima Suleman

Chairperson, National Medicines Pricing
Committee National Department of Health
University of KwaZulu-Natal, Durban, South Africa

Jo Watson

Deputy Chair, Pharmaceutical Benefits Advisory
Committee
Department of Health, Canberra, Australia

External review group

Government agencies or health services

Ministry of Health, United Republic of Tanzania	Siana Mapunjo
Ministry of Health, Malaysia	Faridah Aryani binti Md. Yusof
The King Hussein Cancer Center, Jordan	Saad Jaddoua
Department of Health, Australia	Andrew Rintoul
Estonian Health Insurance Fund	Erki Laidmäe
Norwegian Medicines Agency	Helga Festøy
Comité Economique des Produits de Santé, France	Jonathan Rodrigues
Direção de Avaliação de Tecnologias de Saúde, Portugal	Sónia Caldeira, Claudia Furtado
Egyptian Drug Authority, Cairo, Egypt	Mohamed Amine

Organizations

World Bank Group	Ana Holt
Transparency International	Jonathan Cushing
European Public Health Alliance and European Medicines Agency	Yannis Natsis
Melanoma Patient Network Europe	Bettina Ryll
International Federation of Pharmaceutical Manufacturers & Associations	Fumie Griego
International Generic and Biosimilar Medicines Association	Suzette Kox

Individuals (acting in a personal capacity)

Suerie Moon	Graduate Institute Geneva, Switzerland
Cha-oncin Sooksriwong	Thammasat University, Thailand
Andrew Gray	University of KwaZulu-Natal, South Africa
Maulik Chokshi	ACCESS Health International, India
Asita de Silva	University of Kelaniya, Sri Lanka
Gergely Németh	EURIPID Collaboration

Systematic review production and management team

Systematic review

Aukje Mantel-Teeuwisse

Professor Pharmacy and Global Health
Managing Director
Utrecht Centre for Pharmaceutical Policy and Regulation, Faculty of Science, Utrecht University, the Netherlands

Rianne van den Ham

Assistant Professor
Utrecht Centre for Pharmaceutical Policy and Regulation, Faculty of Science, Utrecht University, the Netherlands

David Tordrup

Doctoral candidate
Utrecht Centre for Pharmaceutical Policy and Regulation, Faculty of Science, Utrecht University, the Netherlands

Christine Leopold

Researcher
Utrecht Centre for Pharmaceutical Policy and Regulation, Faculty of Science, Utrecht University, the Netherlands

Research support:

Lynn Al-Tayara, Lizanne Arnoldy, Tom Buis, Rachelle Harris, Iris Joosse, Daniela Moyo-Holz

Search strategy (commissioned by Utrecht University)

Julie Glanville

Associate Director
York Health Economics Consortium,
University of York, the United Kingdom

Eleanor Kotas

Information Specialist
York Health Economics Consortium,
University of York, the United Kingdom

Search and screening support

Ross Birtles, Mick Arber, Chris Bartlett, James Mahon

Additional grey literature search commissioned by WHO

Deborah Toppenberg-Pejcic

Technical experts supporting the systematic review team (commissioned by Utrecht University)

Zaheer-Ud-Din Babar

Professor in Medicines and Healthcare
Director, Pharmaceutical Policy and Practice
Research Centre, Department of Pharmacy,
University of Huddersfield, the United Kingdom

Kalipso Chalkidou

Professor of Practice in Global Health, Imperial
College London, the United Kingdom
Director of International Decision Support Initiative
Senior Fellow, Center for Global Development,
London

Jaime Espín

Professor, The Andalusian School of Public Health
Escuela Andaluza de Salud Publica, Granada, Spain

Members of the WHO guideline steering group

WHO headquarters

Department of Health Products Policy and Standards

Kiusiang Tay-Teo (Lead)	Allison Colbert
Bernadette Capello	Swathi Iyengar
Andrew Rintoul	Suzanne Hill

Other departments

Melanie Bertram	Tania Cernuschi
Department of Health Systems, Governance and Financing	Department of Immunization, Vaccines and Biologicals
André Ilbawi	Johanna Fihman
Department of Noncommunicable Disease and Mental Health	Department of Immunization, Vaccines and Biologicals

WHO Regional Offices

Regional Office for Africa

Jean-Baptiste Nikiema, Aissatou Sougou

Regional Office for the Americas

Analía Porras

Regional Office for the Eastern Mediterranean

Adi al-Nuseirat, Houda Langer

Regional Office for South East-Asia

Klara Tisocki

Regional Office for Europe

Dorina Pirgari, Sarah Garner

Regional Office the Western Pacific

Socorro Escalante

Annex 2: Declaration of interests of GDG members

Declaration	Management
Lisa Bero declared no conflict of interest.	No further action taken
YingYao Chen declared that Fudan University received research funding from pharmaceutical company Bristol-Myers Squibb and medical technology companies (Medtronic, Braun, Edwards, BGI, Roche Diagnostics) after 2017. The research projects with funding from Edwards, BGI and Roche Diagnostics are ongoing. However, these projects are not directly related to the pricing of the health technologies.	No further action taken
Amadou Moctar Dièye declared no conflict of interest.	No further action taken
Andrew Hill declared consultancy payments in 2015 from Merck and Janssen Pharmaceutical for work not related to pricing of pharmaceutical products.	No further action taken
Tanya Potashnik declared no conflict of interest.	No further action taken
Shadi Saleh declared receiving consultancy payments on three occasions from Novartis and Janssen Pharmaceuticals for technical work on budget impact modelling and his participation as an expert in workshops relating to value-based pricing or price negotiation. He declared that all three projects have concluded and no further works are planned.	Recused from participating in the discussion and recommendation formulation for value-based pricing and tendering and negotiation
Vânia Cristina Canuto Santos declared no conflict of interest.	No further action taken
Sakthivel Selvaraj declared no conflict of interest.	No further action taken
Netnapis Suchonwanich declared no conflict of interest.	No further action taken
Fatima Suleman declared that her affiliated organizations received consultancy payments on four occasions from World Health Organization, consulting firm HERA, and South African National Department of Health. These consultancies related to situational assessment or capacity building activities in lower-income countries.	No further action taken
Sabine Vogler declared that her employer – Gesundheit Österreich – will provide financial payments for the time she will devote to the work of the guideline development group.	No further action taken
Jo Watson declared having provided statements in public forums on the role, processes of the Pharmaceutical Benefits Advisory Committee since 2013, in her capacity as a member of the Committee paid by the Australian Government Department of Health. The topics related to decision-making and the rationale for decisions, including pharmaceutical pricing, value for money and access to medicines.	No further action taken
Rasha Ziada declared no conflict of interest.	No further action taken



ISBN 978-92-4-001187-8

9789240011878



9 789240 011878