WHO Guideline on Country Pharmaceutical Pricing Policies

Web Annex B

EVIDENCE TO DECISION (EtD) TABLES

What is an EtD framework?

The purpose of EtD frameworks is to help groups of people (panels) making healthcare recommendations or decisions move from evidence to decisions. Frameworks can:

- Inform panel members' judgements about the pros and cons of each intervention that is considered;
- Ensure the important factors that determine a decision (criteria) are considered;
- Provide a concise summary of the best available research evidence to inform judgements about each criterion;
- Help structure discussion and identify reasons for disagreements;
- Make the basis for decisions transparent to guideline users or those affected by a policy decision.

Source: https://www.decide-collaboration.eu/evidence-decision-etd-framework

WHO guideline on country pharmaceutical pricing policies, second edition. Web Annex B. Evidence-to-decision tables

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1. External reference pricing

Questions	1. What is the effect of **External Reference Pricing** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **External Reference Pricing**?	
Population	Medicines and vaccines for human use	**Definition:** External Reference Pricing (ERP; also known as international reference pricing) refers to the practice of using the price of a pharmaceutical product[i] in one or several jurisdictions[ii] to derive a benchmark or reference price. The purpose of ERP 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 ERP, but ERP has been used particularly for the pricing of single-source on-patent medicines.
Intervention	External Reference Pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions (administrative units) Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	ERP is a policy widely adopted in many European countries *(1)*, as well as in high- and middle-income countries of other regions (e.g. Brazil, Egypt, Saudi Arabia, Spain, Thailand, Turkey, the United Arab Emirates, South Africa, Iran, Jordan, Lebanon and the Gulf countries) *(2,3)*. Most recently, the government in Malaysia has announced the introduction of ERP *(4)*.	In 2018, the US government has presented a proposal for setting the prices of medicines provided under Medicare Part B (i.e. outpatient physician-administered[iii] medicines) according to an international pricing index (IPI), to be phased in over a five-year period from 2019 to 2023. The IPI would be based on prices from 14 countries: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, the Netherlands, and the United Kingdom *(5)*.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Number of studies included in the systematic review:** No study met the inclusion criteria. The systematic review identified three **other published reviews on ERP**, which have less restrictive inclusion criteria (e.g. inclusion of uncontrolled studies and simulation modelling based on theoretical) *(6–8)*. Main findings from these reviews relating to effects are summarized below for consideration: • Published studies of various methodological designs (e.g. case studies, simulation) have suggested potentially substantial savings for public payers. • The effect size and potential for unintended consequences (see below) are highly dependent on policy design, including country basket, frequency of updates, calculation of reference price. • The policy effectiveness is limited by unavailability price information (e.g. due to prices at different point along the supply chain) and inaccurate information (e.g. due to not having the final net transaction price).	**Co-interventions:** Other criteria considered in ERP price-setting include "the cost of therapy; health gain from the patient perspective; cost-effectiveness; relative benefits compared with treatment alternatives; budget impact analysis; financial resources available for reimbursement and reward for innovation"*(3)*. **Information from excluded studies on the estimated effect size**: Findings cited in *(9)* suggests that €1 price reduction in Germany would lead to a reduction of €0.15 to €0.36 in 15 European countries that used ERR and had Germany in their basket *(10)*. Another study cited in *(9)* (not retrieved) noted that Denmark medicine prices decreased more than 26% after changing from ERP to Internal Price Referencing. The US Department of Health and Human Services projected a savings of "more than $17 billion over its first five years, and more than $50 billion in its first eight years" for Medicare and Medicaid *(11)*. **Duration of effect:** Commentators noted potential "fadeout' effect, where ERP was successful in the short-term but has gradually lost its effectiveness" *(12)* **Frequency of price revision**: A modelling study *(13)* cited in *(6)* "estimated that when systematic price revisions take place every year, the price decrease seen is almost double than the one seen when price revisions take place only every three years".
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Shortages**: Launch delays, product withdrawals and parallel exports have been noted in the literature *(12)*. **Quality issues**: No information **Safety issues**: No information **Anticompetitive, unethical or illegal conduct**: No information **Other potential unintended effects**: Some commentators suggest that ERP would influence not only national medicine prices but also prices worldwide due to the interlinking of prices *(6,9)*. There were assertion that this might lead to price convergence *(6)*, citing evidence from a study that observed narrower range of pharmaceutical prices among countries with different economic status, compared to the price variations for diagnostic and medical services where ERP was not implemented *(14)*	**Caveats on evidence**: Only theoretical discussion or qualitative case studies of potential undesirable effects have been presented in the literature *(6)*. Where presented, the 'evidence' did not clearly articulate the counterfactual. For example, the 'evidence' did not consider whether products would be launched in lower-priced countries at the same or similar time as countries with higher prices in the absence of ERP. Similarly, regarding parallel trade, a pharmaceutical company refusing to satisfy orders to prevent parallel exports could be considered as abusing its dominant position in violation of trade laws (e.g. in Europe, Article 102 of the TFEU), unless the order was apparently disproportionate with respect to the previous business relationships or market needs. **Effects modifiers:** The feasibility and effects of ERP could be hampered by the lack of transparency on net transaction prices in many jurisdictions because of (1) only list prices are published (2) price variations in healthcare systems with multiple payers.
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☒ Don't know	No study was included in the systematic review. Studies included in other systematic reviews *(6–8)* and the excluded study *(9)* suggested confounding factors or variable effects, likely to be influenced by market conditions.	The excluded study *(9)* cited that "other confounding factors are that ERP is only one of many pharmaceutical price regulation policies applied in each country and that discounts from negotiated prices are not taken into account while calculating ERP prices due to confidentiality."
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours policy ☐ Favour the policy	ERP is likely to deliver more desirable than undesirable effects, as indicated by: • Some (un-appraised) evidence on price reduction at least in the short run (albeit limited in the quantity and quality of evidence) • A lack of robust evidence attributing undesirable effects to ERP, including launch delays or product withdrawals in lower-income countries	Effective operationalization of ERP would require accurate and verifiable price data from the referenced countries. These data must be, at least with high degree of confidence, considered as comparable and net of all forms of discounts and rebates. Despite its seeming simplicity in principle, the operation could be complex and would therefore require adequate resources and skilled personnel.

[i] A pharmaceutical product, commonly referred interchangeably with drug, medicine or pharmaceutical, is defined as any manufactured or refined substance for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. For the purpose of this review, the scope includes medicines (both small molecules and biological products) and vaccines for human use.

[ii] Jurisdictions refer to countries, regions, or other organized purchasing authorities.

[iii] In some settings, outpatient refers to "a person who goes to a hospital for treatment, but who does not stay any nights there" while other settings (e.g. Europe), "outpatient medicines" could refer to settings outside of hospital (e.g. community pharmacy).

		☐ Varies ☒ Don't know	• Wide adoption or consideration of ERP as one part of the overall pricing policy.	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	Uncontrolled studies suggest that ERP might be effective in countries, including in 14 European countries *(9)*. Similarly, ERP has been applied in countries outside of Europe but without <u>comparative</u> evidence to demonstrate effectiveness. There is no information about its applicability in low-income countries.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	Literature suggests the potential occurrence of "beggar-thy-neighbour" practices, that under ERP, higher income countries "seem to want to capitalise on any price differences irrespective of (lower income) country archetype or per capita income level." (i.e. referring to the price of product in a lower-income country) "In principle, such practices nurture inequalities among countries, as wealth differences between referrer and referenced country proliferate" *(12)*. However, no empirical evidence was presented to support the statement.	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities**: Wide adoption suggests acceptance of ERP. **Patients and community**: No information	<u>Other stakeholders</u> **Insurers**: No information **Manufacturers or suppliers**: Noted a reduction in revenue, competitiveness, and incentive for innovation *(13,15)*. However, no supporting evidence has been presented. **Service providers:** No information
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Small ☐ Neutral ☐ Varies ☐ Don't know	**Human resource:** Skilled personnel is required for data collection and management, including developing methodology, standardizing price information, revising prices regularly to reflect changes in the reference prices in other markets. **Financial resource:** Mostly associated with human resources and data acquisition **Governance**: Legislative framework and procedures for the use of ERP need to be specified, including decision making processes **IT infrastructure**: Database management	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	The feasibility of implementation in low- and middle-income countries is dependent on: • **Reliability of price information**: Pricing authorities rely mostly on list prices rather than net transaction prices because of confidential agreements implemented in many countries. Differences in list price and (undisclosed) net transaction price of medicine have diminished the effectiveness of ERP, particularly in lower income countries. • **Availability of prices from comparable markets**: Lower-income countries appear to have relied on price information countries with a wide range of national incomes, reflecting different timing of product launch and large price variability, resulting in the need for a large sample of reference prices to better inform pricing decision *(2)*. This might increase technical and resource complexity of ERP in these countries.	Feasibility of implementation would require clear definition of: • **Technical methods**, including the number and criteria of reference countries under consideration, type of prices along the supply chain, and sources of information • **Monitoring**: Frequency of price collection, calculation and revision, and choice of exchange rates • **Rules for exceptional circumstances** arising from currency volatility and during shortages of supply
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely neutral ☐ Probably increase ☐ Increase ☐ Varies ☒ Don't know	Only short-term impacts on price were assessed in literature (not appraised in the literature). Long-term financial sustainability is unclear.	

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendation

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.

- 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 ERP 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 ERP was in favour of implementing the policy.
- Despite the relative conceptual simplicity of ERP, the GDG recognized the complexity of implementing so-called best-practice ERP, 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 ERP, especially in low- and middle-income countries.

Implementation considerations

- Effective operation of ERP 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 ERP 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 ERP is most often applied), with prices determined through ERP being used as the point of reference for further price negotiation.

Considerations towards research needs

- Study the impact of ERP 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 ERP 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 clear null hypothesis (e.g. ERP 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 ERP).

2. Internal reference pricing

Questions	1. What is the effect of **Internal Reference Pricing** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **Internal Reference Pricing**?	
Population	Medicines and vaccines for human use	**Definition:** Internal Reference Pricing, or IRP, refers to the practice of using the prices of a set of pharmaceutical products[iv] 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), or by therapeutic indication.
Intervention	Internal Reference Pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Many countries with pricing policies for pharmaceutical products have commonly employed Internal Reference Pricing, particularly for linking the prices of (closely) substitutable medicines i.e. generics, biosimilars or therapeutically equivalent or closely substitutable products *(17,18)*.	Internal reference pricing has been used to set the reimbursement rates of closely substitutable products, in healthcare 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) product.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☒ Moderate ☒ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** 26 studies. 11 studies on generic reference pricing (**GRP** i.e. ATC 5 level) *(19,20,29,21–28)* and 5 studies 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 (1 study from Sweden and 4 studies from the Republic of Korea) *(30–34)*; 8 studies on therapeutic reference pricing (**TRP** i.e. ATC 4 level) *(35–42)*; 2 studies on mix of generic and therapeutic reference pricing (**GTRP**) *(43,44)*. **Price**: **GRP** was found to reduce prices of both branded and generic medicines, estimated at between 13% *(22)* and 66% *(27)*, with the price reductions largely influenced by generic substitution policies. One study did not observe price reduction because the reference price determined through GRP was higher than the market prevailing price *(29)*. **TRP** was found to reduce the costs of medicines between 10% to 45% *(35,37)*. **Expenditure: GRP** was found to decrease overall expenditure in most studies, but the level of reductions was either not statistically significant, of unknown statistical significance, or smaller than the reduction in average prices *(21)*, possibly reflecting savings being offset by concurrent increase in the quantity of medicines demanded due to lower prices. Studies from the Republic of Korea on policies where prices of generic products were set at 53.55% of the price of the originator product observed statistically significant reduction in expenditure only in the short-term due to concurrent increased in utilization *(31–34)*. **TRP** was found to be associated with a substantial decrease in costs for the insurers *(35–37)* and overall expenditure. **Volume:** The overall evidence suggests that **GRP, TRP** and **GTRP** increased switching to, hence utilization of, generic/lower-cost/fully reimbursed medicines from brand/higher-cost/partially or non-reimbursed medicines without affecting the overall demand. **Availability:** Two studies observed an increase in the number of generics following GRP and a decrease in the number of branded products *(21,25)*. **Affordability**: No information. **Quality:** One study from the Republic of Korea on compulsory price reductions for generic antidiabetic products at a proportion of the originator products found that incidents of medical and surgical procedures relating to diabetic complications were unaffected, but the post-intervention observation period was short *(33)*.	**Co-interventions**: Price cap based on reference price, mark-up adjustment, compulsory price reduction, public tender, policies to encourage generic prescribing/substitutions, in parallel with strengthening of regulatory functions to ensure quality of generic medicines and building public trusts. **Duration of effect:** Most observations are short term (~1 year) post intervention, but one study effects up to 10 years post intervention *(22)*. **Possible externalities:** Global price level and availability and affordability in other countries are not known. **Other systematic reviews:** A review published in Cochrane Library *(45)* found an estimated overall reduction in insurer's expenditure of 18% (range: -53% to 4%), an overall increase in the utilization of the lower priced drugs that set the benchmark price (+15%; range: -14% to +166%) and an overall decrease in the utilization (-39%, range: -87% to -17%) of higher priced drugs for which the patients need to pay the difference in price. Other reviews concluded with similar observations *(46–48)*. citing two studies from British Columbia on the effects of substitutions of ACE Inhibitors within a reference pricing framework, one review *(46)* noted that (therapeutic) reference pricing did not affect patient health outcomes. Review by Galizzi et al made the following qualitative observations on the following effect modifiers that facilitating larger price reduction, savings or market shares: • Generic competition prior to reference pricing • First year of policy implementation • Brand-name drug did not lower price to reference price, launched new formulations, or marketing substitutable on-patent drugs.
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct**: One study did not observe any additional demand shift from off-patent drugs subject to GRP to on-patent drugs in the same therapeutic category *(22)*.	Some commentators have noted that, in anticipation of price reduction following loss of exclusivity due to generic competition and price linkage within IRP, the originator company may engage in practices, such as switching the market to a new formulation that offers little or no therapeutic benefits (i.e. product hopping) or introduce an additional brand (usually) by the originator companies for their own branded medicine (i.e. 'pseudo-generic' or 'authorized generic')[v]. These might weaken IRP's effectiveness.
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☒ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated "moderate" level of certainty on the effects of GRP, TRP, or GTRP on price, "moderate" or "low" for volume; but "very low" on expenditure.	Publication bias not assessed.

[iv] For the purpose of this guideline, pharmaceutical product is defined as medicines and vaccines.

[v] A pseudo-generic medicine is an additional brand marketed (usually) by the originator companies for their own branded medicine, but priced lower than their branded medicine. This business practice may discourage other genuinely generic medicines from entering the market because of reduced market share.

Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☐ Varies ☐ Don't know	GRP and TRP are likely to deliver more desirable than undesirable effects, as indicated by: • Evidence on price reduction and improved expenditure efficiency (through seemingly higher volume) at least in the short and long term (up to 10 years of observation). • A lack of robust evidence to attribute GRP and TRP to undesirable effects, including switching to therapeutically similar on-patent products not subject to price regulations. • Wide adoption or consideration of GRP and TRP as one part of the overall pricing policy.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☒ Don't know	The systematic review included only one study from LMIC for TRP conducted in Taiwan Province of China *(24)*. However, the findings of this study were not different from studies conducted in higher income countries.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	No information.	Although there is no formal evidence examining the impact of GRP or TRP on equity, lower costs of treatments arising from GRP and TRP could enhance affordability and broader access.
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Wide adoption suggests acceptance of IRP **Patients and community**: GRP and TRP were usually accompanied by rules that retained the rights of the patients for choosing not to switch to lower priced generic or therapeutic equivalent products. However, patients might incur higher level of co-payments. A systematic review noted that "A temporary rise in physician visits was observed, probably owing to an adaptation period for both physicians and patients" *(46)*	Other stakeholders **Insurers:** Evidence suggests cost savings for insurers, particularly TRP. **Manufacturers or suppliers**: Evidence from one study suggested that the joint profits of generic producers were positively affected by Reference Pricing (the increase = 185%), for a given number of generics present in the market *(21)*, but another study found a reduction in producers revenue *(25)*. Prior knowledge of price linkage to the lowest priced medicines has been noted as a possible disincentive for generic producers to supply *(49)*. Country experiences suggests higher level of resistance to TRP than GRP. **Service providers:** GRP and TRP were accompanied by rules that retained the rights of the prescribers to choose not to switch to lower priced generic or therapeutic equivalent products.
Resources required	How large are the resource requirements for implementing the policy?	☒ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	**Human resource**: When applying TRP, technical expertise in determining therapeutically equivalent dose is required. **Financial resource:** Mostly associated with human resources **Governance requirements:** Legislative framework and procedures for the use of TRP need to be specified, including decision making processes. **IT infrastructure:** Maintenance of price database to ensure regular revision of prices in accordance to changes in market prices arising from price competition.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	Feasibility of implementing GRP or TRP is dependent on LMICs' 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 effecting price impacts of IRP. Many LMICs currently do not have a generic substitution policy, which may hamper the implementation of GRP. The need for regular revision of prices in accordance to market prevailing prices could have an impact on the overall feasibility too.	Countries have adopted gradual implementation when considering GRP and applied only to a subsample of off-patent substances. In Norway, for example, "this was mainly due to practical reasons and the administrative workload related to implementing reference prices for the relevant products, but also to gain some experience before extending the scheme to more substances." *(21)*
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☒ Probably increase ☐ Increase ☐ Varies ☐ Don't know	Extant evidence suggests that both GRP and TRP could have longer term (2-10 years) impacts on price, although observed impacts were less substantial over time *(22,37)*. This suggests both policies could enhance long-term sustainability of healthcare system.	

Conclusion

☐ Strong recommendation against the policy | ☐ Conditional recommendation against the policy | ☐ Conditional recommendation for either the policy or comparison | ☒ Conditional recommendation for the policy | ☐ Strong recommendation for the policy

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

- IRP 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.B. WHO suggests the use of internal reference pricing for medicines according to the principles of therapeutic reference pricing[vii], under the following conditions.

- IRP 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 IRP 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 IRP 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.

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 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 IRP;
  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 IRP or when authorizing the use of products priced higher than the internally referenced price because of specific patient clinical needs).

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

Considerations towards research needs

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

[vi] Equivalence for the purpose of pricing set through ATC 5th Level, with consideration to factors such as dose and pack size.
[vii] Equivalence for the purpose of pricing set through Anatomical Therapeutic Chemical Classification System 4th Level based on clinical trial evidence of non-inferiority.

3. Value-based pricing

Questions	1. What is the effect of **value-based pricing** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **value-based pricing**?	
Population	Medicines and vaccines for human use	**Definition:** Value based pricing (VBP) is an approach that aims to set prices for pharmaceutical products based on the value or worth that patients and health systems attribute to the pharmaceutical products. 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. It is important to note the broader purposes of HTA[viii] other than setting price.
Intervention	Value based pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: Shadi Saleh

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	World Health Assembly Resolution 67.23 *Health intervention and technology assessment in support of universal health coverage*, WHO has a mandate in supporting Member States on developing the practice of HTA and its uses in evidence-based decision-making to inform allocation of healthcare resources *(50)*. Many countries globally, in collaboration with professional organizations or networks, have 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.	HTAs are not limited to economic evaluation of health technology (i.e. cost effectiveness analysis) (e.g. including budget impact analysis). HTAs have been used as a tool to inform broad reform and divestment decisions. For example, in 1999-2002, The French Government Transparency Commission re-evaluated the actual benefits (known as "SMR and ASMR") of 4,490 medicines, resulting in price reduction for drugs with insufficient benefits in 2000-2002.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☒ Don't know	**Number of studies included in the systematic review:** Three studies on VBP met the inclusion criteria of the systematic review *(43,51,52)*; one investigated the use of HTA as part of national procedure for disinvesting cost-ineffective anti-hyperlipidaemics in the Republic of Korea, unless the manufacturers revise price to meet cost-effectiveness (Not specified) *(52)*. **Price:** A regression analysis showed countries incorporated cost-efficiency analysis as part of pricing policies achieved statistically significant lower prices for one therapeutic class of medicines (ACE inhibitors) *(43)*. **Expenditure:** One study observed an increase in expenditure despite downward price trends following price reduction/delisting process based on cost-effectiveness assessment *(52)*. The expenditure increase was largely due to an increase in demand (see below on "volume"). **Volume:** One study observed an increased consumption of products NOT subject to price reduction (because these products were deemed cost-effective) *(52)*. **Availability:** No information **Affordability**: No information	**Co-interventions**: Reference pricing, substitution policy for generic medicines, mark-up regulations, profit control through claw-back schemes **2015 WHO Guideline** reviewed a small number of studies relevant to VBP. These references discussed, for example, the quality of HTA submissions, the relative merits of HTA versus reference pricing, transferability of economic assessments and availability of locally relevant economic evidence. However, none of those studies examined the impact of VBP on price, volume, availability, affordability.
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know	**Shortages:** A number of qualitative studies have suggested inequitable access to medicines due to differences in the timeframe and processes in undertaking HTA to inform pricing and reimbursement decisions, as well as inconsistencies in how the supporting evidence informs assessment, particularly for medicines deemed lower value *(53,54)*. **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct:** No information	
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☐ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated "very low" or "moderate" level of certainty on the effects of VBP through HTA on price, expenditure, and volume. All three studies had employed broad or incorrect classification of pricing policies in the jurisdictions under study, resulting in considerable measurement bias. For example, the UK was categorized as a "profit control" due to the Pharmaceutical Pricing Regulation Scheme in one of the studies *(51)*, despite the presence of HTA processes to inform pricing (albeit indirectly) and reimbursement decision. There were also substantial methodological shortcomings, particularly in examining the underlying assumption of regression methods, not addressing known but unobserved potential confounding factors (e.g. volume *(43)*, pricing policies on generic entry or prescriber tastes *(52)*).	Publication bias not assessed.
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☒ Varies ☐ Don't know	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 VBP/HTA to undesirable effects, including launch delays due to technical and process complexities • Wide adoption of VBP/HTA as the main pricing policy or a supporting pricing policy. However, desirable effects are likely to dependent on the capacity of the health systems in managing the technical and process complexities of VBP and HTA.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.

[viii] HTA may be applied to support decision makers in numerous instances, among which: (1) rolling-out broad public health programmes; (2) priority setting in health care; (3) including a new medicine into a reimbursement scheme; (4) identifying health interventions that produce the greatest health gain and offer value for money; (5) setting prices for medicines and other technologies based on their cost–effectiveness; (6) formulating clinical guidelines; (7) advising on the organisation systems within which health care is provided; (8) supporting decisions on diagnostics and medical equipment; (9) improving resource allocation and distribution particularly for high cost technologies (10) helping managers of hospital healthcare networks and other healthcare organisations; (11) make decisions regarding technology acquisition or adoption; (12) informing clinicians, providers, and patients about the proper use of healthcare interventions for particular health problems.

Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	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	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	HTA often uses composite metrics such as quality- or disability-adjusted life years (i.e. QALY or DALY) as the measures for quantifying comparative value of a health technology, which were used to inform pricing based on an implicit or explicit willingness to pay threshold. There have been numerous commentaries that highlighted the potential negative impact on health equity due to the application of these measures (e.g. examples listed under "consideration"). There are individual cases where VBP through the use of HTA has given rise to perceived inequitable decision (e.g.*(55)*), but these cases might reflect broader discussion of health system priority setting processes.	Scenarios noted in the literature where the use of QALY could give rise to inequitable decision include: "the discrepancy between aggregate individual utility of health programs on the one hand and, on the other hand, societal valuations that include concerns for fairness" *(56)*; "failing to account for societal values that favor treating more severe illness and ensuring equal access to resources, regardless of pre-existing conditions or capacity to benefit" *(57)*; or age discrimination.
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** The concept and approach of VBP 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 VBP could be strong barriers to acceptance *(58)*. **Patients and community**: Social values or judgements on social values might not be fully or accurately captured through HTA. See examples under equity. *(57)*	<u>Other stakeholders</u> **Insurers:** No information. **Manufacturers or suppliers:** The concept and approach of VBP and HTA seem to have received broad endorsement by industry (e.g. *(59)*). **Service providers:** HTA generally considers costs and benefits/value from the societal or health care sector perspective, rather than the perspective of individual clinicians or patients. Implementation or communication of pricing or reimbursement decisions based on value assessment might be challenging for service providers *(60)*.
Resources required	How large are the resource requirements for implementing the policy?	☒ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	**Human resource**: High level of technical proficiency is required to undertake HTA and VBP. **Financial resource requirement**: High demand for financial resources due to the complexity of the assessment and the technical expertise required. **Governance requirements:** Legislative framework and procedures for the use of VBP and HTA need to be specified, including decision making processes to stakeholders. Given the intensity of resource requirements, collaborations with third party (e.g. academic institutions) might be required, which in turn, requires formal governance to ensure independence and accountability. **IT infrastructure:** HTA is data intensive, which requires robust IT infrastructure and reliable data.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	LMICs without any existing HTA/VBP policies will have to develop the 'institution' gradually, starting with activities that do not require a large amount of resource but must be with clear link to important policy and pricing decisions (e.g. of major public health impacts). Development of HTA and VBP must run alongside clear framework of evidence-based policies and practices, value for money, data infrastructure, policy monitoring. 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 VBP even in the countries with the well-established HTA authorities.	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☐ Probably increase ☐ Increase ☐ Varies ☒ Don't know	Existing healthcare systems featuring the use of VBP through HTA in high-income countries suggest that once established and with timely reform, such institutions and processes are sustainable. However, it is unclear the financial implications of such approach compared to possible policy alternatives.	

Conclusion				
☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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).

Implementation considerations

- Effective operation of value-based pricing using HTA should consider the following factors.
  - Value-based pricing using HTA should be implemented in the context of maximizing health outcomes (cf. other conceptualization of "value" such as innovativeness, industry development, public expectation).
  - Countries should consider value-based pricing and HTA approaches suitable for local decision-making structures and technical capacity.
  - Countries should collaborate to promote exchange of information, and if appropriate, develop common requirements for value-based pricing using HTA.
  - 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.
  - 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.
  - 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:
  - 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;
  - reviewing reports on value-based pricing using HTA submitted by companies with consideration to applicability to the local context;
  - evaluating the availability and completeness of the evidence on the new medicine and any companion technology at the time of value assessment; and
  - undertaking value-based pricing using HTA based on local information (e.g. clinical service and financing models) and data (e.g. demographic structure, costs).

Considerations towards research needs

- 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.

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

Questions	1. What is the effect of **mark-up regulation across the pharmaceutical supply and distribution chain** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **mark-up regulation across the pharmaceutical supply and distribution chain**?	
Population	Medicines and vaccines for human use	**Definition:** 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. A percentage or fixed mark-up could be specified at any point along the supply chain (e.g. ex-factory mark-up; and incorporating fee-for-service remuneration such as fees for dispensing or service quality). 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.
Intervention	Mark-up regulation across the pharmaceutical supply and distribution chain	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Many healthcare 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. People's Republic of China, Kuwait), setting maximum mark-up for medicines supplied at privately owned retail pharmacies (e.g. Oman and Kuwait), fixed or percentage mark-up for most stages of distribution (e.g. Mozambique, Brazil, Jordan, Australia, Lebanon, Syria and Tunisia), fixed or maximum retail prices (e.g. South Africa) *(61,62)*.	
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☒ Small ☒ Moderate ☐ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** 12 studies in total • Mark-up regulation: 7 studies, comprising one study on a series of changes to the Mark-up levels of wholesalers and retailers in Spain *(28)*, one high level assessment of overall Mark-up regulation in six European countries *(43)*, and 5 studies on the removal of 15% Mark-ups previously allowed for essential medicines supplied through public hospitals in China *(63–67)*. • Setting maximum retail or reimbursement prices: 5 studies, comprising one study each on the following policy variants: (i) reducing maximum ex-factory prices in Spain *(28)*, setting maximum retail prices in India *(68)* and antidiabetic medications in China *(69)*; reducing reimbursement rates of antipsychotics in Portugal (during economic recession) *(42)*; realignment of maximum reimbursement rates in Taiwan Province of China according to market prices *(70)*. **Price:** Mark-up regulation was found to have resulted in statistically significant reductions in price. The magnitude of reduction was not certain because regression analyses only presented coefficients that are not readily transformable into magnitude based on information presented in the published articles *(28,43)*. One study on the removal of mark-up for essential medicines supplied through public sector health facilities reported average decrease of 2.46% (uncontrolled finding presented without clear description of method) *(66)*. **Expenditure:** The study from Spain reported savings of around 2.75% associated with Mark-up adjustments, and around 1.7% with lowering the maximum ex-factory prices, over 10 years, estimated based on modelling without the 'dummy' variable for intervention *(28)*. Studies from China on removal of mark-up policy have estimated highly variable impacts on expenditure, with the reported costs of medicines per prescription/visit ranging from a savings of 9% to an increase in expenditure of 25.2%; the expenditure impacts were dependent on factors, such as the structure of compensation scheme to offset the lost revenues from the removal of Mark-up (see below under undesirable effects), timing of observation (i.e. short or long term), and location (different mix of demand for medicines) *(63–67)*. **Volume:** The study from Spain reported non-statistically significant effects on number of prescriptions per capita following Mark-up adjustments and lowering the maximum ex-factory prices *(28)*. One study from China that examined the effect of a series of reductions in maximum retail prices of antidiabetic medicines found that lower retail prices with increases in total per capita utilization of antidiabetic medications without shifts in use between non-regulated and price-regulated products *(69)*. **Availability:** No information **Affordability**: No information	**Co-interventions**: co-payment policies, reference pricing, and provide additional funding (in the form of subsidy) alongside policy that removed Mark-up for medicines in publicly financed facilities **Mark-up structure**: None of the studies included in the systematic review examined the effects of the structure of Mark-ups along the supply and distribution chain i.e. regressive or progressive, fixed amount or percentage, at which point of the supply and distribution chain. .
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct** • **Price convergence** at maximum regulated price for Metformin in India was observed because only 500mg metformin immediate release dose forms were within the scope of policy, but the maximum price for 500mg Metformin was calculated according to the weighted average of the market prices of top three brands *(68)*. • **Supplier induced demand for products with higher Mark-up margin**: Mark-ups on medicines have been used by publicly financed health facilities to generate income to support service operation or by clinicians to meet their income expectation. In China, this had "evolved into a perverse incentive" for clinicians preferring expensive medicines and involving in over-prescribing. This behaviour had contributed to drug price inflation *(63)*. Similarly, studies have noted that the removal of Mark-ups on a select set of products would result in increased expenditures for products NOT subject to the policy, including medicines, diagnostic tests, medical consumables, especially in health facilities having a greater reliance on drug revenues before the reform *(63,64,70)*. This suggests that service providers tried to offset lost income by increasing the provision of services and products with higher margin *(63,64,70)*.	

Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☒ Low ☐ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated "very low" or "low" level of certainty because of methodology shortcomings, including a lack of consideration for important variables that might effect price levels (e.g. volume of medicines as a proxy for demand), only measuring policy impacts in overall expenditure, and omitting to test model assumptions (e.g. parallel trend assumption for difference-in-difference model). Several studies were selective in choosing the medicines for study (e.g. Metformin, ACE-Inhibitors, antidiabetics, antihypertensives), when the policy was more widely adopted.	Publication bias not assessed.
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison ?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☐ Varies ☐ Don't know	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 • Stable or growing demand for the medicines within price regulation However, consideration must be given to the scope of regulation and the design of the Mark-up levels and structure, with a view to minimizing possible undesirable effects documented in the literature, such as price convergence or supplier induced demand for products with higher Mark-up margin.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	The generalizability of the findings is unclear. Evidence included in the systematic literature review was from higher 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.	
Equity	What would be the impact on health equity?	☐ Large positive ☒ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☐ Don't know	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, higher dispensing requirements e.g. sterile dispensing). A regressive mark-up structure, where higher priced medicines are subject to lower level of mark-ups, could also incentivize broader access to lower priced medicines (e.g. generic medicines). • Promoting consistency and transparency of prices across healthcare system and for consumers.	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Consistency and transparency of prices achieved through clear mark-up regulations could enhance government authorities' planning processes, for example, by providing greater predictability for expenditure. Mark-up regulations could also enhance system efficiency if the rebates and discounts in the distribution chain are considered when reviewing and regulating mark-ups and prices. **Patients and community:** Likely to be acceptable because it would provide consistency and transparency of prices, which could lead to greater affordability (e.g. through disclosure of rebates and discounts).	Other stakeholders **Insurers**: Depending on the complexity and structure of policy **Manufacturers or suppliers:** Depending on the complexity and structure of policy **Service providers:** Depending on the complexity and structure of policy
Resources required	How large are the resource requirements for implementing the policy?	☒ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	**Human resource**: Depending on complexity of the policy, the design, planning, implementation, and enforcement of mark-up regulations would require personnel with strong technical expertise and managerial skills. **Financial resource requirement**: Depending on the complexity of the policy, it might require high demand for financial resources in connection to human resource and governance requirements. **Governance requirements:** Legislative framework and procedures for Mark-up regulations need to be specified, including the method for determining the Mark-up levels (e.g. modelling), and stakeholder engagements. **IT infrastructure:** Database is required for managing information pertaining to medicine prices, rebates and discounts, and supply of medicines.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	The feasibility of implementing mark-up regulations would be dependent on various system factors, including existing healthcare system context, complexity of the policy, and the level of stakeholder engagement required.	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☒ Probably increase ☐ Increase ☐ Varies ☐ Don't know	If well-structured and implemented, mark-up regulation would probably enhance the long-term financial sustainability of healthcare system by improving government's ability to manage expenditure.	

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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.

Implementation considerations

a. Effective operation of mark-up regulations along the supply and distribution chain requires the following:
   - 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;
   - a mechanism for monitoring medicine prices, use, and sales, supported by adequate information technology infrastructure, and arrangements for seeking inputs from concerned stakeholders;
   - consideration of potential effects on non-regulated products; and
   - consideration of potential negative and positive effects on the operational revenue of health services following changes to mark-up regulations.

b. Methodology of mark-up regulations along the supply and distribution chain should consider the following factors:
   - point or points along the supply and distribution chain (e.g. ex-factory, ex-wholesaler, ex-pharmacy) at which mark-ups should be applied;
   - magnitude of mark-ups at each point on the supply and distribution chain, price level, product type and facility type, where appropriate;
   - design of the regressive mark-up structure, defined by percentage or fixed mark-ups;
   - methods for data collection and determining mark-up levels (e.g. financial impact modelling); and
   - non price-related measures, such as specifying dispensing fee and performance incentives.

Considerations towards research needs

- 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.

5. Promoting price transparency

Questions	1. What is the effect of promoting **price transparency** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **promoting price transparency**?	
Population	Medicines and vaccines for human use	**Definition:** 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). It also involves sharing and publication of the contents of pricing arrangements such as risk-sharing schemes, managed-entry agreements, patent status and licensing arrangements.
Intervention	Promoting price transparency	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	In 2019, the Seventy-Second World Health Assembly adopted resolution WHA72.08 on *Improving the transparency of markets for medicines, vaccines, and other health products (71)*. This resolution urges Member States, inter alia, to take appropriate measures to publicly share information on the net prices of health products. Some countries have already implemented voluntary or mandatory reporting of prices to improve price transparency, while others have initiated new policies. For example, lawmakers in France have recently proposed the disclosure of the amount of public research and development investment from which private pharmaceutical companies have received for the development of the drugs. It was proposed that this amount could be accounted for by the pricing committee when setting the sale price of the medicines *(72)*. The EU Transparency directive is another transparent pricing policy which requires the publication of the list prices of all reimbursable medicines in Europe *(73)*. It is well recognised that price and pricing transparency are essential for the design and implementation of pricing policies.	There is a proliferation of confidential agreements on rebates and discounts to facilitate faster access to high-cost medicines with uncertain clinical benefits *(74)*. These agreements have masked market transparency, including the level of price competition *(2)*.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** Two studies from three publications were included. Two publications from South Africa *(75,76)*, which examined a transparency measure for the private sector known as *Single Exit Price (SEP)* - mandatory disclosure for each medicine of the weighted average of all sales prices after taking into account all discounts and off-invoice rebates. The disclosed prices are subsequently made available on the South African Medicine Price Registry website. The SEP clarifies to logistics service providers or medicine dispensers at which price a manufacturer may sell a pharmaceutical product *(75,76)*. The third study was from the UK *(77)* which examined a 'cost-feedback' policy aiming to inform the prescribing clinicians about the price of drugs through on-screen display of price (or 'cost') in prescribing software upon selection of a drug. **Price:** The studies on the impact of SEP in South Africa observed statistically significant reductions in price (1999-2014) for 66 of 73 generic medicines *(75)* and 35 out of 50 originator medicines *(76)* examined. The observed price reductions were highly variable, ranging between 1.77% to 55.86% for originator medicines, and -0.70% to 91.5% for generic medicines. **Expenditure:** The UK study on displaying price in prescribing software demonstrated that a 14% reduction in weekly expenditure on antibiotics observed immediately after the intervention was not sustained as there was a gradual increase in expenditure over the following 12 months. No statistically significant difference was observed for inhaled corticosteroids after the 'cost-feedback' intervention, except when implementing a change local prescribing policy (i.e. prescribing policy was more influential than displaying price) *(77)*. **Volume, Availability, Affordability:** No information	Qualitative assessment: A qualitative study of WHO has noted favourable outcomes achieved through greater price transparency, such as better contract negotiations, and price reduction, resulting in savings in some countries (e.g. Countries in the WHO Western Pacific Region, and Indonesia, Lebanon) **System efficiency:** Some commentators have noted that "Price transparency for off-patent products could improve market efficiency if capacities are there to use the data to inform procurement decisions whilst protecting against supplier collusion" *(78)*
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Shortages:** Some commentators have presented theoretical arguments noting that price transparency might "increase prices paid by the poor, deter business entry in poor markets, reduce competition, lower investment, and mislead if inaccurately measured by a third party" *(79)*.. For similar reasons, other 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" *(78)* The counterarguments asserted that such theoretical assertions were based contestable assumptions, such as that profit-maximizing firms are likely to set lower prices in lower-income countries, and that firms would be more willing to launch products in countries with lower capacity to pay if prices were not disclosure *(2)* **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct**: Some commentators noted theoretically that price transparency might "facilitate collusion among sellers" and make "cartels easier to enforce" *(79)*. In contrast, others have noted that price transparency could "help curb price gouging, price manipulation, and overpayments. Importantly, data can illuminate patterns and any outliers, which may suggest that there are over-payments, collusion, or kickbacks happening in the procurement process." *(80)*	Undesirable effects of NOT achieving price transparency • **Conflict with the principles of good governance:** Confidential agreements may compromise clear lines of accountability – a commonly espoused objective of national medicines policies. A lack of price and process transparency may even lead to corruption, especially in health care systems with weak overall governance *(2)* . • **Impair public confidence;** Growing differences in list price and net transaction price may invite distrust *(2)*. • **Impair the effectiveness of existing pricing approaches**, such as external reference pricing *(2)*.

Evidence certainty	What is the overall certainty of the evidence of effects?	☐ Very low ☐ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The certainty of the evidence presented in the studies was rated as "moderate". There are gaps in the evidence on other primary and secondary outcomes of the systematic review.	
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☐ Varies ☒ Don't know	The evidence presented in the systematic review suggests that mandatory disclosure of the weighted average of all sales prices after taking into account all discounts and off-invoice rebates, as per the SEP program in South Africa, might deliver lower prices for the health care system. Disclosure of price information to prescribers, a per the UK study, is not likely to produce sustained effects.	WHO Secretariat report *on Pricing of cancer medicines and its impacts* concludes that "Theoretical arguments on whether greater price transparency would lead to higher or lower medicine prices are inconclusive. There is a lack of evidence of the effectiveness of confidential agreements in lowering prices and improving access. On the other hand, there is limited context-specific evidence that improving price transparency has led to better price and expenditure outcomes. Nonetheless, improving price transparency should be encouraged on the grounds of good governance" *(2)*.
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	The generalizability of the findings is unclear. The SEP program might be generalizable in other lower income countries, provided the program suitability for the national legal requirements and contexts.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	As noted under "Undesirable effects", some commentators have expressed opposition to price transparency for <u>on-patent medicines</u>, 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" *(78)* 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, other commentator has argued that increased transparency would enable more evidence based policy making, therefore could be equity enhancing by improving access (76).	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☒ Varies ☐ Don't know	**Government authorities:** Acceptable to most countries considering the adoption of WHA resolution 72.08 on *Improving the transparency of markets for medicines, vaccines, and other health products (71)*. **Patients and community**: Likely to be acceptable as indicated by wide patient and community supports expressed by patient or non-profitable organizations.	<u>Other stakeholders</u> **Insurers**: Varies **Manufacturers or suppliers:** Not acceptable *(81)* **Service providers:** Varies (e.g. *(82)*)
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Neutral ☒ Varies ☐ Don't know	**Human resource**: Depending on the level of transparency and scope of data **Financial resource requirement**: Depending on the level of transparency and scope of data **Governance requirements:** Depending on the level of transparency and scope of data **IT infrastructure:** Database management with data standards as a prerequisite	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☒ Varies ☐ Don't know	The feasibility of implementation in low- and middle-income countries would be dependent on the level and design of transparent reporting. These include: • Voluntary or mandatory • Number of points along the supply and distribution chain for which price data need to be collected or reported • Local, regional, national or international (e.g. WHO PIEMEDS) management of database and analytics The legal systems in many countries (and trade agreements) may not allow price transparency from private entities to be obtained	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☐ Probably increase ☐ Increase ☐ Varies ☒ Don't know	Sustainability would depend on the design and maturity of data infrastructure over time.	

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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.

Implementation

- 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 population most likely to benefit, or placing a limit on budget;
     - are operationally manageable without having to dedicate a disproportionate amount of resources for complex monitoring and contract management; and
     - 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. Enact 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.

Considerations towards research needs

- 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.

6. Tendering and negotiation

Questions	1. What is the effect of **tendering and negotiation** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **tendering and negotiation**?	
Population	Medicines and vaccines for human use	**Definition:** 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 discussion aimed at reaching an agreement. The outcome of tendering and negotiation might include price reductions through discounts and rebates. Discount is the general term to describe to a price reduction granted to specified purchasers under specific conditions prior to purchase. Different types of price reductions include a rebate (payment made to the purchaser after the transaction has occurred), or upon meeting certain pre-agreed terms and conditions as specified in so-called managed-entry agreements (MEA). The latter arrangements are usually classified into financial-based MEA (e.g. flat discounts, price-volume agreements, capping) and performance-based MEA (e.g. risk-sharing agreement, coverage with evidence development).
Intervention	tendering and negotiation	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: Shadi Saleh

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	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 was used primarily in hospital settings and public services, such as pandemic plans *(83)* and HPV vaccines *(84)*	
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Number of studies included in the systematic review:** One study from Mexico that examined the introduction of a new Commission with a mandate for negotiating prices to achieve discounts on patented medicines (ARV medicines) *(85)*. **Price:** The included study found an <u>average</u> reduction of 38% and 8% (in real terms) for the selected ARVs achieved by the Commission through two rounds of negotiation. The level of reductions was more than the pre-Commission/negotiation average reduction of 9% (in real terms and largely due to inflation adjustment), but the prices were still eight times higher than ARV combination prices of other upper-middle-income countries because there were concurrent reduction of prices in these countries for most of the medicines included in the study *(85)*. **Expenditure:** The included study found a savings of 45% in ARV following the implementation of negotiation through the Commission, but the level of savings could have been greater had Mexico benchmarked its price with other countries. **Volume:** No information **Availability:** No information **Affordability**: No information	Co-interventions: Negotiation can be used in combination with other pricing approaches (e.g. reference pricing and value-based pricing), with a view to reaching a final arrangement that would, ideally, present benefits to all parties involved. Literature has documented three factors potentially influencing the effectiveness of tendering and negotiation *(86)*: • Number of participating suppliers • High purchasing power in scale and scope • Information symmetry: accurate and detailed information on the relative attributes of pharmaceutical products and services on offer. Some purchasers have commented that they felt "pressurized" into accepting offers and conditions proposed by pharmaceutical companies, despite having insufficient information to be confident if a favorable deal or offer had been achieved or not *(87)*. Other factors that could modify the effectiveness of tendering and negotiation include: • Structure of tender and effective execution • Product lifecycle e.g. Tendering might not be as effective in achieving lower prices for pharmaceutical products that have already achieved low price through competition. • Pooled procurement
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Shortages:** Some commentators noted the reliance on fewer suppliers overtime might cause shortages *(88)*. While there are individual reported cases of shortages, whether it was related to the use of tendering was uncertain. In fact, some government authorities using tendering and negotiation as the primary price setting and procurement approach have noted few shortages (e.g. New Zealand *(89)* citing *(90)*) **Quality issues:** Commentators have noted that the capacity of the procurement program to eliminate unqualified suppliers and poor-quality products, after bids have been received or after tenders have been awarded, could impact on the overall risk of receiving poor quality pharmaceutical products, particularly if the process exclusively focus on price *(88)*. **Safety issues:** No information. **Anticompetitive, unethical or illegal conduct:** "Reallocation of demand", which means that savings are offset by prescribing medicines with a similar therapeutic indication that does not fall under the tendering procedure *(83)*. **System efficiency:** Some commentators claimed that tendering would lead to higher prices over time, following the concentration of market over time as non-award manufacturers exit the market**.** However, a study examined the impact of pharmaceutical tendering on prices and market concentration in South Africa between 2003 and 2016 found that the assessed tenders were moderately to highly competitive over time, as indicated by Herfindahl-Hirschman indexes of 2500 for most product groups (except for anti-TB medicines, drops and inhalers, and family planning agents) *(89)*. This suggests that when well implemented, such risk of market concentration could be minimized.	Country experiences also suggest that poorly structured and executed tendering and negotiation could result in undesirable effects (e.g. low participation from manufacturers, non-transparent selection processes etc).

Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☐ Don't know	The systematic review noted high or uncertain risk of bias and imprecision in the study included.	
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☐ Probably favours policy ☒ Favour policy ☐ Varies ☐ Don't know	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: • long-standing implementation of the policy in many countries and international agencies, including when used with pooled procurement. • Commentaries on the beneficial effects observed in several jurisdictions where tendering and negotiation have been the primary method of procurement for pharmaceutical products (e.g. South Africa *(89)*, New Zealand *(90)*, Chile *(91)*, as documented in the literature).	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☒ Don't know	Insufficient information. The one study identified in this review is limited to ARV procurement in an upper-middle income country. However, tendering and negotiation are commonly used in many contexts and seem to have been largely effective in meeting the needs of procurement authorities.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	No information. Assuming that lower prices might result in broader access, policy focusing on reducing the prices of single source medicine might enhance equity. In the study included in the systematic review, hospital programme managers and health system managers could not say if lower prices achieved through centralized negotiation would increase ARV procurement, availability or access *(85)*.	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Likely to be acceptable given wide adoption. **Patients and community**: Likely to be acceptable. However, patients and community might express dissatisfaction when the duration of the tendering and negotiation affects the timeliness of access.	Other stakeholders **Insurers**: No information **Manufacturers or suppliers:** Some suppliers have implied dissatisfaction for "single-winner, price-only tenders" by noting that this type of tenders "cause severe price erosion, reduce the number of suppliers on the market, offer short lead times and apply harsh penalties on companies severely increase the risk of shortage of medicinal products" *(92)* Similar argument was also noted recently in Norway *(93)* **Service providers:** No information
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	**Human resource**: Dependent on complexity and process design **Financial resource requirement**: Dependent on complexity and process design **Governance requirements:** Dependent on complexity and process design **IT infrastructure:** Required for the publication of tender outcomes.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	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).	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☒ Probably increase ☐ Increase ☐ Varies ☐ Don't know	Wide adoption suggests that tendering and negotiation is probably likely to increase long-term financial sustainability of health care systems.	

Conclusion				
☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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.

Implementation

The GDG suggests readers of this guideline to refer to the principles described in *WHO Operational principles for good pharmaceutical procurement* (*87*), 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

Considerations towards research needs

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

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

Questions	1. What is the effect of promoting the use of quality assured generic and biosimilar medicines an effective policy on price, volume, availability and affordability of these products? 2. What contextual factors and implementation strategies may influence the effects of promoting the use of quality assured generic and biosimilar medicines?	
Population	Medicines and vaccines for human use	**Definition:** Strategies have been directed at patients, prescribers or pharmacists to encourage the use of quality assured generic medicines[ix] or similar biological medicines (I.e. biosimilar medicines). 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.
Intervention	Promoting the use of quality assured generic and biosimilar medicines	
Comparison	Other policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Promoting the use of quality assured generic medicines has been an important public health policy globally since the 1990s. Governments have implemented a suit of supply and demand side measures. Supply side measures include removing regulatory barriers; using voluntary license agreements where possible; applying WTO 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 copayment plans for generic medicines, mandatory substitutions, or education campaigns to raise awareness about the efficacy and safety of generic medicines *(95)*. Similar policies have been used to promote the use of biosimilar medicines, albeit to a lesser extent *(96)*.	Although not having a direct role in regulating pricing of pharmaceutical products, major regulators, such as USFDA and EMA, have implemented policies that could enhance market price competition. For example, the US FDA have implemented *Drug Competition Action Plan* that aims to expedite the review of generic drug applications until there are three approved generics for a given product *(97)*. There have also been efforts towards greater harmonization of regulatory requirements for biosimilar medicines (e.g. comparative trials for less complex biologicals e.g. insulin *(98)*).
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☒ Moderate ☒ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** 16 studies[x] were included in the systematic review. • **Generic dispensing policy**: 6 studies on mandatory substitution *(26,27,30,43,99)* or generic dispensing by default unless opt out *(100)* • **Preferential reimbursement policies**: 4 studies investigated zero or low patient copayments for generic medicines in the US, Belgium, and Taiwan province of China *(101–103)* or delisting of brand product *(42)* • **Generic prescribing policies**: 4 studies on policies designed to incentivize or mandate generic prescribing *(28,104–106)*, including compulsory requirement to dispense the cheapest generic medicine in Spain *(28)*; a set of initiatives in Sweden encompassing educating prescribers, setting prescribing targets with financial incentives, and imposing prescribing restrictions on patented medicine *(104)*; compulsory INN prescribing in Argentina *(105)*; and providing physicians with vouchers who could then offer patients 30-day instead of 5-10 supply of generics *(106)*. • **Other policies**: 1 study on mixed regulatory and reimbursement policies for generics *(107)* and 1 study on regulatory bioequivalence requirements *(108)*. **Price** • Generic dispensing policies: Studies reported statistically significant price reductions *(26,27,30,43,99,100)*. Only one study estimated a 3.1% reduction in price across OECD countries *(99)*. • Removing patient copayments for generic medicines: One study observed lower or non-statistically different increase in the average costs per prescription *(101)*. • Prescribing policies: Removing the requirements for prior-authorization before prescribing generics in Belgium was found to increase the proportion of generic acid-blocking agents used, which indirectly reduced reimbursement price because of internal reference pricing *(102)*. Mandatory INN prescribing in Argentina was observed to have resulted in a statistically significant 7.9% decrease in generic drugs prices over brand prices. However, the policy had no significant effect on overall drug prices (or market share), with brand drugs observed to have a 27% increase in price *(105)*. In Sweden, the set of initiatives aiming to incentivize generic prescribing reduced the price of generic losartan by 90% below pre-patent loss prices *(104)*. In contrast, the study on Prescription Quality Improvement Programme in Catalonia in 2004 did not have statistically significant effect on price (and expenditure and volume) *(28)*. • Mixed policies to incentivize uptake of generic medicines was found to have reduced prices of generic medicines, ranging from 25% to 33% *(107)*. Bioequivalence requirements had produced mixed effects on price depending on medicines *(108)*. **Expenditure:** Studies on generic dispensing policy reported highly variable reductions in expenditure after implementing mandatory generic substitution policy. The reported reductions range from 6.6% in costs per DDD in Sweden (and a joint effect of 18.4% with other pricing reform measures) *(30)*, to 43% in daily costs of antipsychotics in Finland *(26,27)*. The set of initiatives for incentivizing the prescribing of generic losartan in Sweden significantly reduced the expenditure/DDD and increased the utilization of losartan, resulting in cumulative	**Co-interventions**: Internal reference pricing; price cap regulation; Patient participation in case management and/or wellness program in return for zero dollar copayment *(101)*; removing prior-authorization before prescribing generics *(102)*, academic detailing. **Adherence**: One study found that removal of co-payment, together with participation in wellness program, resulted in statistically significant maintenance of adherence over time among users of antidiabetic and anti-hyperlipidaemic medications *(101)*. **Other influential factors**: • **Consistency with practice guidance**: Inconsistencies of clinical guidance from professional bodies can have strong impacts on the uptake of biosimilar medicines (e.g. substitution guidance in the US for the different indications of a biosimilar *(109)*). • **Pharmacy vs Physician-driven**: Generic price competition is greater in pharmacy-driven markets than in physician-driven markets, provided that pharmacies face financial incentives to prefer cheaper products (e.g. Not linking dispensing fee to the price of products) *(107)*. **Practices from manufacturers that might hamper the effectiveness of policy to promote the use of generic and biosimilar medicines:** Originator companies might engage in "co-branding" strategies by introducing a 'pseudo-generic'[xi] (Also known as 'authorized generic')., employ "**product hopping**" (switching a patented medicine to a modestly reformulated product that offers little or no therapeutic advantages in order to preserve market exclusivity), and wasteful non-value-added activities, such as **lobbying or filing patent clusters** to delay generic/biosimilar entry. To avoid competition and maintain business stability, competing companies may engage in explicit or tacit agreement (i.e. collusion) either by **fixing price at high level or sharing the market**. For example, in a legal case lodged in 2017, the Attorney Generals of 45 states and the District of Columbia in the USA have alleged that 18 generic companies and subsidiaries have

[ix] Generic product, 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 names by their manufacturers.

[x] Please note that there are literature documenting the benefits of generic policies more broadly not included in the systematic review because of the scope of the review on pricing policy.

[xi] A pseudo-generic medicine is an additional brand marketed (usually) by the originator companies for their own branded medicine, but priced lower than their branded medicine. This business practice may discourage other genuinely generic medicines from entering the market because of reduced market share.

			reduction of 26% in total expenditure on single ARBs (patented and generic losartan) in 6 months after policy *(104)*. **Volume:** The study in Belgium observed an inverse relationship between copayment rates and sales volume of generic medicines. It also observed lower market share of generic medicines after abolishing a distinction in the maximum cumulative annual co-payment level for the originator and generics (i.e. removing the incentive for patients to use generics) *(102)*. In Sweden, generic prescribing policies significantly increased the use of generic losartan *(104)*. **Availability:** No information **Affordability**: No information **System efficiency:** Some authors have noted increased workload in pharmacies at the initial phase of implementation due to new dispensing software, substitution and managing queries relating to the mandatory substitution policy *(100)*.	engaged in price fixing and market sharing for 15 medicines *(110)*.
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct:** No information	In countries with weak National Regulatory Agencies and systems (e.g. as indicated by the "maturity level" of the WHO Global Benchmarking Tool (GBT)), the capacity to ensure the quality of generic and biosimilar medicines could be limited, thereby are unable to prevent the occurrence of substandard and falsified medicines.
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☒ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated: • Very low or low level of certainty for the effects on price (mostly) • Moderate level of certainty for the effects on expenditure (mostly) • Variable levels of certainty for the effects on volume and utilization	Publication bias not assessed.
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours policy ☐ Favour policy ☐ Varies ☐ Don't know	The evidence reviewed <u>indicated</u> effects on price and expenditure in favour of the policies appraised, if the overall policy design encompasses a combination of strategies reflecting the context and goals of the healthcare systems.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	The generalizability of the evidence is variable because: • Most studies (n = 11) examined high income countries in Europe and the US. Only one study assessed data from Asia and two from Latin America and none from Africa. • Six out of sixteen studies focused on assessing the effects of the intervention on only one medicine group. This limits generalizability of the results as findings might be linked to contextual factors for the specific medicine group (i.e. prescription guidelines). • Ten studies mentioned other co-interventions, but it is likely to be more common. • Lack of research and evidence on the promotion of biosimilar medicines use and substitution.	
Equity	What would be the impact on health equity?	☐ Large positive ☒ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☐ Don't know	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. This could free up financial resources for funding medicines for which there is no lower cost options available.	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Likely to be acceptable given broad adoption **Patients and community**: While there is increasing acceptance of generic medicines in higher income countries, a significant proportion of patients (and clinical service providers) have misperception about the efficacy or safety of generic medicines in lower income countries *(111,112)*	<u>Other stakeholders</u> **Insurers**: Likely to be acceptable given its possibility of reducing costs while achieving some health outcomes **Manufacturers or suppliers:** Varies. Originator companies **Service providers:** Acceptability would depend on the program structure and the existing service delivery model (e.g. physician driven, or pharmacist driven). For example, many lower income countries have physician driven service model; pharmacist-driven generic substitution policy would require prior engagement with prescribers to ensure acceptability. Clinicians knowledge, particularly on biosimilar

				medicines, may also have an impact on overall acceptability of these products (e.g. *(113)*).
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	**Human resource**: Dependent on complexity and process design, including current policies. National Regulatory Agencies in lower income countries may not have the capacity to ensure the quality of generic and biosimilar medicines, thereby may need to rely on third-party quality control laboratory. **Financial resource requirement**: Dependent on complexity and process design **Governance requirements:** Dependent on complexity and process design. **IT infrastructure:** New computer software for pharmacies to facilitate substitution (e.g. default lowest priced medicine) is needed.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	Policies to promote the use of generic medicines are commonly used in high- and low-income countries, although the scope and processes might differ. Policies to promote the use of biosimilar medicines might consider some learnings from generic medicines, with recognition of the differences in regulatory complexity.	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☐ Probably increase ☒ Increase ☐ Varies ☐ Don't know	Wide adoption and the beneficial effects documented in the literature, albeit with some limitations, suggest that promotion of the use of generic and biosimilar medicines is probably likely to increase long-term financial sustainability of health care systems.	

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☐ Conditional recommendation for the policy	☒ Strong recommendation for the policy

Recommendations

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 production[xii]. 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; 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..

Implementation

- 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 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).

[xii] 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.

- 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).

Considerations towards research needs

- 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

8. Pooled procurement

Questions	1. What is the effect of **pooled procurement** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **pooled procurement**?	
Population	Medicines and vaccines for human use	**Definition:** 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 the individual purchasing authorities. Four models of pooled procurement reflecting different levels of collaboration and integration have been documented: 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. *(114)*.
Intervention	Pooled procurement	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Pooled procurement has been used at different levels of administrative jurisdiction. • **Subnational** e.g. voluntary centralized procurement systems implemented in Denmark and Norway for medicines used in hospitals; Regional Central Purchasing Bodies (called "Centrali di Committenza Regionali") in Italy • **National** e.g. Thailand "high-cost medicines E2 access program" for medicines for rare disease and complex conditions. • **International:** e.g. Pharmaceutical Procurement Services of the Organization of Eastern Caribbean States; Pooled Procurement Services for Member States of Southern African Development Community (SADC); joint HTA / pricing agreement through BeNeLuxA; pilot projects among signatories of the Valletta Declaration; and Group Purchasing Programme of Gulf Cooperation Council. • Third-party Funds: e.g. UNICEF Supply Division, Global Fund, Pan American Health Organization (PAHO) PAHO Regional Revolving Fund for Strategic Public Health Supplies.	WHO South-East Asia Region is working with Member States to achieve "greater transparency of information on procurement price, and the first steps towards pooled procurement, starting with antidotes" *(115)* There is increasing interest in using pooled procurement arrangement for single source medicines, especially for products with small demand at individual country level (e.g. rare disease *(116)*), although this approach could be used for multiple source medicines.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☒ Moderate ☐ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** Six studies, with 3 studies at the regional (subnational) *(117–119)*; 1 study each at the national *(120)*, international *(121)* and responsible agencies *(122)* levels. **Price**: All studies in the systematic review with price as an outcome measure supported an association between pooled procurement and lower prices. The beneficial effects of pooled procurement on price were modified by two known factors: (i) purchasers' collective credit risk (i.e. risk of non-payment for suppliers), with prices become higher when buyers with poor credit rating joined the "procurement pool" *(122)*; (ii) level of competition, with higher prices when suppliers hold greater market power due to being the single supplier or in a highly concentrated market *(118,120,122)*. One study *(119)* suggests that pooled procurement (presumably being preconditioned with appropriate governance design) could achieve lower prices by mitigating the risks and consequences of inefficient procurement in institutions at risk of corruption or other poor institutional processes. **Expenditure:** The Italian system of regional Central Purchasing Bodies did not result in statistically lower expenditure for health goods (however, the corresponding trend on prices and volume was not presented) *(117)*. **Volume, Availability, Affordability:** No information	**Co-interventions**: Pooled procurement is often used in conjunction with another policy in practice, including tendering and negotiation. **Information from excluded studies:** Ferraresi et al *(117)* cited studies (un-appraised) that pooled procurement could improve **system efficiencies:** "Centralization of purchases can effectively streamline the procurement processes (Karjalainen, 2011), allowing the reduction of single transaction costs by decreasing the number of contracts to be negotiated, implemented and managed. Moreover, the organization which is empowered of the centralization of purchases allows the sharing of best practices among the centralized entities (Faes et al., 2000), favouring a reduction of administrative workload (Arnold, 1999)."
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Shortages**: No information **Quality issues**: No information **Safety issues**: No information **Anticompetitive, unethical or illegal conduct:** No information **System efficiencies:** Level of market competition might be reduced because of the introduction of stringent requirements on suppliers who may participate in the pooled procurement tenders (e.g. supply volume, medicine types). This could raise the entry barrier for smaller suppliers *(117)*. Poor forecasting and inventory management could result in wastage.	
Evidence certainty	What is the overall certainty of the evidence of effects?	☐ Very low ☐ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated "moderate" level of certainty on the effects of pooled procurement on price. Uncertainty stemmed from a lack of consideration for statistical analysis (e.g. parallel trend for difference in difference analysis, collinearity), insufficient description on control selection, or inadequate methods for addressing missing data or variable (e.g. volume) and their implications.	Publication bias not assessed.
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison ?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☒ Varies ☐ Don't know	On balance, pool 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 market and health system characteristics, including level of competition, collective credit risk, and institutional quality.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.

Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	The 6 studies included in the systematic review differ in research scopes, settings and some findings. While the effects on reduced price of pooled procurement due to economies of scale is likely to be generalizable, authors of these studies have also noted the importance of considering contexts of different healthcare systems, such as languages and legislative frameworks.	
Equity	What would be the impact on health equity?	☐ Large positive ☒ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☒ Varies ☐ Don't know	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	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities**: implementation of pooled procurement requires 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 & finance. **Patients and community**: No information	Other stakeholders **Insurers**: No information. **Manufacturers or suppliers**: Smaller suppliers might not be able to meet the new pooled procurement requirements (e.g. Volume), thereby preventing their participation. Pooled procurement might also incur costs relating to staff training and IT tools. However, once established, transaction costs for some participating manufacturers and suppliers might reduce. **Service providers**: No information
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☒ Varies ☐ Don't know	Resource requirements would highly depend on the level of integration and cooperation. Upfront resource requirements to set up pooled procurement mechanism would likely be significant.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	Feasibility would highly depend on the level of integration and cooperation. Feasibility would be contingent upon harmonization or clear arrangements on issues pertaining to legal, regulatory, policy and administrative requirements and processes.	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☒ Probably increase ☐ Increase ☐ Varies ☒ Don't know	Existing pooled procurement mechanisms have been in place for a considerable period (e.g. PAHO Regional Revolving Fund for Strategic Public Health Supplies), suggesting that such arrangement could be sustainable financially in the long term. The sustainability of the initial regional pooled procurement efforts is dependent on predictable and timely financing and ability to mobilize resources for capitalization *(114)*. The Thailand's pooled procurement program minimise wastage due to inaccurate forecasting (e.g. anti-venom) by pooling demand across the geographic regions.	Additional financing mechanism is critical to the financial sustainability of PAHO Strategic Fund and PAHO Revolving Fund. The Fund offers a non-interest credit line through its capitalization account to facilitate the continued availability of basic products. In 2016, it provided 17 credit line to 12 countries. This solidarity financing is possible because Member States pay an additional 3% with each acquisition to contribute towards funding the Capital Account destined to these solidarity loans in addition to an administrative expenses rate (1.25% of the total cost of the products purchased) *(123)*.

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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.

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.
  - 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).

Considerations towards research needs

- 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

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

Questions	1. What is the effect of **cost-plus pricing** on price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **cost-plus pricing?**	
Population	Medicines and vaccines for human use	**Definition:** Cost-plus pricing refers to the pricing practice for setting the price[xiii] of pharmaceutical products that considers the manufacturing costs, costs of research and development, costs associated with regulatory processes and compliance, overheads and other operational expenses, and a profit to determine a price..
Intervention	Cost-plus pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☒ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	Cost-plus pricing has not been widely used for setting medicine prices at the ex-manufacturer or ex-wholesaler levels. A small set of countries have noted cost-based pricing as part of the country pharmaceutical pricing policies (e.g. "cost accounting system" in Japan for products with no comparable products *(124)*, Australia). However, the extent of use in practice and the practical details are not widely known. This is likely to be due to practical challenge 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 manufacturer 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) *(2)*.	
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	No study met the inclusion criteria of the systematic review.	
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	**Shortages:** Economic theory suggests that firms holding monopoly over a medicine would exit the market and cause medicine shortages if the medicine prices were set equal to marginal cost of production because it would result in the monopolist making insufficient profit because the marginal cost for a monopolist would typically be below the average total cost of production *(125)*. **Quality issues:** No information **Safety issues**: No information **Anticompetitive, unethical or illegal conduct**: In theory (not evidence-based), a cost-plus pricing structure may create perverse incentives for the companies to undertake R&D and production inefficiently so that the product would achieve a higher price, and a higher profit margin, if a percentage mark-up structure were in place and if there is no robust method to ascertain the efficiency of production. Furthermore, any regulation on profit margin based on the costs of production may result in weak incentives for the pharmaceutical sector to innovate *(125)*.	
Certainty of evidence	What is the overall certainty of the evidence of effects?	☐ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☐ Don't know	Not applicable	
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison ?	☐ Favour comparator ☐ Probably favours the policy ☐ Favour the policy ☐ Varies ☒ Don't know	No information	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	No information	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies	No information	

[xiii] Please note that mark-up regulation along the supply and distribution chain is covered in Section **Error! Reference source not found.** of this guideline.

		☒ Don't know		
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☒ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** There is a renewed interest from Member States to understand R&D costs *(71)*, particularly public contribution to R&D (e.g. France *(72)*). It is unclear how this information would be used to inform pricing, if any. **Patients and community:** No information	Other stakeholders **Insurers:** No information **Manufacturers or suppliers:** Unacceptable *(59)* **Service providers:** No information
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	**Human resource:** Application of cost-plus pricing to medicines requires significant technical and human resources, particularly on obtaining and validating reliable estimates of component prices. **Financial resource:** Likely to be high due to information management. **Governance requirements:** Likely to be high due to managing reporting requirements and dispute resolution processes. **IT infrastructure:** Likely to be high due to database management	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☒ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know	It is unlikely to be feasible unless transparent reporting of cost components is mandated i.e. Data collection from industry on cost components would be difficult under current arrangement. Feasibility would also dependent on standardized methods for allocating joint costs to a specific medicine, with consideration to 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 research and development.	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☐ Probably increase ☐ Increase ☐ Varies ☒ Don't know	No information.	

Conclusion

☐ Strong recommendation against the policy	☒ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☐ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations

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 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.

Implementation

- 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 .
- 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.

Considerations towards research needs

- 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.

10. Tax exemptions or tax reductions for pharmaceutical products

Questions	1. What is the effect **tax exemptions or tax reductions** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **tax exemptions or tax reductions?**	
Population	Medicines and vaccines for human use	**Definition:** 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 taxes.
Intervention	Tax exemptions or tax reductions	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	Medicines may be subject to different taxes in countries that consider medicines like other consumer goods for the purpose of taxation. These include the application of **import tariffs/custom duties** and **value-added tax** (VAT). Many countries, particularly high-income countries, have eliminated custom duties for pharmaceutical products. These include signatories to the World Trade Organization's 1994 reciprocal Pharmaceutical Tariff Elimination Agreement, or the "zero- for-zero" initiative *(126)*. 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%. Nonetheless, some countries apply a reduced rate for pharmaceutical products compared to the standard tax rates.	
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	No study met the inclusion criteria of the systematic review.	**Co-interventions:** No information
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct:** Reduction in tariffs and taxes might not directly transferred to service providers or patients.	
Certainty of evidence	What is the overall certainty of the evidence of effects?	☐ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☐ Don't know	No information	
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison ?	☐ Favour comparator ☐ Probably favours comparator ☐ Probably favours the policy ☒ Favour the policy ☐ Varies ☐ Don't know	No information	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	No information	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	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	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☒ Varies ☐ Don't know	**Government authorities:** Some governments might consider the lost revenue due to reduction or removal of taxes for pharmaceutical products as unacceptable. However, evidence suggests that VAT does not substantially contribute to revenue goals (e.g. ≈1% of public revenue) but can make medicines unaffordable for patients *(127,128)*. **Patients and community**: Acceptable	Other stakeholders **Insurers**: Likely to be acceptable **Manufacturers or suppliers:** Likely to be acceptable **Service providers:** Likely to be acceptable
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☐ Moderate ☒ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	**Human resource**: If tax exemption or reductions were to be initiated, additional upfront resource requirements for implementing the new policy are anticipated. Over longer term, additional resources would be minimal because of integration into the overall taxation regime. **Financial resource requirement**: ibid **Governance requirements:** ibid **IT infrastructure:** ibid. In addition, IT infrastructure would also need to be able to track tax/costs from importation to finished products.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	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	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☒ Likely to be neutral ☐ Probably increase ☐ Increase ☐ Varies ☐ Don't know	Tax exemptions or tax reductions for pharmaceutical products policy is likely to have a neutral impact on the long-term sustainability of healthcare system. However, it would be likely to enhance patient affordability over the long term.	

Conclusion

☐ Strong recommendation against the policy ☐ Conditional recommendation against the policy ☐ Conditional recommendation for either the policy or comparison ☒ Conditional recommendation for the policy ☐ Strong recommendation for the policy

Recommendations

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.

Implementation

- 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.

Considerations towards research needs

- 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.

11. Price discounts for single source pharmaceuticals

The GDG considered this policy as part of the tendering and negotiation. Content has been incorporated under Section 6 *Tendering and negotiation* accordingly

Questions	1. What is the effect of **seeking price discounts for single source pharmaceuticals** on the price, volume, availability and affordability of these products? 2. What contextual factors and implementation strategies may influence the effects of **seeking price discounts for single source pharmaceuticals**?	
Population	Medicines and vaccines for human use	**Definition:** Single source pharmaceuticals are pharmaceutical products supplied by a company that holds the patent rights, exclusive marketing rights, or supply agreements in a specific jurisdiction. Discount is the general term to describe to a price reduction granted to specified purchasers under specific conditions prior to purchase. Different types of price reductions include a rebate (payment made to the purchaser after the transaction has occurred), or upon meeting certain pre-agreed terms and conditions as specified in so-called managed-entry agreements (MEA). The latter arrangements are usually classified into financial-based MEA (e.g. flat discounts, price-volume agreements, capping) and performance-based MEA (e.g. risk-sharing agreement, coverage with evidence development).
Intervention	Price discounts for single source pharmaceuticals	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	The reasons why pharmaceutical products could only be obtained from a single source in countries are many, including that (1) the products are on patent; (2) there is only a single product registered in the country; (3) there is only a single importer for the products (3) the existing contractual arrangements preclude sourcing from other sources. If there are no close substitutes for the product, countries commonly used negotiation, alongside other pricing related policies, to achieve lower price through discounts or rebates, administered through standard or the so-called managed-entry agreements. As noted under Section 6 *Competitive Pricing*, negotiation, tendering and MEA are commonly used.	
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	No study met the inclusion criteria of the systematic review.	
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct:** No information	
Certainty of evidence	What is the overall certainty of the evidence of effects?	☐ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☒ Don't know	No information	
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☐ Probably favours policy ☐ Favour policy ☐ Varies ☒ Don't know	No information	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ Don't know	No information	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	No information	

Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Likely to be acceptable **Patients and community**: Likely to be acceptable	Other stakeholders **Insurers**: Likely to be acceptable **Manufacturers or suppliers:** varies depending on the contractual arrangements on the discounts or rebates **Service providers:** Likely to be acceptable
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☐ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	No information	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know	No information	
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☐ Probably increase ☐ Increase ☐ Varies ☐ Don't know	No information	

Conclusion				
☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendations
N/A

Justifications
N/A

Implementation
N/A

Considerations towards research needs
N/A

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