

Medicines regulation, pricing and reimbursement in Brazil

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Abstract

Brazil is an upper-middle-income country with a high human development index (HDI) of 0.765 (2019). The Unique Health System (SUS) is a universal, decentralised system, free at point-of-care, although 27% of Brazilians have voluntary supplementary health insurance. Medicines are provided free-of-charge through the SUS, though there are a few exceptions where co-payment is required. Around 87% of the country's expenditure with medicines and medical devices corresponds to out-of-pocket, highlighting the importance of price regulation. Marketing authorisation and maximum price approval are mandatory market entry requirements for medicines. Pricing policies include maximum price approval, regulation of mark-ups, tax exemption, annual price adjustment and a mandatory discount for government procurement and enforcement mechanisms. The pricing of new drugs considers the patent status and added therapeutic benefit. It is a combination of health technology assessment and external or internal reference pricing, while drugs with active ingredients in the market follow internal reference pricing. The maximum price of generics must be up to 65% of the reference's price. The maximum approved prices and public procurement prices are publicly available. Brazil has a value-based decision-making process for incorporating medicines and other technologies at the SUS. Current areas of work include horizon scanning, participation of patients in decision-making and re-assessment of technologies. As a decentralised system, medicines are procured by the Ministry of Health, states and municipalities, according to their level of responsibility. Pricing and reimbursement policies, including a consolidated generics policy, have been important in promoting transparency, predictability, and price stability, in turn contributing to cost-containment and access. Ongoing challenges include high rates of judicialisation, medicines with excessive prices not commensurate with their clinical benefits, no provision for pricing review, problems related to governance and politics. To address these challenges, the authors have three main recommendations. First: improving regulatory governance, second: incentivising the development and promoting access to medicines with stronger evidence, added clinical benefit and fair prices, and third: increasing awareness among stakeholders, avoiding judicialisation and minimising its impact; contributing to closing the gap between innovation and access to medicines.

Keywords: Brazil; access to medicines; pricing; reimbursement; health technology assessment; legislation

Regulação, precificação e incorporação de medicamentos no Brasil

Resumo

O Brasil é um país de renda média-alta com um alto índice de desenvolvimento humano (IDH) de 0,765 (2019). O Sistema Único de Saúde (SUS) é universal, descentralizado e gratuito. No entanto, 27% dos brasileiros têm seguros privados de saúde voluntários. Os medicamentos são dispensados gratuitamente no SUS, com pequenas exceções em que o co-pagamento é necessário. Cerca de 87% do gasto com medicamentos e produtos para saúde no país correspondem ao gasto familiar, ressaltando a importância da regulação de preços. O registro e a aprovação do preço máximo de medicamentos são requisitos obrigatórios para a entrada no mercado. As políticas de preços no Brasil incluem a aprovação de preço máximo, regulamentação de margens, isenção de impostos, reajuste anual e um desconto obrigatório para compras governamentais. A precificação de novos medicamentos considera o status da patente e o benefício terapêutico adicional, com uma combinação de avaliação de tecnologia em saúde e precificação por referenciamento externo ou interno. Já os medicamentos antigos no mercado seguem a precificação por referenciamento interno. O preço máximo dos genéricos deve ser no máximo 65% do preço do referência. Os preços máximos aprovados e preços de compras públicas são disponíveis publicamente. O Brasil tem um processo de decisão de incorporação no SUS baseado em valor. Por ser um sistema descentralizado, os medicamentos são adquiridos pelo Ministério da Saúde, estados e municípios, de acordo com seu grau de responsabilidade. As políticas de precificação e incorporação, incluindo a consolidação da política de genéricos, têm sido importantes para proporcionar transparência, previsibilidade e estabilidade de preços, por sua vez, contribuindo para a contenção de custos e o acesso. Os desafios atuais incluem a alta taxa de judicialização, medicamentos com preços excessivos, não proporcionais com seus benefícios clínicos, ausência de provisão para a revisão de preços, além de problemas relacionados com governança e "politics". Para enfrentar estes desafios, os autores têm três recomendações principais. Primeiro: a melhoria da governança regulatória; segundo: incentivo ao desenvolvimento e promoção do acesso a medicamentos com evidências mais robustas, benefício clínico adicional, e preços justos e terceiro: ampliar a conscientização entre os afetados, evitando a judicialização e minimizando seu impacto, contribuindo para diminuir a lacuna entre inovação e acesso a medicamentos.

Palavras-chaves: Brasil; acesso a medicamentos; precificação; incorporação; reembolso; legislação



Brazil and the Unified Health System (SUS)

Brazil is an upper-middle-income country with a high human development index (HDI) of 0.765 (2019) and an estimated population (2021) of 213 million inhabitants, with an area of 8,510,345.5 km².¹⁻⁴ In 2020, Gross Domestic Product (GDP) was \$3.182 trillion [Purchasing Power Parity (PPP), current prices] and the GDP per capita was \$8,897.5.⁵ In 2019, life expectancy was 75.9 years at birth, infant mortality 12.4 per 1,000 live births and mortality 6.5 per 1,000 people.⁶ Brazil has a Gini index of 53.4, with approximately 39.9 million people living in extreme poverty, and 14.1% unemployment.^{3,7,8}

The core principles of Brazil's SUS are universality, comprehensive actions and services free at the point-of-care, and equity. The system's organisational principles are decentralisation, regionalisation, a service network with hierarchical levels of care, control and social participation.⁹⁻¹¹ As a decentralised system, its management, funding and service delivery are shared by the Ministry of Health (MoH), states and municipalities. The latter is mostly responsible for primary health care services delivery.^{9,10,12} The SUS has 100% coverage, with about 73% of the Brazilians essentially relying exclusively on its actions and services, while nearly 27% have voluntary supplementary private health and/or dental insurance.^{9,13}

Brazil has a positive list of covered medicines, the national list of essential medicines (Rename) which includes five components of pharmaceutical services: basic, strategic, specialised, medical devices, and in-patient medicines.¹⁴ It is accompanied by a national therapeutic formulary (last updated in 2010).¹⁵ Rename can be adapted according to the local epidemiological characteristics by states and municipalities, who must ensure the availability of the medicines free-of-charge at the point-of-care, considering clinical and therapeutic guidelines.¹⁴ The exception is a co-payment scheme at accredited private community pharmacies at the so-called "Popular Pharmacy" [*farmácia popular*] programme.¹⁶ Medicine availability at the SUS ranges from 30% to 94.3%.^{12,17-19}

People covered by private insurance still benefit from SUS through its public health actions and services, such as health surveillance, health promotion, regulation of products and services, vaccination, among others.²⁰ There is a mandatory list of services, procedures and medicines covered by private health and dental insurance plans [*rol de procedimentos*].^{21,22} When high priced medicines are not covered by private insurance, patients resort to SUS.²⁰

Health and pharmaceutical expenditures

In 2019, total health expenditure was \$311.5 billion PPP (8.9% of GDP), of which \$127.3 billion (3.9% of GDP) corresponded to government, \$96 billion to private health insurance, and \$77.5 billion to out-of-pocket household expenditure (5.4% of GDP health expenditure).¹³ Pharmaceuticals and medical devices were the second-largest component (20.5%) of health expenditure in Brazil (approx. \$63 billion PPP, 2% of the GDP).¹³ In 2020, pharmaceutical expenditure was 7.5% of federal health expenditure.²³ The increase in pharmaceutical expenditure in recent years is due to the strengthening of the pharmaceutical services and the increase of mostly high-priced new specialty medicines, sometimes forced by judicialisation.²⁴ Out-of-pocket corresponded to 87.7% of the expenditure with medicines and

medical devices in 2019, evidencing the importance of having medicines prices regulated for both private and public settings.¹³ Pricing and reimbursement policies, including the use of generic drugs, are important cost-containment measures.²⁵

The Pharmaceutical sector in Brazil

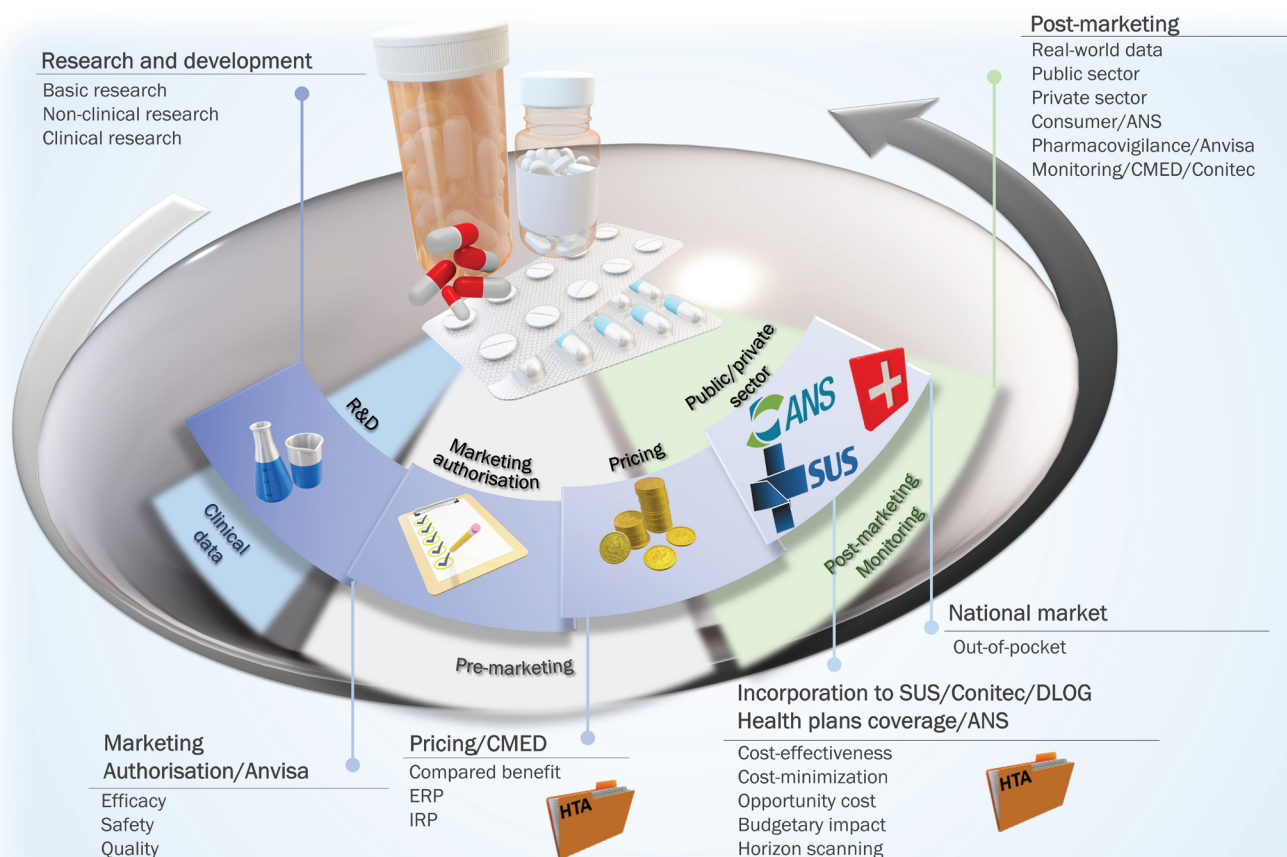
In 2019, there were 5,897 pharmaceutical products in the Brazilian market, with 1,935 active ingredients or fixed-dose combinations, from 224 marketing authorisation holders (MAH). The pharmaceutical revenue was \$37.7 billion PPP in 2019, of which \$13.4 billion PPP were new drugs [35% in nominal value, 16.9% of the sales volume (units)]. Together, generics (\$5.2 billion PPP, 13.7%) and brand generics [*similares*] (\$7.6 billion PPP, 20.1%) accounted for 33.7% of the revenue (nominal value) and 70.7% of the sales volume (Table S1, supplementary material).²⁶ From 2015 to 2019, pharmaceutical revenue increased 33.3% (nominal value, 34.5% in volume).²⁶ In 2018 there were 59 importers, 4,436 wholesalers, 87,794 private community pharmacies, 11,251 public ambulatory pharmacies, and 6,934 hospital pharmacies (public and private).²⁷

An overview of the Brazilian pharmaceutical policies and regulation ecosystem

In the 1990s, the Brazilian pharmaceutical sector was marked by a structural crisis. A lack of access to medicines, stockouts, counterfeit and substandard medicines, excessive prices, among other problems, jeopardised the health system and the fragile regulatory system.^{28,29} The Medicines Parliamentary Enquiry Committee considered that quality, safety and efficacy (QSE) regulation and price (de)regulation experiences were inadequate. Its conclusions and recommendations, alongside the National Medicines Policy (1998) had a key role in the development and approval of new regulatory frameworks and institutional arrangements, the introduction of generics, among other strategies.²⁹⁻³¹

An ecosystem comprises "all the living things in an area and the way they affect each other and the environment".³² It is possible to consider pharmaceutical policies and regulation as part of an ecosystem, due to their inter-sectoral characteristics, influences and implications in other policies and regulatory frameworks. This ecosystem includes the Brazilian Health Regulatory Agency (Anvisa), the Drug Market Regulation Chamber (CMED); the Secretariat of Science, Technology, and Strategic Inputs (SCTIE) in the Ministry of Health (MoH) and the National Committee for Health Technology Incorporation at SUS (Conitec), among other related ministries as part of the health industrial complex.³³⁻³⁷ Different stakeholders interact along the medicines' life-cycle with synergic and complementary roles (Figure 1; Table S2 and Figure S2). To be available to the Brazilian market, medicines require market authorisation by Anvisa and maximum price approval by CMED. Once in the market, medicines can be purchased out-of-pocket or can be covered by SUS and/or private health insurance.³⁸ Reimbursement is defined as coverage of the cost of reimbursable medicines by a public payer, such as social health insurance or the national health system (NHS).³⁹ In this article, reimbursement is used interchangeably with incorporation [*incorporação*], indicating the uptaking or coverage of medicines by the Brazilian Unified Health System (SUS).

Figure 1. Medicines life-cycle in Brazil.



ANS: National Regulatory Agency for Private Health Insurance and Plans; Anvisa: Brazilian Health Regulatory Agency; CMED: Drug Market Regulation Chamber; Conitec: National Committee for Health Technology Incorporation to the Unified Health System; DLOG: Logistics Department/Ministry of Health; ERP: External Reference Pricing; HTA: Health Technology Assessment; IRP: Internal Reference Pricing; R&D: Research and Development; SCMED: Executive secretariat of CMED; SUS: Unified Health System.

Regulation of quality, safety and efficacy of medicines

Anvisa is responsible for the regulation of health-related products and services, including aspects of QSE of medicines along their life-cycle, such as authorisation of clinical trials and marketing authorisation.^{31,33} Post-marketing surveillance, enforcement and other regulatory activities (eg. licensing and inspections of manufacturing sites, wholesalers and pharmacies), are conducted with the steering role of Anvisa in cooperation with states, municipalities and other components of the system, including the network of public health laboratories (Figure 2; Table S2).⁴⁰⁻⁵²

Medicines' economic regulation

Overall, the Brazilian economic regulatory framework is a hybrid arrangement of policies promoting the availability and minimising market failures that restrict competitiveness, to ensure access to medicines. (Figure 3A, Figure S2; Table S2).^{34,53} The pricing policy provides transparency and predictability, with clear rules, including:

- i. Price cap
- ii. Tax exemption
- iii. Mandatory public procurement discount
- iv. Mark-up regulation

Marketing authorisation holders (MHA) of prescription drugs must apply for maximum price approval (price-cap) after marketing authorisation and over-the-counter medicines need to set out the proposed price, both are subject to monitoring. Traditional plant-based medicines are exempt from price approval.

The main pricing regulation is Resolution 02/2004, which is currently under review (Figure S3).⁵⁹⁻⁶¹ Medicines can be classified into two clusters: categories I and II for new molecules (synthetics or new chemical entities) or moiety and categories III to VI for molecules already in the market (Figure 4). The review time for the first decision of price approval varies from 60 to 90 days. Medicines for rare diseases must submit price applications within 30 days of marketing authorisation. There is no deadline for other drugs, but marketing without a price approval or at prices higher than the CMED approved price are infractions, subject to penalties.^{62,63} Medicines from categories III and VI can be commercialised when the application is submitted, while products from other categories must wait for CMED's decision.⁶⁴

CMED uses Health Technology Assessment (HTA) for establishing whether a medicine has added therapeutic benefits in relation to comparators, which are drugs in the Brazilian market for the same condition (categories I, II and V).⁶⁴ Analysis is based on evidence provided by the applicant and a technical literature review conducted by the Executive Secretariat of the Drug Market Regulation Chamber (SCMED).^{57,64} Cases not covered by the six

Figure 2. Regulation of quality, safety and efficacy (QSE) of medicines in Brazil.

Anvisa's mission is "to protect and promote the health of the population, by intervening in the risks arising from the production and use of products and services subjected to health surveillance, in a coordinated and integrated action within the scope of SUS". It is regarded as a SUS sub-system and medicines is one of the products regulated by it.⁴¹ Key regulatory processes to ensure QSE along the medicine's life-cycle include:

Clinical trials: The clinical trials to be conducted in Brazil for marketing authorisation purposes must be authorised by Anvisa, which oversees the aspects related to QSE, while the National Council of Research Ethics oversees the ethical aspects. The Brazilian Clinical Trial Registry (ReBEC) is a public registry of clinical trials conducted in Brazil, managed by the Oswaldo Cruz Foundation (Fiocruz). Before their application to Anvisa, all clinical trials phases I, II, III and IV, must be registered at ReBEC, or the International Clinical Trials Registration Platform (ICTRP/WHO), meeting the minimum data set required by the International Committee of Medical Journal Editors (ICMJE) and the World Health Organisation (WHO). It contributes to increasing the transparency of clinical trials.^{40,45,49}

Marketing authorisation: Marketing authorisation is a mandatory requirement in Brazil to ensure medicine's QSE. Among the marketing authorisation requirements, applicants must submit the clinical development plan.⁴⁶ Less robust evidence can be accepted from medicines for rare diseases, defined as medicines aiming to treat, diagnose or prevent a rare disease (committing 65 per 100.000 individuals). The timeframes for Anvisa's review of marketing authorisation applications are 365 for normal reviews and 120 days for priority reviews. Companies can apply for a priority review for medicines for rare diseases, neglected, emerging or re-emerging diseases, public health emergencies or seriously debilitating conditions, in situations where there is no alternative therapy available or when there is a significant improvement in safety, efficacy or adherence to treatment.^{40,47,48,50} Marketing authorisation is valid for 10 years, except for medicines with conditional approval under priority approval regulation for rare diseases and other conditions or situations of public health interest which can be approved with preliminary evidence and are obliged to present complementary QSE information, as established in a specific signed agreement. For these medicines, the renewal period is three, five and ten years consecutively, once the complementary information is considered satisfactory.⁴⁴ Brazil is a member of the International Council for Harmonisation (ICH) since 2016, therefore, the marketing authorisation requirements are harmonised according to its standards and guidelines.⁵¹ The supporting legislation, Medicine's Public Assessment Reports (PPAM), marketing authorisation status, leaflets (professional and patients' versions with historical information since approval), among other information, are publicly available on Anvisa's portal, where it is also possible to check on the status of products' reviews (Table S2 - supplementary material).⁵²

Enforcement and Post-marketing surveillance: post-marketing surveillance is a shared responsibility, not only within the health regulatory system but also the marketing authorisation holders (MAH), health professionals and patients. MAHs are obliged to provide a Periodical Report of Benefit-risk Assessment (RPBR) regularly, while for other stakeholders, reporting suspicious adverse drug reaction is spontaneous on VigiMed (Notification system for unexpected reactions to drugs and vaccines). There is also a "Sentinel network", that works as an observatory for identifying and reporting adverse drug reactions with focal points (risk managers) at health services in most Brazilian states. More information of aspects related to surveillance and enforcement, pharmacovigilance and how to report a suspicious drug or vaccine adverse drug reaction or another drugs can be consulted on the specific webpages (Table S2).⁴²

Transparency: Anvisa is subject to the Access to Information Law (LAI; Law 12,527 of 2011).⁸⁶ Therefore, it is possible to have access to non-confidential data from regulatory activities of Anvisa upon request, for instance, documents related to marketing authorisation or price approval. To improve transparency, it is also possible to consult the status of review and marketing authorisation, Medicine's PPAM (for both negative and positive decisions), leaflets (professional and patient versions are available, historical information since approval), among other information.⁵² The same applies to ongoing evaluations of clinical studies carried out in the country. It is also possible to access information on irregular and withdrawn products. The agency's portal displays health alerts for products subject to regulation and informs changes to protocols, legislation, manuals, and guidelines (Table S2). Anvisa has an Open Data Plan, part of the Brazilian Open Data Portal (dados.gov.br) and the National Open Data Infrastructure (INDA).⁴³

The definitions of the different regulatory categories and concepts related to medicines regulation are available on Anvisa's portal. Other regulatory processes carried out and the details on specific regulations can be consulted at the thematic libraries (Table S2).⁵²

categories are decided by the Executive Technical Committee (CTE), such as non-original biologicals (me-toos) and changes of MAH (Figure 4).⁶⁵ There are two levels of appeal, the SCMED and the CTE.^{64,71}

CMED uses external reference pricing (ERP) (Table 1) and/or internal reference pricing (IRP) criteria to calculate the maximum price, guided by HTA. In any case, the approved price is the lowest of ERP and/or IRP and the requested price by the applicant.^{64,67} The price can be provisional if official prices for ERP are not available in at least three countries, being subject to revision every 6 months until this threshold is achieved.⁶⁴ Once the provisional period has ended, prices are definitive and there is no provision for revision.^{64,66}

Once the maximum price is approved, companies must report sales volume and revenue annually. If a product is withdrawn, marketing authorisation is cancelled or expired, or it is not commercialised for three consecutive years, CMED inactivates it on the Medicines Market Monitoring System (Sammed). If the company intends to commercialise the product again, a new application is required, followed by a new assessment.⁶⁸

Price applications, commercialisation reporting and any other communication between applicants and SCMED are paperless, via Sammed or exceptionally via Electronic Information System (SEI).^{69,70}

CMED also has provisions to regulate mark-ups from manufacturers, importers/wholesalers, and pharmacies. Currently, wholesalers'

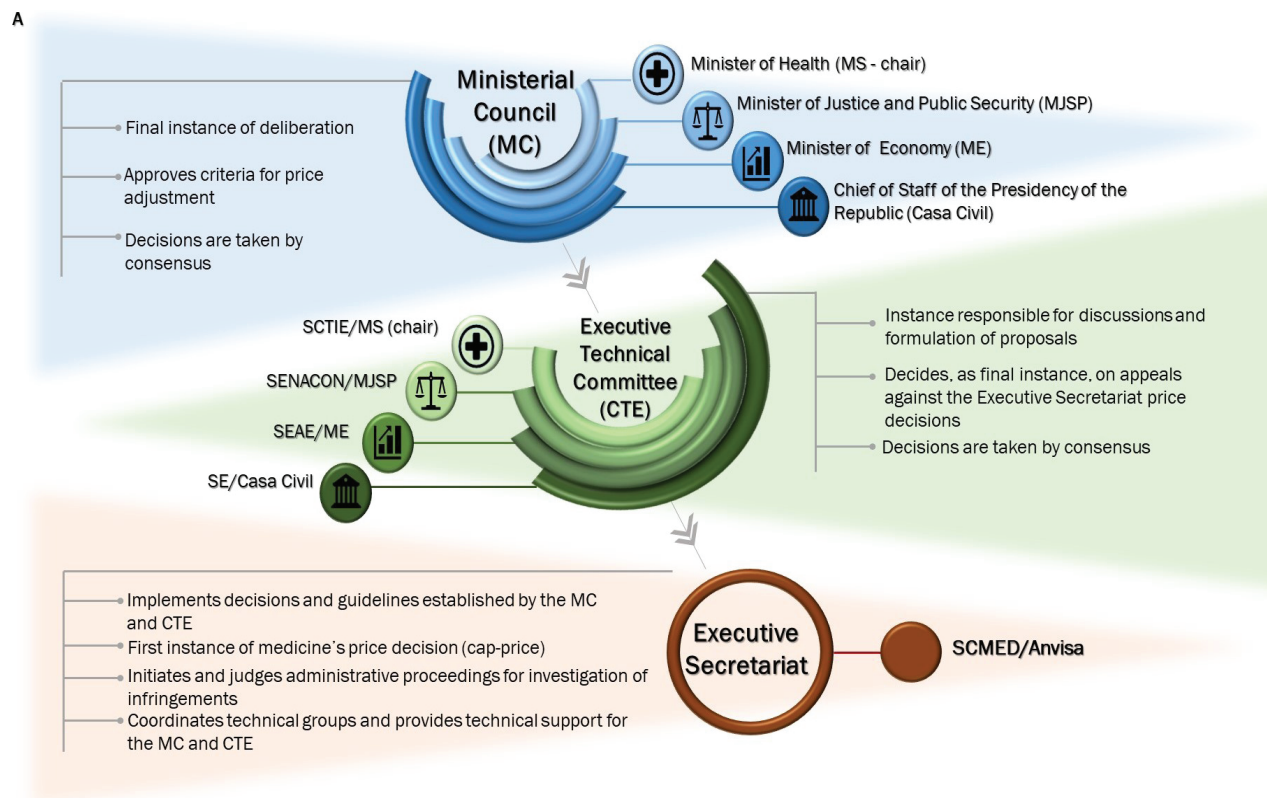
mark-ups, result from negotiations with drug manufacturers. The maximum ex-factory price (PF) and the maximum consumer price (PMC), already include these margins.³⁴ New drugs don't have distribution mark-ups incorporated in the price.

The following federal taxes are applied to medicines in Brazil: Social Integration Programme/Civil Servant Heritage Formation Programme (PIS/Pasep) taxes that form the Worker's Support Fund (FAT) for funding unemployment insurance and Contribution for the Financing of Social Security (Cofins). States and the Federal District have a tax on commerce and services (ICMS), which varies from 12 to 20%. Most prescription medicines are exempt from taxes (positive lists of Pis/Pasep and Cofins and/or ICMS). The Treasury Council (Confaz) publishes a consolidated list of ICMS exemptions.^{34,54,66,72,73} A bill for tax reform approved by the Chamber of Deputies on September 2nd 2021 (pending approval by the Senate) changed the income tax and suspended tax exemptions for medicines. It can mean an increase in the prices of prescription medicines.^{74,75}

The Price Adequacy Coefficient (CAP), a mandatory discount for government procurement applies to a positive list of medicines and to all medicines procured to comply with judicialisation (lawsuit decisions). CAP is updated annually, and in 2020, it corresponded to 21.53%. In addition, government procurement is exempt from taxes. CMED publishes a dedicated list with maximum government procurement price (PMVG) and tax exemptions.⁷⁶⁻⁷⁸



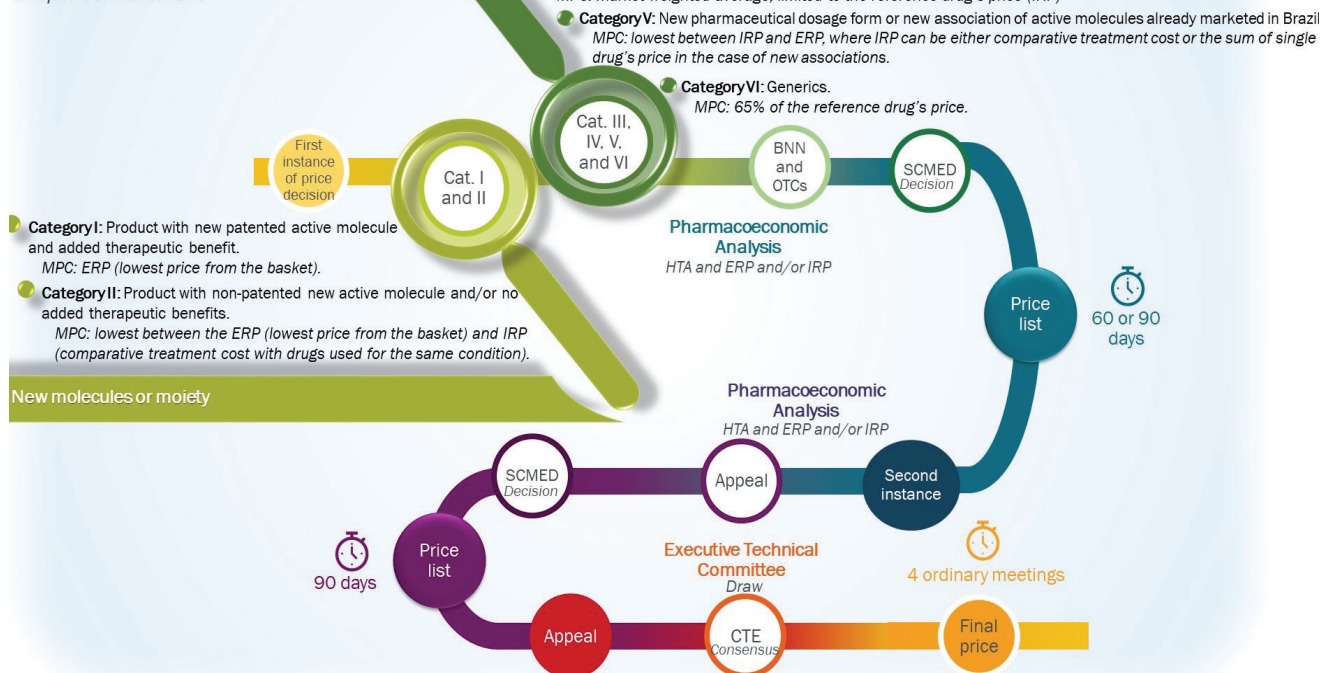
Figure 3. Brazilian Drug Market Regulation Chamber structure (A) and simplified flowchart of price decision (B).



Anvisa: Brazilian Health Regulatory Agency; CTE: Executive Technical Committee; MC: Ministerial Council; MS: Ministry of Health; MJSP: Ministry of Justice and Public Security; SCMED: Executive Secretariat of the Drug Market Regulation Chamber; SCTIE: Science, Technology, Innovation and Strategic Supplies Secretariat; SE: Executive Secretariat; SEAE: Competition and

Categories I to VI, BNN and OTCs

Simplified Flowchart



IN: Non-original Biologicals (me-toos); Cat.: Category(ies); CTE: Executive Technical Committee; ERP: External Reference Pricing; HTA: Health Technology Assessment; IRP: Internal Reference Pricing;

Source: Drug Market Regulation Chamber (CMED)^{34,64}



Drug prices are adjusted annually, based on an index composed of three factors: a productivity factor (Factor X), a share of relative price adjustment factor across sectors (Factor Y) and a portion of the intra-sector relative price adjustment factor (Factor Z).⁷⁹ The adjustment has three levels, according to the Anatomical Therapeutic Classification (ATC) of the European Pharmaceutical Market Research Association (EphMRA) and the competitiveness profile of the active ingredient, defined by the Herfindahl Hirschman Index (HHI). The more concentrated the market (higher HHI) for an ATC group, the lower the price adjustment level. As a mathematical equation, however, depending on the value of the other factors, annual adjustments can be linear.^{34,55,79,80} Pharmaceutical market monitoring and enforcement are part of SCMED activities. From 2012 to 2017, CMED withdrew 2,000 presentations.⁸¹ In 2018, CMED updated and consolidated its regulation regarding penalties for non-compliance, cutting red tape.^{82,83} CMED can define maximum prices *ex-officio* (and apply penalties) if the MAH fails to apply for price approval.⁶² In 2021, about USD 27.7 million (R\$150 million) of fines were applied to companies non-compliant with pricing regulation during the Covid-19 pandemic, an increase of 400% compared to 2020.⁸⁴

The medicines' maximum approved prices, as well as the CTE's and Ministerial Council's meeting agenda and decisions, are publicly available on CMED's website.⁸⁵ Both price lists with PF, PMC, and PMVG include information on regulatory category, the active ingredient, EphMRA therapeutic classification, taxes applied, among other information, such as approval/appeal status.⁶⁶ CMED also publishes a yearbook with an overview of the Brazilian pharmaceutical market, based on mandatory information submitted by companies.²⁶ Although pricing review reports are not publicly available on CMED's website, any interested party can request access to information about government acts (except confidential documents), according to the Access to Information Law (Law 12,527/2011).⁸⁶ Public participation is not included in pricing approval, although, CMED can organise meetings and training when needed. In recent years, it has not had an active communication with civil society.⁸⁷

Reimbursement of medicines and other health technologies into the SUS

Brazil uses a value-based approach for incorporating medicines and other health technologies to the SUS. Conitec's objective is to advise the MoH regarding the uptake, exclusion or changes in the use of new medicines, health products or procedures at the SUS, as well as to develop or change clinical protocols and therapeutic guidelines (Figure S2). All technologies require marketing authorisation and medicines require approved prices by CMED before Conitec's appraisal, which can be requested by anyone (Table S2).⁸⁸⁻⁹¹

The appraisal of medicines and other health technologies (Figure 4) is summarised in the Technical-Scientific Report (PTC), with the mandatory use of HTA.⁸⁸ It includes a systematic review of comparative clinical evidence related to the technology's efficacy, effectiveness, safety and accuracy, in relation to other incorporated technologies to the SUS.⁵⁶ The studies are evaluated for risk of bias (with tools such as RoB 2.0, Robins-I, and AMSTAR-2) and quality (with the GRADE tool).⁵⁷ Economic evaluations are also performed (cost-effectiveness, cost-utility and budgetary impact studies).⁵⁶⁻⁵⁸ Since December 2020, evaluations also includes patients' reported outcomes (PRO).

After reviewing the PTC, Conitec issues a preliminary recommendation and launches a public consultation. Its executive secretariat consolidates all contributions and based on the consolidated document, Conitec issues a final recommendation.⁵⁶⁻⁵⁸ The MoH, through SCTIE, can accept or reject Conitec's recommendation based on technical reasons.⁹² The MoH has 180 days (with the possibility of a 90 days extension) from the request date to issue a final decision (Figure 4). Once a technology is officially incorporated, it must be available to SUS patients within 180 days. SCTIE develops or updates the corresponding clinical protocols and therapeutic guidelines (PCDT).⁵⁶⁻⁵⁸ Brazil does not have an officially adopted cost-effectiveness threshold and a report with proposals for decision-making was recently published by Conitec.⁹³

Table 1. Examples of sources of external reference pricing (non-exhaustive list).

Country	Source	Link to Website
Australia	The Pharmaceutical Benefits Scheme: Pricing Matters	http://www.pbs.gov.au/info/industry/pricing
Canada	Québec. Regie de l'assurance maladie: List of medications	http://www.ramq.gouv.qc.ca/en/publications/citizens/legal-publications/Pages/list-medications.aspx
France	Base des Médicaments et Informations Tarifaires	http://www.codage.ext.cnamts.fr/codif/bdm_it/index.php?p_site=AMELI
Greece	Ministry of Health/ Price Sheets	http://www.moh.gov.gr/articles/times-farmakwn/deltia-timwn
	Virtual Pharmacy	http://www.virtualpharmacy.gr/E_nest.htm
Italy	Gazzetta Ufficiale	https://www.gazzettaufficiale.it/
	Agenzia Italiana del Fármaco/ Prezzi e Rimborso	https://www.aifa.gov.it/web/guest/prezzi-e-rimborso
New Zealand	Pharmac	http://www.pharmac.govt.nz/patients/Schedule
Portugal	Infarmed	http://www.infarmed.pt/web/infarmed/servicos-on-line/pesquisa-do-medicamento
Spain	Ministerio de Sanidad, Consumo y Bienestar Social: Información sobre los productos incluidos en la prestación farmacéutica del SNS (dispensables a través de oficinas de farmacia)	http://www.msbs.gob.es/profesionales/nomenclador.do
United States	United States Veteran Affairs Department/ National Acquisition Center (CCST)	https://www.va.gov/nac/Pharma/List

In 2021, a new law for public procurement and contracts was enacted, allowing discounts (single source medicines), besides bids and negotiations, with CMED's maximum government approved price (PMVG) serving as the maximum procurement price.⁹⁴ In Brazil, confidential discounts are not allowed and all procurement prices are publicly available.⁵⁶ There are no managed entry agreements in place, although an unsuccessful attempt was made.⁹⁵ The cost-effectiveness analysis to support public procurement decisions considers the PMVG when applicable.⁵⁷

Horizon scanning is part of Conitec's appraisal report. They also regularly publish technology horizon scanning alerts. Conitec is currently developing procedures for re-assessment of medicines and other technologies, with a life-cycle perspective and commissioned studies from the Brazilian Network of Health Technology Assessment (Rebrats). A few re-assessments are already available on Conitec's website.^{89,96,97}

Recommendations and supporting documents are publicly available on Conitec's website, as well as applications received since 2012 and their status, with an overview of Conitec's recommendations.⁹⁰ From 2012 to November 2021, Conitec received 854 applications, from which 389 (45%) had a negative decision, withdrawn or excluded, 374 (43.7%) were recommended to be incorporated or maintained, and 10.7% (91) were under review.⁹⁰

Since 2020, all meetings' agendas and recordings are available on Conitec's website.⁹¹ Reports with adjusted lay language directed to the public are also available, facilitating contributions through public consultation.⁹⁸

To promote price transparency, the MoH created in 1998 the Health Price Registry [*Banco de Preços em Saúde – BPS*] which contains procurement prices of public and private institutions. Although its use by private institutions is voluntary, the use by the MoH, states and municipalities is mandatory. The registry is connected to the

Integrated System of General Services Administration (SIASG), which contains information on federal procurement prices of medicines and health products in Portuguese, English and Spanish (Table S2).⁹⁹

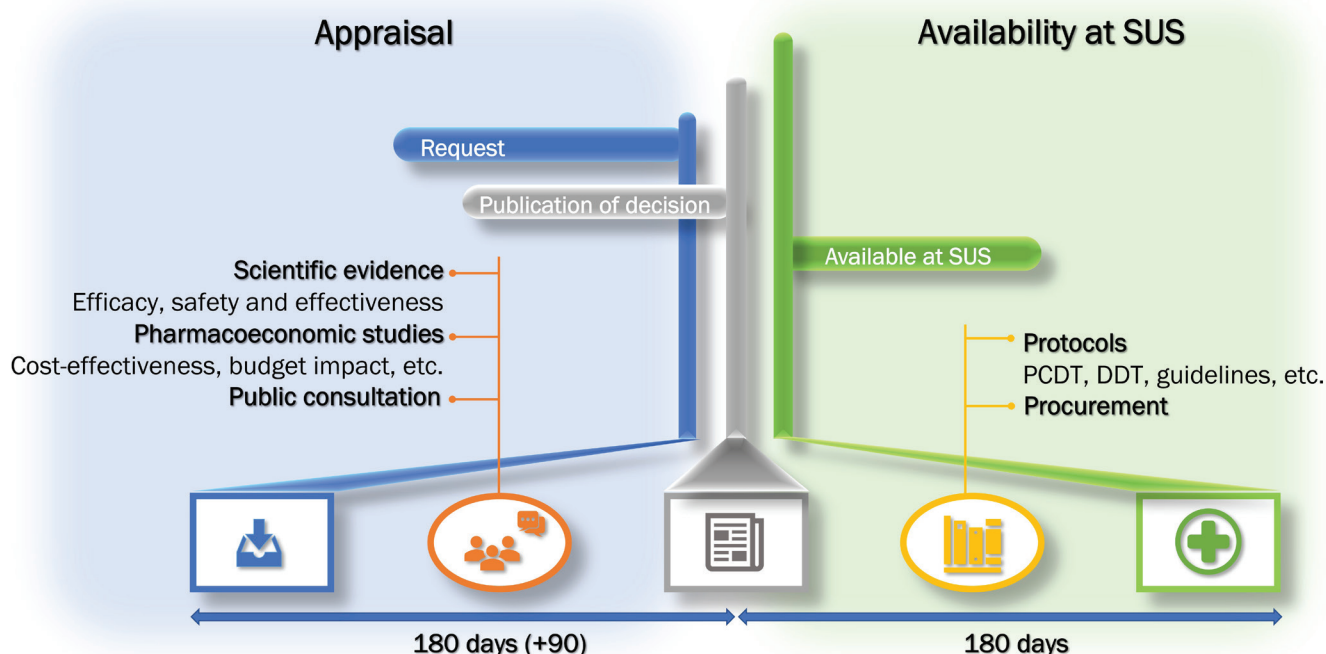
Reimbursement of medicines and other technologies by Private Health Insurance and Plans

All procedures, medicines and other technologies covered by Private Health Insurance are part of a positive list of procedures [*rol de procedimentos*], updated regularly using ATS and published by the National Regulatory Agency for Private Health Insurance and Plans (ANS). A "provisional measure" [*medida provisória*] from the Brazilian President established that, additionally, they must cover medicines and other technologies incorporated by the SUS within 30 days of Conitec's decision, with the PF by CMED as the cap reimbursement price.^{100–102} For updating the list, ANS is advised by the Permanent Committee of Regulation and Attention to Health (COSAÚDE) (Table S2).¹⁰³

Pricing and reimbursement outcomes, effects on the health system and policy recommendations

Medicines have the curious quality of being both a social good and a lucrative industry.¹⁰⁴ In Brazil, the pharmaceutical sector is in a better place than it was in the 1990s.²⁹ Economic regulation aims to provide price stability, predictability and transparency, discouraging opportunistic behaviour, reducing abuse of market power, contributing to access to medicines and competitiveness, with a constantly growing pharmaceutical market.^{26,29} Brazil is one of the eleven countries that corresponded to roughly half of the global pharmaceutical spending in 2020 (around \$618 billion).¹⁰⁵ Despite the increased availability of medicines at the SUS, ranging from 30–94.3%, 87.7% of the country's expenditure on pharmaceuticals and

Figure 4. Flowchart of technologies incorporation to the Unified Health System (SUS).



DDT: Diagnostic and Therapeutic Guidelines; PCDT: Clinical protocols and therapeutic guidelines.

Source: Conitec.^{56–58}

health products is out-of-pocket (in contrast with an average of 42% in the OECD), with medicines corresponding to 71.8% of household health expenditure.^{12,13,17-19} At the same time, the number of lawsuits related to access to medicines and other health products more than doubled from 2015 to 2018, from 200,090 to 544,378 (Figure S1).

Despite positive aspects, there are several challenges and gaps to be addressed related to pricing and reimbursement policies.^{38,55,106} Studies addressing some of these challenges are available, but there is a lack of comprehensive studies. Systematic and comprehensive assessments of the impact of pricing and reimbursement policies on the access to medicines in Brazil, throughout the medicine's life-cycle, would be welcome.

Ongoing challenges include high rates of lawsuits (judicialisation) for the provision of medicines and other technologies, even before regulatory approvals, pricing and coverage decisions.^{95,107,108} In 2016, ten medicines mandated through judicialisation, corresponded to 30% of the SUS pharmaceutical-expenditure.²⁴ One of them was eculizumab, constituting the highest expenditure of the MoH on a single medicine, costing USD 114.4 million (median unit price of \$5,095). In 2017, the PMVG approved by CMED represented a 55.5% expenditure reduction, allowing the MoH to treat more than double the number of patients (from 190 to 431 in 2018) with a similar expenditure.¹⁰⁹ Another example of judicialisation is elosulfase alfa, procured at \$569,925 PPP (R\$1.3 million) per patient in 2015, making Brazil one of the world's biggest buyers of this drug. The \$412.34 (R\$2.234,84) PMVG was established in 2017. Had this been done earlier, the Brazilian government could have saved at least \$21.9 million PPP (R\$50 million).¹¹⁰ Up to October 2021, to comply with lawsuit decisions, the Ministry of Health was obliged to provide \$181,12 million PPP to patients to import onasemnogene aberparovect at an average cost of 4.12 times the maximum approved price by CMED, representing 3.8% of the MoH pharmaceutical expenditure in 2020, because the manufacturer decided not to commercialise the medicine at the authorised price.^{23,66,111} These are a few examples of companies not complying with price decisions and judicialization, with huge opportunity costs for the SUS, showing the importance of pricing and reimbursement policies.

Brazil also faces the same challenges as other countries around the world when it comes to medicines with limited evidence and high prices not commensurate with their clinical benefits.^{111,118-123} For instance, concerning 253 new medicines, with marketing authorisation and approved prices from 2004 to 2016 in Brazil, only 14% had added therapeutic benefit and 8.2% were assessed by *Prescrire* as therapeutically innovative.¹¹² Another study comparing new cancer drugs approved in the US from 2010-2019, with marketing authorisation and price approved in Brazil before December 2020, found that 48.2% had added therapeutic benefit, with a median price reduction from requested to the authorised price of 2.0% (IQR: 0-9.2%) vs 6.1% (IQR: 0-27.8%) for drugs without the benefit.¹¹³ By preventing medicines without added therapeutic benefit costing more than the existing treatments in the market, the pricing system is protecting both the consumer and the health system.

An economic analysis had shown that the introduction of generics reduced market concentration; and prices, consequently increasing demand elasticity, while increasing competitiveness and access. It also stimulated pharmaceutical companies with innovative medicines to adapt, producing their correspondent generics.¹¹⁴ From 2015 to 2019, generics' revenue increased by 37.6%, evidence of their market expansion in Brazil.²⁶

In 2010, actual prices of generics at community pharmacies were 20% to 295% lower than CMED's maximum prices, considered

by the Consumer's Protection Institute (IDEC) as evidence of low regulation power.¹⁰⁶ Even though, great variations can also be interpreted as a result of competitiveness, measures are needed to shorten the differences between approved and actual prices.

The Federal Audit Court [*Tribunal de Contas da União*, TCU], consumer organizations and academics have been pointing out the static approach of the regulation at market entry and the basing of price adjustments, mostly positive, only on economic factors. These stakeholders urged CMED to update the regulation with provisions for price revisions, to reduce the huge differences between maximum approved and actual prices, taking into account new evidence, expiry of patents, entry of competitors or adjustment to actual commercialisation prices, among other factors.^{55,106,115}

Problems related to governance, shortage of technical staff, underuse of regulatory impact analysis and other tools and resources to ensure decisions informed by evidence, and politics, are among the challenges faced in Brazil.^{60,61,116-118} While the industry calls for more flexible rules, civil society and public health organisations call for more balance in respect of public policies which serve the public interest.^{61,107,119-121}

Final considerations

As acknowledged by WHO, improving access to medicines and other health technologies is a multidimensional challenge. It affects countries with different levels of development, especially those with more limited resources. There are serious concerns about high prices, that require adequate action and knowledge of the entire medicines value chain, with a life cycle perspective, therefore, increasing transparency and cooperation, both internally and among countries.¹²²

To address the existing challenges, the authors have three main policy recommendations. First: pricing regulation would benefit from greater regulatory governance, maintaining SCMED at Anvisa, and strengthening its technical capacity, while expanding efforts to implement good regulatory practices, increasing information publicly available, such as pricing approval reports, and updating the pricing regulation accompanied by regulatory impact assessment with the participation of the different stakeholders. These efforts could contribute to increased transparency and accountability, in line with efforts by Anvisa's open data plan, Open Government, Good Regulatory Practices and recommendations of the World Health Organisation (WHO) and the Organisation for the Economic Cooperation for Development (OECD).^{83,123,124}

Second: incentivise the development and promote access to medicines with stronger evidence, added clinical benefit and fair prices, more commensurate with their clinical benefits by mainstreaming HTA elements, reviewing the regulation and strengthening the integration of Anvisa's regulatory processes with pricing and reimbursement and other relevant stakeholders with a life-cycle perspective, allowing for early engagement with companies, improving methodological aspects.¹²⁵⁻¹²⁷

Third: increasing awareness among different stakeholders about the role and importance of pricing and reimbursement policies, improving compliance in respect of regulatory decisions and Conitec recommendations, and developing alternatives to improve public pharmaceutical expenditure and avoid judicialisation and minimising its impact in the health system, in the perspective of comprehensive care for those who need it.^{61,118} These strategies can contribute to closing the gap between the potential benefit of innovation and access to medicines.



Collaborators

AMIB: conceptualisation, writing original draft, writing – review and editing; DPK: conceptualisation, writing original draft, writing – review and editing; RRA: conceptualisation, writing – review, and editing; PGL: conceptualisation, writing – review, and editing. All authors. reviewed and approved the final version of the work and agreed to be accountable for all aspects of the work.

Conflict interests statement

The authors have no interests to declare. The views expressed in this article are from its authors, and do not necessarily reflect those of the Brazilian Health Regulatory Agency (Anvisa), the Executive Secretariat of the Drugs' Market Regulatory Chamber (SCMED) or the Ministry of Health.

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