VALUE IN HEALTH REGIONAL ISSUES 20 (2019) 191–195

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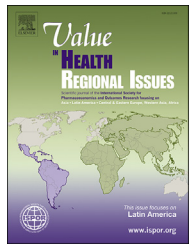

Policy Perspective

Challenges in the Regulation of High-Cost Treatments: An Overview From Brazil

Lara C. Pereira, BA [1], Daniela V.R. Sturzenegger, MSc [2], Juliana Ortiz, MSc [3], Nadia M.E. Ayad, BS [4], Wilian A. Cortopassi, PhD [5], Leandro P. Safatle, BS [1], Natalia Khuri, MBA, PhD [6,7,]*

[1]*SCMED, Brazilian Health Regulatory Agency, Brasilia, Brazil;* [2]*General Office for Regulation and Good Regulatory Practices, Brazilian Health Regulatory Agency, Brasilia, Brazil;* [3]*Pharmaceutical Market Regulation Chamber, Brasilia, Brazil;* [4]*Graduate Program in Bioengineering, University of California, Berkeley and University of California, San Francisco, CA, USA;* [5]*Department of Pharmaceutical Chemistry, University of California, San Francisco, CA, USA;* [6]*Department of Bioengineering, Stanford University, Stanford, CA, USA;* [7]*Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA*

ABSTRACT

Regulation of drug prices that ensures adequate access to effective treatments and promotes innovation is a global challenge. In the United States, the government does not regulate drug prices when they come onto market. On the other hand, in countries such as France and Brazil, government agencies are responsible for setting up price limits by leveraging the interests of the companies and the countries' population. In Brazil, safety and efficacy of drugs are regulated by the Brazilian Health Regulatory Agency, and drug prices are regulated by the Pharmaceutical Market Regulation Chamber with a participation of Brazilian Health Regulatory Agency. Here, we introduce the current challenges faced by the Brazilian government in the drug price regulation and present proposed initiatives aiming to streamline access to innovative treatments for its citizens.

Keywords: Brazil, drug pricing, judicialization of health

Introduction

Overview of Drug Price Regulation Worldwide

Regulation of quality, efficacy, and safety of medical products is usually a task of government agencies, whose mission is to provide the best standard of care for their citizens. Although there seems to exist a worldwide consensus on overseeing what is needed for the approval of a drug, there is less agreement about how to regulate the prices of medical products. In the United States, drug prices are determined by the market; therefore, the final price is usually negotiated between manufacturers and buyers. Conversely, a considerable number of European countries (eg, France, Spain, Italy, and Portugal) and non-European countries (eg, Australia, Japan, and Brazil) have government-associated agencies with authority to regulate drug prices, each of them with their own specific criteria.[1-3]

Despite different policies for regulating medicines, most countries are now facing a common challenge of keeping pace with rapid innovations in the pharmaceutical market, resulting in novel treatments at dramatically increased costs.[4] For instance, recent advances in research and technology, alongside with regulatory incentives for the development of drugs for the treatment of rare diseases, enabled the emergence of more effective drugs, personalized treatments, and alternatives to once untreatable conditions. In 2017, among the 46 new drugs approved by the US Food and Drug Administration, 40% (18 of 46) had orphan disease designation.[5] Nevertheless, these new therapies are expensive,

LC Pereira, DVR Sturzenegger, and J Ortiz contributed equally to this manuscript.

Conflict of interest: LP Safatle was the former Executive Secretary of SCMED (2014-2019) at the time of the writing.

The opinions expressed in this manuscript are the authors' own, are intended for academic purposes, and do not reflect the view of the Brazilian Health Regulatory Agency, US Department of Health & Human Services, or US Food and Drug Administration. They are a summary of the group discussions during the 2018 Immersion Program in Regulatory Science.

* Address correspondence to: Natalia Khuri, MBA, PhD, Department of Computer Science, Wake Forest University, North Carolina, USA

Email: natalia.khuri@wfu.edu

2212-1099/$36.00 - see front matter © 2019 ISPOR–The professional society for health economics and outcomes research. Published by Elsevier Inc.

https://doi.org/10.1016/j.vhri.2019.07.006

posing a challenge for limited healthcare budgets. This trend is expected to continue in the next years as pharmaceutical industries' research portfolio continues to include more personalized treatments and orphan drugs than ever before.[6]

Historically, these innovative treatments have been marketed first in the United States, after Food and Drug Administration's evaluation of their safety and efficacy. Companies may also decide to submit to other countries' agencies, depending on their internal strategic decisions.[7] Nevertheless, a higher number of pioneering drugs are being simultaneously submitted for evaluation in different countries owing to global market expansion of pharmaceutical and biotechnology companies and unmet needs of patients, especially when there are no alternative medical products in the local market.[7,8] For countries where a universal healthcare system is in place or for countries with significant public healthcare programs, in addition to the evaluation of safety and efficacy, costs and their economic impact on healthcare budgets are also considered. Although determination of drug pricing policies is a global challenge, in this article we aim to discuss the unique regulatory landscape in Brazil, highlighting local and international pricing policies currently under consideration in the country.

The Public Healthcare System in Brazil

In Brazil, 78% of the population is assisted exclusively by its public universal healthcare system, Sistema Único de Saúde (SUS), and 22% is also covered by private health insurance companies.[9] The SUS was created in 1988, alongside the implementation of the 1988 Brazilian Constitution, which established health as a citizen's fundamental right.

The National Commission for the Incorporation of Technologies (Comissão Nacional de Incorporação de Tecnologias [Conitec]) recommends to the Ministry of Health (Ministério da Saúde) medicines to be included in the lists of treatments and drugs to be provided by the SUS.[10] Consumers can purchase drugs and treatments that are not included in these lists through out-of-pocket spending or private insurance.

Before any drug or treatment becomes available for the patients, either through SUS, private insurance, or out-of-pocket spending, their safety and efficacy must be evaluated by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária [ANVISA]), and their price limits must be determined by the Pharmaceutical Market Regulation Chamber (Câmara de Regulação do Mercado de Medicamentos [CMED]).[11] When drugs are purchased by the SUS, CMED also establishes a mandatory discount over the ceiling price—the coefficient of price adjustment (*coeficiente de adequação de preços*).[12] This is a policy that sets a starting point for the negotiation process when drugs are purchased by public administration entities, aiming at promoting efficiency in the healthcare budget.

Drug Price Regulation Policies in Brazil

Brazil's modern healthcare regulatory landscape was shaped in the end of the 1990s in response to cases of falsification of medicines along with increasing high prices and shortages of drugs. In response, two institutions were created, ANVISA and the Pharmaceutical Chamber (Câmara de Medicamentos). In 2003, the Pharmaceutical Chamber became CMED.

ANVISA is the national regulatory agency with a broad mandate to promote public health. Companies interested in marketing a drug in Brazil should register a drug by proving its safety and efficacy, following ANVISA's regulations and guidelines, which are harmonized with international requirements (Fig 1).

Once the new drug is registered by ANVISA, companies must submit an application to CMED, which will determine the maximum allowed price of the product. CMED is an institution charged with setting the pricing rules, composed of four state ministries: Chief of Staff's Office (Casa Civil), Ministry of Justice, Ministry of Economy, and Ministry of Health (Fig 2). The Technical Executive Committee of CMED is responsible for adopting, implementing, and coordinating activities related to economic regulation of drugs. The implementation of the rules created by the ministries is carried out by CMED's Executive Secretariat, which is a department of ANVISA (Fig 1).

The rationale for setting the ceiling prices for drugs was established by Resolution CMED 2/2004. Two criteria are used in determining prices of new drugs, namely (1) external reference pricing, and (2) the cost of available treatments. If a new drug is better than the standard of care, the external reference pricing method will be applied, and the ceiling price for the Brazilian market will be the lowest among nine reference countries (Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain, and the United States). The prices used in the comparison are ex-factory prices, that is, manufacturer prices before taxes and profit margins, and at least three reference prices should be available for setting a definitive ceiling price for drugs entering the Brazilian market. If there are fewer than three prices, CMED will set a provisional price based on the currently available reference prices until the third one is available. If a drug under consideration has no significant advantage in comparison with its alternatives, the ceiling price of the new drug is calculated as to not result in a higher cost of treatment than that of currently available treatments in Brazil. Regarding comparison with the standard of care, a drug is considered to have an advantage over its alternatives available in Brazil if there is scientific evidence of (1) greater efficacy compared with drugs with the same therapeutic indication, (2) same efficacy

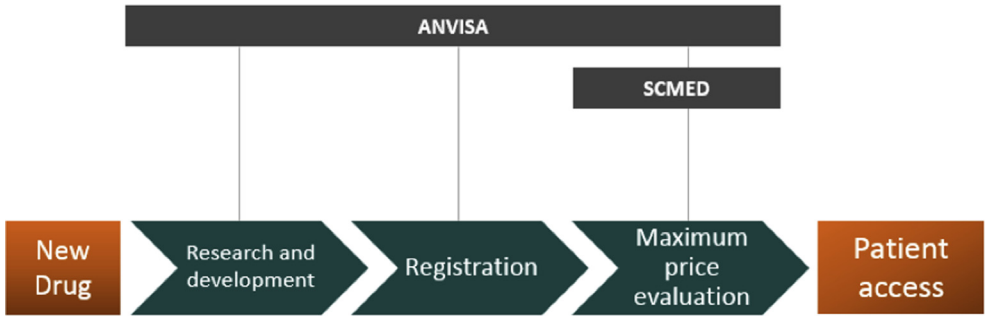

Fig. 1 – ANVISA's process for evaluating new drugs entering the Brazilian market. ANVISA indicates Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária); SCMED, Pharmaceutical Market Regulation Chamber (Câmara de Regulação do Mercado de Medicamentos) executive secretariat.

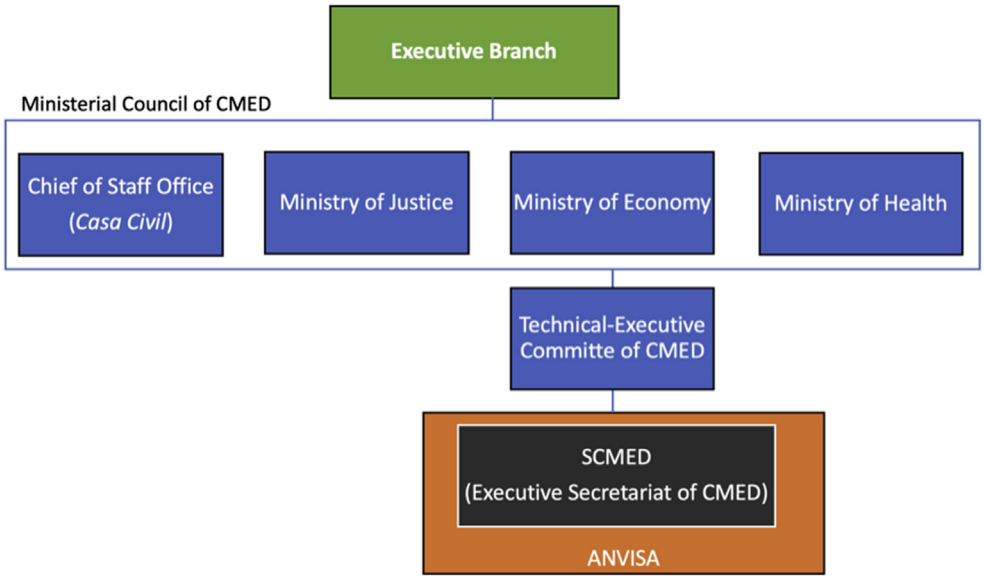

Fig. 2 – CMED's organizational structure in blue and ANVISA's in orange. SCMED, in black, interfaces with both organizations. ANVISA indicates Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária); CMED, Pharmaceutical Market Regulation Chamber (Câmara de Regulação do Mercado de Medicamentos); SCMED, CMED's executive secretariat.

with fewer adverse effects, or (3) same efficacy with significant reduction of global costs of treatment. To support the claim of the drug's superiority, companies should submit head-to-head studies or indirect comparisons for CMED evaluation.

These price control policies stabilized drug prices in Brazil and brought economic benefits to SUS without hindering the growth of the pharmaceutical market. In 2016, Brazil was the eighth largest pharmaceutical market in the world and it is expected to be the fifth by 2021.[13]

Discussion

The Increasing Number of High-Cost Drugs and Its Consequences for Brazilian's Healthcare Budgets

The evolution of medical sciences has resulted in a rising number of personalized treatments and drugs indicated for rare conditions.[12] On one hand, these drugs require large investments in research and development, and on the other hand, they are targeted at small groups of patients, so prices tend to reach unparalleled levels.

In Brazil, the high cost of drugs launched in the last decade has resulted in unaffordable treatments even for the wealthier percentages of the population.[14] Owing to insufficient evidence of superiority of the new drugs in comparison with existing treatments, and given the significant impact for the health budget, SUS has not automatically included these new drugs in its lists of covered treatments. Therefore, to have access to new and expensive drugs, part of the population has appealed to the constitutional right to health, and a rapidly rising number of lawsuits has been filed by patients against the Brazilian State to demand access to high-cost drugs through SUS—the *judicialização da saúde* phenomenon.[15,16] In most cases, after courts' decision, the State has been obliged to supply the medicine, even if it has not been approved for the incorporation into the lists, because it has not shown clinical benefit when compared to other treatments already in the market. The number of lawsuits has sharply risen in the last decade (Table 1 and Fig 3), which coincides with the period of the proliferation of high-cost drugs in the market.

The federal spending on pharmaceutical products demanded by lawsuits is rapidly increasing, and it can be presumed that the same is happening with federal state and city budgets because they are the target of most lawsuits.[17] Most of these products are either high-cost drugs or specialty drugs with high unitary price and indicated for the treatment of complex or chronic conditions, for example, cancer and rare diseases. According to an analysis by the Ministry of Health, the total amount spent owing to lawsuits was $68.2 million in 2010 and $324.1 million in 2015 (Fig 3), demonstrating a dramatic increase in spending over the last years.

In 2017, the judicialization expenditure reached $307 million, with $274 million or 89% of the total spent for 11 drugs for the treatment of 1334 patients with rare diseases (Fig 3). Most of these drugs were assessed or are under evaluation by Conitec for incorporation by SUS, but at the time, some of these drugs, for example, Soliris (eculizumab), had not been registered by ANVISA, and none of the drugs had a maximum price established by CMED, so it was not possible for Conitec to start an analysis. Most of the time, it was the company's decision not to submit the petition to ANVISA or CMED.

Soliris was registered by ANVISA and had its maximum price defined by CMED in October 2017, resulting in an estimated saving of $94 million per year for SUS. Myalept (metreleptin) still has not been registered by ANVISA, and its maximum price has not yet been established by CMED. As of May 2019, the Supreme Court of Brazil has decided that drugs with no registration by ANVISA can only be supplied by SUS when demanded in court under exceptional circumstances. Therefore, a better compliance of companies in following ANVISA and CMED rules is expected.

The *judicialização da saúde* phenomenon and the considerable increase in government expenditures on pharmaceutical products has been a matter of concern for policymakers because it can reinforce social inequalities. Given that access to the justice system is unequal in Brazil, most lawsuits would be filed by high-income patients.[18] Moreover, increasing expenditures destined to high-cost drugs targeted at a small group of patients can result in

Table 1 – Judicialization of rare disease drugs in 2017.

Drug	Rare disease	Number of patients	Total spent (USD in millions)
Soliris (eculizumabe)	Paroxysmal nocturnal hemoglobinuria and Atypical hemolytic uremic syndrome	406	79
Naglazyme (galsulfase)	Mucopolysaccharidosis VI	150	48
Vimizim (elosulfase)	Mucopolysaccharidosis type IVA	75	27
Translarna (ataluren)	Duchenne muscular dystrophy	68	34
Replagal (agalsidade alfa)	Fabry disease	220	27
Elaprase (idursulfase)	Hunter syndrome	126	17
Fabrazyme (agalsidase beta)	Fabry disease	122	15
Myozyme (alglucosidase alfa)	Pompe disease	39	9
Myalept (metreleptin)	Lipodystrophy	22	8
Juxtapid (lomitapide)	Homozygous familial hypercholesterolemia	15	6
Aldurazyme (laronidase)	Mucopolysaccharidosis type I	91	5

Note. To convert from Brazilian currency (R$) to USD (in millions), we used the average annual rate of commercial exchange and updated it to 2019 with the US consumer price index. Source: Ministry of Health, Central Bank of Brazil and US Bureau of Labor Statistics.

fewer resources available for the treatment of conditions that affects large numbers of citizens, like hypertension and diabetes.

After court approval, the judicial decision to supply the drug is mandatory and immediate for SUS. Taking advantage of this, some pharmaceutical companies have neglected the obligation to file a price petition with CMED before starting to sell their drugs. This has caused a negative impact on the Brazilian healthcare budget because without price setting by CMED, companies can charge freely for these drugs. To ensure the effective economic regulation of the drug market and to minimize losses caused by this practice, a legal resolution was published in August 2018 allowing CMED to establish price limits even if a company fails to submit a price-cap petition, as previously determined in Resolution 2/2004.

The phenomenon of *judicialização da saúde* is complex, and all involved players—judges, healthcare experts, patients, and government officials—are currently engaged in a dialogue to streamline the drug approval process while respecting Brazilians constitutional rights.

High-Cost Drugs: The Brazilian Regulatory Approach to Rare Diseases

Aiming to provide fast access to patients, ANVISA recently issued Resolution number 205/2017, which speeds up approval of orphan drugs in Brazil. More specifically, drugs that met the criteria established under this resolution will have a period of up to 365 days to be commercialized, counted from the date of publication of the registry. This resolution established procedures for submission under the rare diseases category regarding (1) consent of clinical trials in Brazil, (2) good manufacturing practices, and (3) health registration of new drugs for rare diseases.

As Brazil becomes an attractive market to pharmaceutical companies and given the expedited process established by ANVISA, some novel drugs, including for rare diseases, have been submitted for market authorization in Brazil without marketing approval in any other country or only in the United States. This challenges the usual price-setting method, where CMED uses reference countries to determine ceiling prices. If these drugs follow the criteria established by resolution number 205/2017 for the treatment of rare diseases, they undergo an expedited process, and decisions have to be taken in much shorter times. Moreover, most of the times, there is no existing alternative therapy for rare diseases for price comparison. Therefore, CMED is carrying on discussions with manufacturers, partner countries, academia, and other health experts to develop a new methodology for price setting for these challenging situations.

Beyond Domestic Initiatives: A Shared Problem Demands International Cooperation to Be Solved

The challenge of high-cost drugs is shared by all countries, regardless of their development status and their national price control policies or lack thereof. Even in the United States, where no governmental price control policy exists, the topic of drug prices is under debate.[19] Each country deals with the problem of drugs' rising prices individually, and some of the most common solutions comprise external reference pricing, direct price negotiations, and health technology assessment.[20,21] These measures, however, have proven insufficient to deal with the impact on the sustainability of healthcare systems of the proliferation of high-cost drugs and their rising prices.

Therefore, international discussions about this topic have recently emerged in forums, such as the Fair Pricing Forum organized in 2017 by the Organisation for Economic Co-operation and Development and the World Health Organization. According

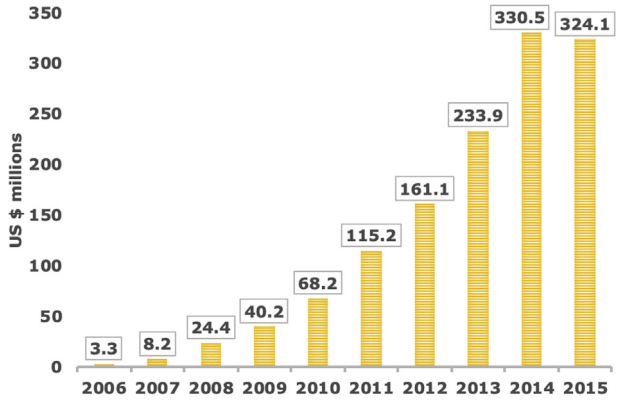

Fig. 3 – Growth of federal spending with pharmaceutical products demanded by lawsuits from 2006 to 2015 in Brazil. As in Table 1, to convert from Brazilian currency (R$) to USD (in millions), we used the average annual rate of commercial exchange and updated it to 2019 with the US consumer price index. Source: Ministry of Health, Central Bank of Brazil, and US Bureau of Labor Statistics.

to an Organisation for Economic Co-operation and Development report, a rebalancing of the negotiating powers of payers and manufacturers is needed through increased transparency and co-operation between payers.[22] Thus, a cooperative and multilateral approach could benefit all nations by exchanging good practices, harmonizing procedures, and promoting actions that could only be implemented if buyers act together rather than as isolated agents with limited bargaining power.

Most regulatory agencies worldwide are focused on the implementation of regulatory policies, but a thorough analysis of the current trends and gaps of the pharmaceutical industry remains mostly an academic interest. Given the complexity of the drug pricing regulation issues, a global solution may need mutual collaborations among different players—public regulatory agencies, universities, and the pharmaceutical industry.

Conclusion

The challenges of rising drug prices are global. Recent advances in medicine and pharmaceutical sciences provide alternatives to a considerable number of diseases that were considered unmanageable a decade ago, making society optimistic about having access to state-of-the-art healthcare solutions. Nevertheless, these advances come at a cost, which is not always affordable to everyone. Brazil's constitution grants health as a right to all citizens, but the government is currently facing great challenges on how to quickly respond to these pioneering innovations and provide the best treatments to everyone despite its limited budget. Although initiatives to reduce the overall cost of pharmaceutical products are ongoing, for example, by addressing the dramatic spending on lawsuits, questions remain on what constitutes a fair pricing system for innovative and recent treatments. Open and transparent communication among government agencies, academia, and companies may help to improve price regulation of medicines not only in Brazil, but also in a global perspective, and contribute to better access by patients to the most innovative, effective, and safe available treatments.

Acknowledgments

We acknowledge Russ B. Altman, Terrence F. Blaschke, Katia Alves, Lais R.M. Oliveira, and Jaqueline Tran for useful and impactful discussions during the 2018 Immersion Program.

Source of financial support

This publication was made possible by Grant Number U01FD004979/U01FD005978 from the FDA, which supports the UCSF-Stanford Center of Excellence in Regulatory Sciences and Innovation. This work was partially supported by the Lemann Foundation Award (L.C.P. and D.V.R.S.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the the Brazilian Health Regulatory Agency, HHS or FDA. L.P. Safatle was the former Executive Secretary of SCMED (2014-2019) at the time of the writing.

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