

# Pharmaceutical regulation, pricing, coverage and policy reform in the United States of America

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## Abstract

The United States (US) is the largest economy in the world and the largest pharmaceutical market, accounting for 40% of the global expenditure on pharmaceuticals and almost half of the global pharmaceutical pipeline. This review describes prescription drug regulation, pricing and coverage in the US and provides perspectives for policy reform. With an unregulated market-based pricing system for drugs, the US pays on average 3 to 4 times higher prices for branded prescription drugs than other industrialized countries. Challenges posed by rising drug prices create affordability problems that threaten the American population's health as well as the sustainability of the US healthcare system. The US stands out as the country with the highest health expenditure per capita, at about 17% of its gross domestic product, and with pharmaceuticals representing over 12% of the total health expenditure. Health coverage is strongly dependent on employment-based private insurance, with government programs like Medicare and Medicaid providing coverage to older and poorer populations, respectively. Coverage for outpatient prescription drugs is included in most, if not all, private health insurance plans and government programs. Although some drug pricing policy reforms have been proposed in recent years, no major nationwide initiatives have been successful in the US thus far. High drug prices might not only impact the US care system's efficiency, but can also have a ripple effect to other countries like Brazil that use the US for external reference pricing, even if those countries may have other price regulation mechanisms in place. This is particularly important for new therapies for which no other international prices may be available in the global market besides the one from the US. The growing budgetary pressures from rising drug prices underscore the need for US drug pricing reform and highlight the need for global pricing mechanisms that can help ensure early access to new technologies at fairer prices.

**Keywords:** access to medicines; healthcare systems; pharmacoeconomics, prescription drugs; health care market; United States.

## Regulação, precificação, cobertura e reformas nas políticas de medicamentos nos Estados Unidos da América

## Resumo

Os Estados Unidos da América (EUA) são a maior economia do mundo e possuem o maior mercado farmacêutico, representando 40% dos gastos globais com medicamentos e quase a metade dos produtos na *pipeline* global de terapias em desenvolvimento. Essa revisão descreve a regulação, precificação e cobertura de medicamentos nos EUA, e propõe perspectivas para reformas nas políticas. Com um sistema não-regulado de precificação de medicamentos, os EUA enfrentam preços em média 3 a 4 vezes mais altos para medicamentos patenteados do que outros países industrializados. Os desafios apresentados pelos aumentos de preços de medicamentos ameaçam a saúde da população americana assim como a sustentabilidade do sistema de saúde dos EUA. Os EUA se destacam como o país com a mais elevada taxa de gastos em saúde per capita do mundo, representando cerca de 17% do seu produto interno bruto, e com gastos em medicamentos representando mais de 12% dos gastos totais em saúde. A cobertura de saúde nos EUA depende fortemente de planos de saúde privados financiados para os trabalhadores por meio de seu emprego, com programas governamentais como o *Medicare* e o *Medicaid* fornecendo cobertura para as populações com idade avançada e de menor renda, respectivamente. A cobertura para medicamentos de uso ambulatorial está incluída na maioria, se não em todos, os planos de saúde privados e programas governamentais. Embora algumas reformas nas políticas de precificação de medicamentos tenham sido propostas nos EUA recentemente, nenhuma iniciativa de caráter nacional foi bem-sucedida até o momento. Os altos preços de medicamentos podem afetar não somente a eficiência do sistema de saúde dos EUA, mas também outros países como o Brasil que usam os preços dos EUA no referenciamento externo de preços, ainda que estes países possam ter outros mecanismos para regulação de preços já estabelecidos. Isso é especialmente importante para novas terapias para as quais nenhum outro preço internacional esteja disponível no mercado global além daquele dos EUA. As pressões orçamentárias advindas da ascensão dos preços de medicamentos reforçam a necessidade de reformas no sistema americano de precificação de medicamentos e ressaltam a necessidade de mecanismos globais de precificação que possam auxiliar a garantir o acesso rápido a novas tecnologias a preços mais justos.

**Palavras-chaves:** acesso a medicamentos; sistemas de saúde; farmacoeconomia; medicamentos sob prescrição; mercado de saúde; Estados Unidos.



## Introduction

The United States (US) is the largest economy in the world and the third largest country, with over 3,7 million sq mi (9,8 million km<sup>2</sup>).<sup>1</sup> According to the U.S. Census Bureau, over 330 million people live in the US.<sup>2</sup> The US spends far more than any other country on health care – about 17% of its gross domestic product (GDP) – but has a lower life expectancy than most of its peers.<sup>3</sup> The latest UN reports show a Human Development Index of 0.926 and a life expectancy at birth of 78.9 years in 2020 (the 46<sup>th</sup> in the world), while the most recent GINI index was 41.5 in 2019.<sup>4,5</sup> The US also has a higher birth rate than most industrialized countries, with a high mortality rate, which results in a dependency ratio (number of people of non-working age compared with the number of people of working age) expected to grow more slowly than in other high-income countries. This ratio expresses the pressure on the working population, and the aging population poses several concerns to the US health care system, with expected increases in the demand for health care, budgetary pressures, and concerns about the system's efficiency.<sup>6</sup>

The US pharmaceutical market is the number 1 in the world, at over USD \$500 billion per year, representing about 40% of

the entire global market and largest than the next five largest markets combined.<sup>7</sup> Per-capita expenditure on pharmaceuticals is the world's highest (\$1,376 at purchasing power parity – PPP), representing more than double the average expenditure of other industrialized countries (\$571 PPP).<sup>8</sup> Drug expenditures corresponded to 12.6% the national health expenditure (NHE) in 2019, and it has been estimated that by 2026, spending on prescription drugs will account for 15.4% of NHE (Table 1).<sup>3,9,10</sup>

The main factor behind the US exceptionally high pharmaceutical spending is its higher drug prices. The US pays, on average, 3 to 4 times more for brand-name drugs as compared to other industrialized countries.<sup>11</sup> The US is also an outlier in that patients are responsible for a great portion of their drug costs – in 2019, Americans paid over USD \$80 billion out-of-pocket for medications, representing more than 10% of the entire spending on pharmaceuticals in that year.<sup>12</sup> High drug prices and high out-of-pocket burden place significant pressure on American patients, who often report not being able to take their medications as prescribed due to costs.<sup>3,10</sup>

This article reviews the regulation, pricing, and coverage of prescription drugs in the US.

**Table 1.** Health and pharmaceutical expenditure in the US and in OECD countries.

Expenditure data <sup>1</sup> (adjusted by purchasing power parity)	Health Expenditure			Pharmaceutical Expenditure <sup>2</sup>		
	US	OECD	Brazil	US	OECD	Brazil <sup>3</sup>
Expenditure per capita (USD PPP)	10,948	4,087	1,482	1,376	571	296
Share of GDP or HE <sup>4</sup> (%)	16.8	8.8	9.6	12.6	13.9	20.5

<sup>1</sup>Data refer to 2019. <sup>2</sup>Only retail pharmaceutical expenditure (outpatient sector). <sup>3</sup>Pharmaceutical expenditure in Brazil includes pharmaceutical products and medical devices. <sup>4</sup>Health expenditure = share in % of gross domestic product (GDP); pharmaceutical expenditure = share in % of health expenditure (HE). Source: OECD and Brazilian Ministry of Health.<sup>3,10</sup>

## Pharmaceutical Regulation

The Department of Health and Human Services (HHS) plays the main regulatory role in the US pharmaceutical market, through its agencies such as the Food and Drug Administration (FDA), which oversees drug development, pharmaceutical marketing approval, and post-marketing drug surveillance.<sup>5</sup> In addition, the National Institute of Health (NIH) is the main catalyst for drug discovery and early drug development, and the Drug Enforcement Administration within the Department of Justice has a role in the regulation of controlled substances.<sup>6</sup> A number of federal and state laws and statutes regulate pharmaceuticals' intellectual property rights as well as the commercial activities of pharmacies and drug distributors.<sup>13</sup>

The regulatory pathways governing drug approval depend on drug type. Drug manufacturers must obtain marketing authorization from the FDA to enter the market, for which they are required to demonstrate quality, safety and effectiveness (QSE) of their products.<sup>13,14</sup> New drugs must obtain marketing approval through the New Drug Application pathway (NDA) if they are "conventional" or "small molecule" products, or through the Biologics License Application pathway (BLA) if they are biologic products. Both of these pathways require the drug manufacturer to present evidence from phase III clinical trials demonstrating the drug's QSE for its proposed indication(s) (Figure 1), even though in some cases, phase II trials may be accepted.<sup>13-18</sup> A number of expedited review programs are available for drugs that treat serious conditions – for example, for breakthrough therapies (drugs that provide substantial improvement over the existing therapeutic options), and accelerated approval for drugs that fill an unmet need in the treatment of a serious condition and are approved based on a surrogate endpoint.<sup>19</sup>

New FDA-approved drugs are granted market exclusivity periods of up to 12 years, which may be concurrent with patent exclusivity.<sup>20-22</sup> FDA grants market exclusivity periods, while patents grant exclusive legal rights to inventions and are approved by the United States Patent and Trademark Office (USPTO), with 20-year market protection that typically start during the drug discovery phase.<sup>21,22</sup> Market monopolies are granted in order to stimulate research and development (R&D), and the patent term restoration can extend the exclusivity up to 14 years to compensate for the time spent in regulatory review and clinical trials.<sup>20</sup> Some drug manufacturers have been able to use patents, such as through patent thickets or product evergreening, to extend their market monopoly for many years.<sup>21</sup>

There are also programs to incentivize drug development for conditions of greatest public health importance, including orphan conditions. Established by the Orphan Drug Act of 1983, the incentives for new drugs to treat rare conditions (defined as prevalence under 200,000 individuals in the US) include tax credits to offset the costs of clinical trials and 7-year market exclusivity periods for the orphan drug's indication.<sup>23</sup> The Orphan Drug Act has been highly successful,<sup>24</sup> with over 600 drugs approved since its inception (data of May 17, 2022).<sup>25</sup> In the last 5 years, 51% of new drugs have had orphan designation.<sup>26</sup> Because of these incentives, the number of orphan drug designation requests increased from 2012 through 2016 and has remained steadily greater than 500 annually since then. The recent major concern is that this number is accelerating quickly. From 2019 to 2020, the FDA experienced an increase of 41% in the number of orphan drugs designations requested, beating the record in 2020. Studies show orphan drugs



tend to be charged 4.5 times higher than nonorphan drugs, on average.<sup>27</sup> In addition, seven out of ten top-selling drugs in the US have an orphan designation, which has raised concerns as to the potential use of orphan drug incentives by drug manufacturers as a measure to over-extend market monopolies and increase drug prices. Reports of new drug approvals are publicly available on the FDA's website, as well as information on guidelines, safety, shortages and recalls.<sup>28</sup> Since 1970, a variety of laws were enacted aiming for transparency of government decisions, requiring authorities to publicize their decisions and related documents.<sup>13</sup>

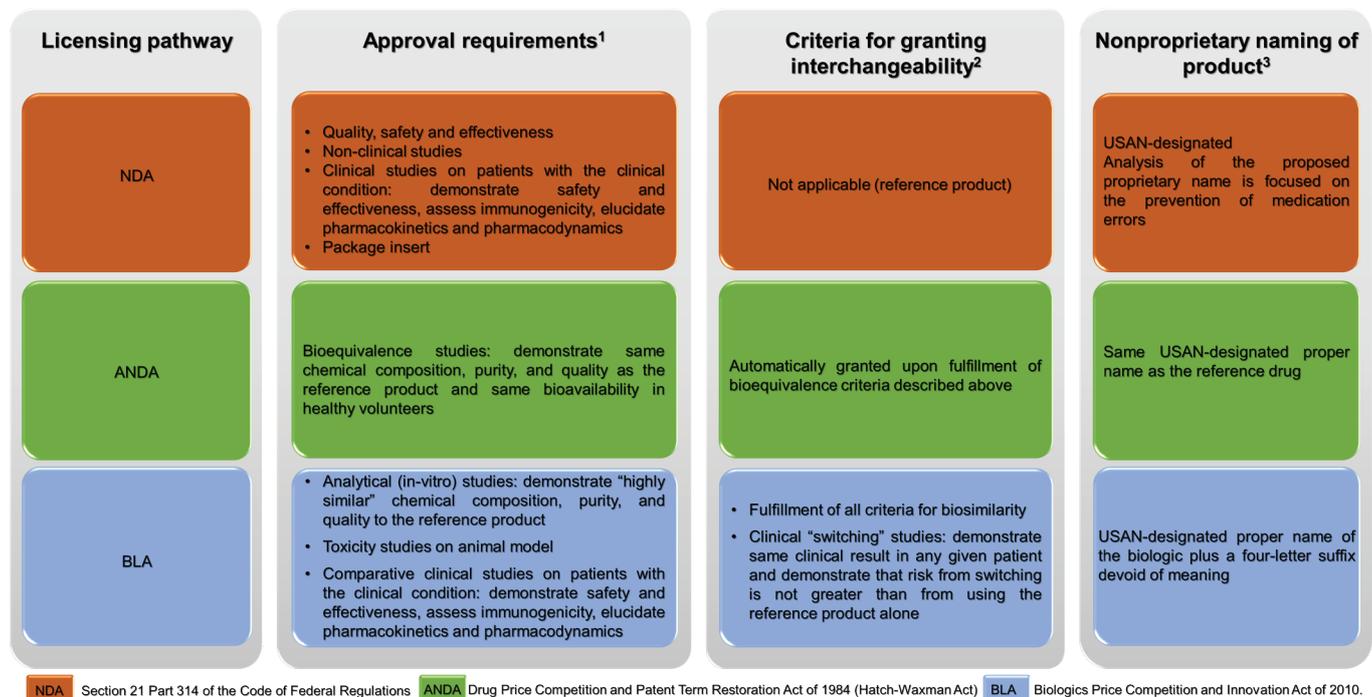
The US relies on the entry of follow-on products such as generics and biosimilars in the pharmaceutical market, after the exclusivity periods of originator products are over, to provide competition and lower drug prices. Generic drugs must meet FDA standards to be approved, and may use the Abbreviated New Drug Application (ANDA) licensing pathway created by the Hatch-Waxman Act of 1984 to obtain market approval without the need to conduct clinical trials.<sup>9,18</sup> The first generic drug may also have 180 days of market exclusivity if the criteria are met.<sup>22</sup> Follow-on biologics have higher approval standards than conventional generics. Biosimilars must be approved by a BLA process, which requires the demonstration of "highly similar" chemical composition to the reference product, purity, and quality, as well as toxicity studies on animal models and comparative clinical studies on patients who have the clinical condition, demonstrating comparable safety and effectiveness to the reference product.<sup>17</sup>

Once a drug is approved for marketing, there are several pharmacovigilance mechanisms in place to monitor safety signals

that may develop over time, all of them under the purview of the FDA.<sup>29</sup> Manufacturers are required to report to the FDA any safety signals that they may identify or receive from consumers and providers concerning their products. A passive surveillance system (the FDA Adverse Event Reporting System - FAERS) is available to providers and consumers to directly inform adverse effects and other drug safety concerns to the FDA. Lastly, an active surveillance system – the Sentinel System – is in place where nationwide data partners share structured information that allows for queries of clinical situations of concern and their relationship to specific pharmaceuticals.<sup>30</sup> Once safety signals are identified, actions may vary from communicating safety information to the medical community to removing a drug from the market. MedWatch is a FDA Safety Information and Adverse Event Reporting Program that provides a platform to ensure that new safety information is rapidly communicated to the medical community.<sup>29</sup> In addition, the FDA may choose to implement Risk Evaluation and Mitigation Strategy (REMS) programs for certain drugs of greater safety concern in order to ensure that patients and providers are aware of the risks and to support the safe use of the particular drug.<sup>31</sup> Finally, the FDA also monitors medication errors and drug shortages.

Advances in technology and R&D have resulted in the US becoming the biggest global source of drug innovation. According to IQVIA, out of 84 new-molecule drugs launched globally in 2021, 85.7% were launched in the US.<sup>32</sup> Also, U.S.-headquartered companies account for 44% of the R&D pipeline of the more than 6,000 products in active development globally.<sup>32</sup>

**Figure 1.** Comparison between small-molecule generics, biosimilars and new drug applications in the US.



ANDA. Abbreviated New Drug Application. BLA. Biologics License Application. NDA. New Drug Application. USAN. United States Adopted Names.  
<sup>1</sup> The specific requirements for biosimilar approval may vary on a case-by-case basis. <sup>2</sup> Interchangeability is defined as allowing for the drug to be substitutable for the reference product by a pharmacist without the intervention of the prescriber. The FDA has recently modified the criteria for interchangeability for the specific case of insulins, such that proof of biosimilarity will be sufficient for granting interchangeability.<sup>3</sup> The nonproprietary names of all reference biologics approved by the FDA as of March 2020 will also contain a four-letter suffix devoid of meaning, which is different than the suffix of their biosimilars.

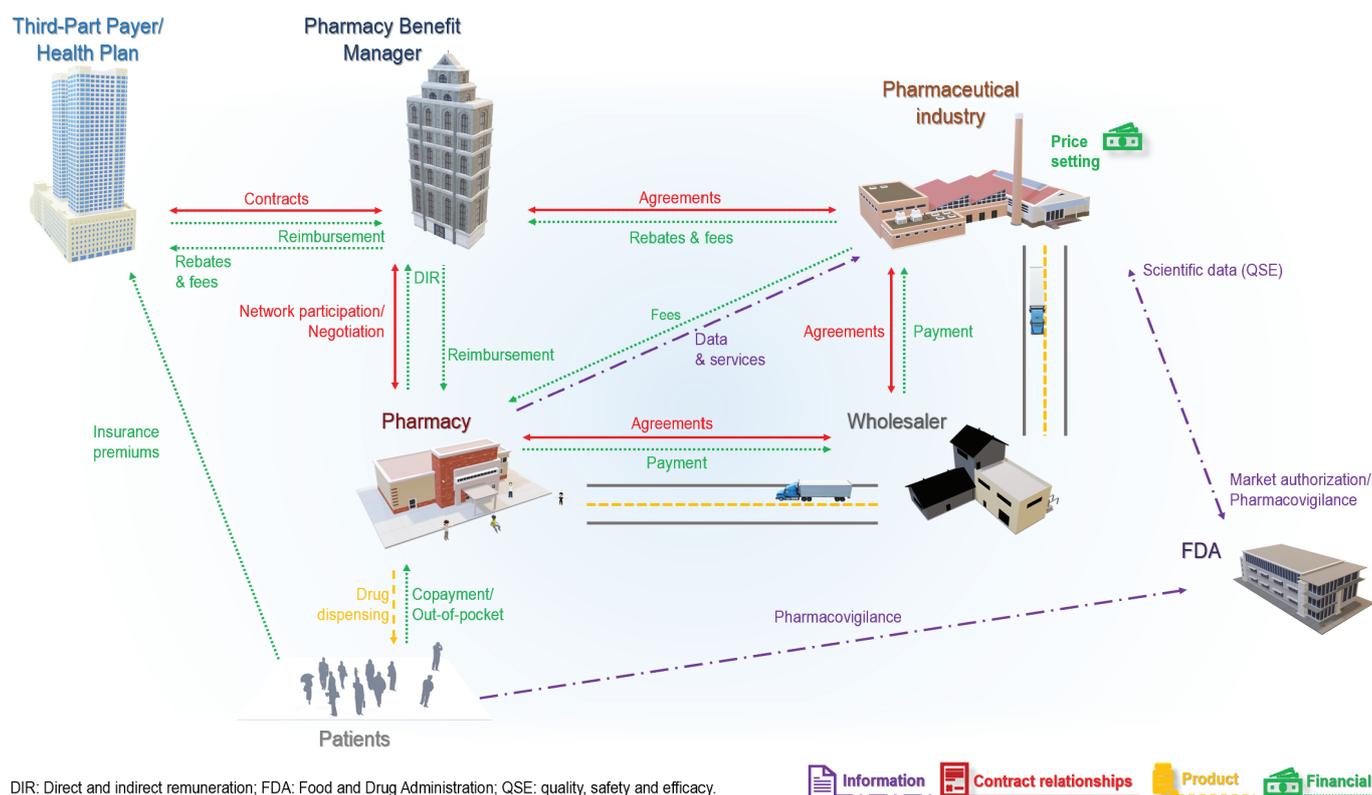
Source: authors' rendering. Based on information from the following source: Mariana P. Socal, Jace B. Garrett, William B. Tayler, Ge Bai, Gerard F. Anderson; Naming Convention, Interchangeability, and Patient Interest in Biosimilars. Diabetes Spectr 1 August 2020; 33 (3): 273–279. <https://doi.org/10.2337/ds19-0065>

## Pharmaceutical Pricing

The US has a market-based pharmaceutical pricing model. Drug prices are not regulated by the US government. Drug manufacturers set the price for the drugs they produce at the level they deem appropriate.<sup>33</sup> The drug price set by the manufacturer is called the *list price*. There are two main price metrics that capture the list

price: the Wholesale Acquisition Cost (WAC), which represents the list price charged by the manufacturer to wholesalers, and the Average Wholesale Price (AWP), which represents the price offered at the wholesale level. Importantly, list prices do not include any discounts or rebates that are negotiated in the supply chain (Figure 2).<sup>34,35</sup>

**Figure 2.** Overview of the pharmaceutical market in the United States.



DIR: Direct and indirect remuneration; FDA: Food and Drug Administration; QSE: quality, safety and efficacy.

Source: authors' rendering. Based on information from the following sources: Drug Channels, "The 2022 Economic Report on U.S. Pharmacies and Pharmacy Benefit Managers," 2022.<sup>35</sup> and Johns Hopkins, Pharmaceuticals: innovation, access and affordability. 2019.<sup>33</sup>

In the US pricing model, the *market* – represented by health care payors – is in charge of negotiating discounts and rebates off the list prices established by the drug manufacturers in order to lower drug costs. Discounts represent reductions in the price paid to acquire the drug through the supply chain. Rebates represent payments that are made by the drug manufacturer to pharmacy benefit managers (PBMs) acting on behalf of health insurers.<sup>34</sup> Rebates are generally negotiated based on drug price and sales volume; therefore, rebate amounts can fluctuate and may take several months to be adjudicated. The final negotiated price for a drug, after rebates and discounts, is called the *net price* and is confidential to the drug manufacturer and the payors. Therefore, although some negotiated prices may be public (such as the prices published by the Veterans Affairs National Acquisition Center-NAC), the final net prices for drugs, after accounting for discounts and rebates, are not publicly known.<sup>34</sup>

The difference between list and net drug prices in the US has been progressively growing in recent years and is especially large for brand-drugs. Analyses by the IQVIA Institute and the US Government Accountability Office (GAO) have estimated that rebates and discounts reduced list prices by 28% in 2018 and up to 36% in 2019,

respectively, and doubled in size in less than a decade.<sup>36,37</sup> Such analyses are aggregated, and price concessions for specific drugs can be higher. In 2021, the difference between sales at list prices and actual net price revenues for branded drugs in the US was estimated at USD \$204 billion.<sup>38</sup>

In order to control prices, the market-based pharmaceutical pricing model requires the presence of competition – usually in the form of generics and biosimilars – in order to exert pricing pressure on brand-name products and reduce spending. The entry of generic drugs in the US market has resulted in price reductions of 80% or more in the last decade, and generics have been estimated to have saved the U.S. healthcare system USD \$1.334 trillion since 2017.<sup>39,40</sup> Currently, generic drugs correspond to about 90% of prescriptions in the US, but represent less than 20% of spending.<sup>40</sup> Generics tend to offer greater discounts over branded drug prices when more generic manufacturers are able to participate in the same market. The average price reduction provided by generics is estimated at about 50% of the branded price when 2 generic manufacturers are competing in the market; with 5 competitors, it is estimated to be about 70%; and with 15 or more competitors, it is estimated to be up to 90%.<sup>41</sup>

In the market-based model, the ability to lower prices of drugs that do not have competition is very limited. Drug manufacturers, therefore, may employ several strategies such as pay for delay agreements, evergreening, product-hopping, and others, in order to keep their market monopolies, prevent competition, and maintain high drug prices.<sup>42</sup> Branded products without competition represent most of the US prescription drugs spending, although they represent a minority of prescriptions.<sup>39</sup> Branded specialty drugs (a term that identifies high-cost products) account for 53% of the US drug spending, having doubled in spending since 2010.<sup>43</sup> Biologicals daily doses cost averagely 22 times more than synthetic molecules and represent 93% of global spending since 2014. In 2017, biologics represented 37% of drug spending, although only accounted for about 2% of US prescriptions.<sup>42</sup>

The lack of a national drug pricing regulation in the US can also result in higher prices over time, as in the same period, in countries with regulated prices, a price decrease is observed with the use of cost-containment mechanisms, such as the expiration of patents, entry of new drugs on the market, scientific data or periodic price review.<sup>11</sup> For branded drugs, each additional year in the US market was associated with, on average, 33% higher prices as compared to the United Kingdom and 25% higher prices as compared to Ontario, Canada. Also, since there are no mechanisms to control generic prices, in markets where there are few competitors, generic prices may also increase, and drastically raised prices due to reduced competition have occurred.<sup>33,41</sup>

A few federal programs determine prices paid to manufacturers and wholesalers (in some cases) for prescription drugs: the Federal Supply Schedule (FSS) program, the federal ceiling price (FCP) program, the Department of Veterans Affairs' (VA) pharmaceutical prime vendor program, the Department of Defense's (DoD) TRICARE pharmaceutical program, the Medicaid rebate program, and the Public Health Service's 340B drug pricing program.<sup>44</sup> Average prices vary across programs and according to buyers, since each calculate prices differently.<sup>45</sup> Since the Veterans Health Care Act of 1992, brand-name drugs to be purchased directly by Federal Agencies and Medicaid have prices listed.<sup>46</sup> The FCP is the maximum price calculated annually for brand-name drugs to be purchased by the Big Four (the four largest federal purchasers of pharmaceuticals: VA, DoD, the Public Health Service, and the Coast Guard). Big Four prices are lower than FSS price and the FCP cap.<sup>44</sup> The price list for the NAC programs is updated twice a month and publicly available.<sup>47</sup>

## Pharmaceutical coverage

In the US, prescription drugs are part of the package of services covered by most private and public health insurance plans. With the exception of drugs sold without the need for a medical prescription (*over-the-counter* products), patients may use their insurance plan to help offset the expenses of any prescription drug, as long as the drug is covered by their plan. Prescription drug coverage is understood as the benefit that helps patients access drugs for outpatient use, or drugs that can be purchased at a pharmacy. Drugs used in the hospital setting, such as chemotherapy infusions or drugs used during a hospital stay, are typically covered as part of the insurer's medical coverage policies and are beyond the scope of this article.<sup>48</sup>

According to the U.S. Census Bureau, 8.6% of Americans (28.0 million) did not have health insurance in 2020.<sup>49</sup> Most Americans (66.5%)

have private health insurance coverage, with 54.4% of the population having employment-based insurance. The remaining 34.8% of Americans are covered from public programs (mainly Medicare and Medicaid), although it is important to point out that an impact in the estimates is expected due to the Coronavirus Covid-19 pandemic.<sup>49</sup>

While Medicare, the federal program that offers health coverage to senior citizens (65 or older), provides universal health coverage for elderly Americans, approximately 28.9 million non-elderly people in 2019 were uninsured in the US. However, the number was much higher before the publication of The Patient Protection and Affordable Care Act, referred to as the Affordable Care Act or "ACA".<sup>50</sup> In 2010, 46.5 million non-elderly Americans were uninsured, which represents a consistent drop since the program was implemented in 2010.<sup>51</sup> The ACA is an important policy that aims to make health insurance more affordable and cover a higher portion of US population. The ACA provides consumers with subsidies ("premium tax credits") that lower costs for households with incomes between 100% and 400% of the federal poverty level (FPL), expands the Medicaid program to cover all adults with income below 138% of the FPL and supports innovative medical care delivery methods designed to lower the costs of health care generally.<sup>51</sup>

A study showed that in 2016, patients participating in employer health benefit programs paid out-of-pocket 53% more for the top 5 patent-protected specialties and 9 traditional brand-name drugs when compared to 2010 (adjusted by inflation), while median insurance payments after rebates and discounts increased by 64% and drug wholesale list prices increased by 129% over the same period.<sup>52</sup>

Medicare provides prescription drug coverage through Part D standalone prescription drug plans or through Medicare Advantage prescription drug plans. Patients may choose whether or not to enroll in a prescription drug plan. Those who choose to not enroll must pay 100% out-of-pocket for prescription drugs. Medicare patients who choose to enroll may choose between a variety of prescription drug plans that operate similarly to a private health insurance plan, only for prescription drugs. However, the amount of patients' out-of-pocket payments may vary greatly within the program because each plan independently negotiates drug prices with manufacturers and pharmacies. The federal government cannot negotiate on behalf of all patients.<sup>53</sup>

Medicaid, the state program that provides health coverage to low-income citizens, has the lowest drug prices in the US health care system. The Medicaid Drug Rebate Program is a federal statute that ensures Medicaid coverage for most of the manufacturers' drugs that participate in the program. In exchange, manufacturers are required to provide Medicaid with steep rebates on those drugs.<sup>54</sup>

Public and private health insurers typically contract with a pharmacy benefit manager (PBM) to design the insurer's drug formulary (the list of drugs covered by the plan) and to negotiate prices with drug manufacturers on behalf of the insurer. PBMs are an entity unique to the US health care system. Currently, three PBMs concentrate more than 80% of the US prescription drug market.<sup>55</sup> PBMs intermediate transactions not only on behalf of private health insurers but also on behalf of public plans such as Medicare prescription drug plans, and Medicaid managed care programs. The drug formulary contains a list of the covered drugs as well as their cost-sharing requirements (what portion of the drug's cost the patient will be responsible for) and any utilization restrictions – for example, if the drug requires a prior authorization, or whether the patient must have taken a first line of treatment before being eligible to access the requested drug.<sup>56</sup>



PBMs use drug coverage—the placement of a drug in the formulary – to negotiate discounts and rebates with drug manufacturers. Manufacturers offer greater discounts and rebates in order to get their drug placed on a lower cost-sharing tier of the formulary or to be made available with fewer utilization restrictions.<sup>56</sup> A favorable formulary placement helps the drug manufacturer achieve a greater volume of sales and obtain a larger market share for their drugs. PBMs usually pass to health insurers most, but not all, price concessions they receive from drug manufacturers. PBMs may keep a portion of the rebates and discounts which they negotiate on behalf of insurers for their own profit.<sup>57</sup>

The strong reliance on PBMs as intermediaries between drug manufacturers and US payors has not been beneficial to reduce drug prices. The revenue structure that allows PBMs to make a profit off of the rebates and discounts that they negotiate on behalf of plan sponsors incentivizes PBMs to place high-cost drugs more favorably on health insurers' drug formularies as compared to lower cost therapeutic alternatives.<sup>57</sup> Estimates have shown that, in the Medicare program for example, 70% of prescription drug plans had at least one branded product placed more favorably on the formulary than the corresponding generic, and 100% of the plans excluded the generic and covered only the branded drug for at least one drug for which generics were available.<sup>56</sup> Generic substitution had a direct impact on the reduction of average net unit prices of prescription drugs between 2009 and 2018 in Medicare Part D (from USD \$57 to USD \$50) and Medicaid (from USD \$63 to USD \$48).<sup>58</sup>

Correcting the misaligned incentives could generate significant savings. The Medicare program, for example, could save about USD \$3 billion per year only by expanding the use of generics instead of branded products.<sup>59</sup> Generic substitution, however, is voluntary, and laws differ from state to state.<sup>41</sup> A study analyzed data from 2012–2017 across 26 therapeutic classes in order to identify determinants of generic substitution and showed the substitution rate varied from 64 to 100%, where thyroid hormones had the lowest rate. The worst rates were from prescriptions filled at retail pharmacies, with little impact from State substitution laws and patient consent laws, further suggesting a role of financial incentives in determining product choice and drug utilization.<sup>39</sup>

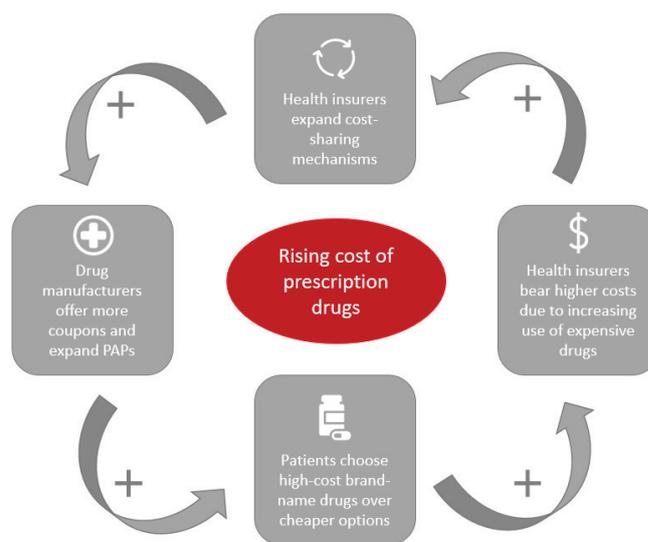
The US has few other cost-containment mechanisms aside from market competition, including demand-side levers to control costs by insurers such as tiered pricing and increased patient cost-sharing, and supply-side measures such as selective provider contracting and risk-sharing payments.<sup>20,60</sup>

### Patients perspective

In the past two decades, an important improvement in access to prescription drugs is observed, mainly due to the expansion of private health insurance coverage in the US.<sup>61</sup> Nevertheless, a rising in the costs of prescription drugs has also been observed over the same period (Figure 3).<sup>53,62,63</sup>

**Figure 3.** Patient perspective and growth cycle of patient assistance programs (PAPs) and offering of coupons by drug manufacturers.

Although an improvement in access to medicines has been noticed in the last decades since the expansion of coverage, insurers only pay for part of the cost of prescription drugs. Patients usually have to pay a portion of this cost due to cost-sharing mechanisms, such as co-payment, coinsurance and deductibles. Deductible is the total amount a patient has to pay in a year in order for the insurer to begin providing coverage. For example, if the deductible for prescription drugs is \$1,000.00, a patient will have to spend this amount in less than a year before having prescription drugs covered by their health plan. Co-payment is a fixed amount patients have to pay each time they use a specific service. Thus, whenever a patient fills a prescription, they have to pay a fixed fee. Coinsurance is a percentage of the total cost of a service that patients have to pay each time they use it. This means the amount that patients have to pay will vary according to the total cost of their prescription.<sup>53</sup> The amount that patients are required to pay out-of-pocket may vary greatly depending on the drug type. For high-cost drugs, patients usually have to pay higher co-payment or coinsurance, while for low-cost generics, the amount of out-of-pocket payment is usually low. Among other factors, lower cost-sharing requirements for generics may help explain the rise in generic drugs use in the US. However, patients with cancer, hepatitis C, Chron's disease and other rare pathologies often need high-cost drugs and are faced with large amounts of out-of-pocket payments. This problem also affects patients with chronic conditions that need long-term treatment with multiple medications. To help these patients, drug manufacturers offer coupons that eliminate or reduce the out-of-pocket payment for certain brand-name drugs. They also have patient assistance programs (PAPs) that give financial aid or free drugs to eligible patients.<sup>53</sup> PAPs spending rose exponentially in the past two decades. Studies show that PAPs spending increased from \$376 million in 2001 to \$6.1 billion in 2014.<sup>62</sup> Even though drug manufacturers claim that these programs aim at improving access to treatments patients would not be able to afford otherwise, public authorities worry that they might have an unintended negative effect.<sup>53</sup> Because out-of-pocket payment is reduced or even eliminated, patients who receive this kind of assistance tend to choose high-cost brand-name drugs even when generic drugs or cheaper options are available. Insurers, on the other hand, must bear the higher drug costs associated with these choices. Therefore, insurers have adopted several cost control measures, which include increasing coinsurance and co-payments, expanding the use of tiered pricing, and even excluding certain drugs from formularies. Drug manufacturers in turn expand PAPs and increase the offering of coupons so that patients may keep using high-cost brand-name drugs. This phenomenon creates a positive feedback loop that contributes to the rising cost of prescription drugs in the US. Another factor that contributes to this problem is that the US is one of only two countries in the world that allow direct to consumer advertising of prescription drugs, which boosts the use of high-cost brand-name drugs.<sup>63</sup> In most countries, regulatory agencies prohibit this type of advertising and only allow drug manufacturers to advertise prescription drugs to physicians.



Source: authors' rendering. Illustration based on information from Congressional Service Research. Prescription Drug Discount Coupons and Patient Assistance Programs (PAPs). 5th version. 2017.<sup>53</sup> Additional information from sources cited in the text.

## Challenges and Perspectives

The multiple factors resulting in cost increases allied to the non-adherence to prescription drugs have detrimental impacts on the US health care system, which has stimulated a few attempts on

policies changes to address those problems. Nevertheless, the US high-prices can have impacts on on many different countries, such as Brazil (Figure 4).

**Figure 4.** Challenges and perspectives: current and future.<sup>27,43,58,64-80</sup>

**Challenges & Perspectives for Policy Reform:** With biopharmaceutical industrial innovation growth in the last decades, drug prices have also risen substantially. A report from the Congressional Budget Office (CBO) analyzing the 1980–2018 period showed that brand-name drug average net prices per unit more than doubled in this period, increasing from an average of USD \$149 to USD \$353 (a 236% increase) in Medicare Part D and from USD \$147 to USD \$218 in Medicaid (a 48% increase).<sup>58</sup> Price increases have made several products inaccessible to the population. About a quarter of US adults have reported having rationed or skipped drug doses due to high costs, and some have resorted to crossing international borders to purchase needed treatments.<sup>71,72</sup> Cost-related non-adherence to prescription drugs has detrimental effects not only to patients, but also to the US health care system, as they raise the demand for medical services and increase costs. Rising drug costs may subsequently also have a negative impact in the broader US economy.<sup>27</sup> Prescription drug prices have been at the forefront of public debate and political agendas in recent years. In both 2019 and 2021, the US House of Representatives successfully passed a proposed legislation allowing the Medicare program to negotiate drug prices on behalf of its beneficiaries.<sup>73</sup> The 2021 package also created a mechanism to penalize drug manufacturers who increased their prices higher than the rate of inflation.<sup>73</sup> Unfortunately, such legislative packages have failed to pass the US Senate. The federal administration has also attempted to implement policies to reduce drug spending. In 2018, the Trump administration proposed to use an International Pricing Index to use foreign prices to reduce drug costs in Medicare Part B (the program that pays for drugs administered in a physician's office), without success.<sup>74</sup> Most recently, the Biden administration released a Comprehensive Plan for Addressing High Drug Prices Aiming to increase competition and promote development and availability of new generic drugs.<sup>75</sup> The key element that has prevented broader policy reform in the US pharmaceutical system from taking place is the argument by drug manufacturers that the free market-based US pharmaceutical pricing model is a crucial prerequisite for ongoing drug innovation. Drug manufacturers claim that the ability to charge higher prices for new drugs is essential to incentivize them to continue pursuing drug discoveries and advancing pharmaceutical technologies.<sup>76</sup> However, the prerogative that high prices are justified by high investments in research and development (R&D) does not hold. Empirical evidence demonstrates that high drug prices are most frequently distributed in the form of high remuneration for executives through high salaries, dividends and share buybacks - which artificially inflate company prices on the stock market. From 2006 through 2015, the 18 drug companies in the Standard & Poor's 500 index spent 11% more on buybacks and dividends than in R&D during the period.<sup>77</sup> Yet, effective opposition against drug pricing reform has been achieved by the strong lobbying influence, by both drug manufacturers and the PBM industry, over attempts to lead policy changes that care about Americans health.<sup>64</sup> In the absence of nationwide reform, several states have stepped up and developed pioneer initiatives to control drug spending. Several states have passed laws increasing transparency in PBM contracting and requiring mandatory reporting of drug rebates and net prices.<sup>65</sup> Maryland created a first-in-the-nation Prescription Drug Affordability Board, which is tasked with reviewing prices and establishing upper payment limits for high-cost drugs for state employees, a model that has been replicated by other states like Maine, Colorado and Washington.<sup>66</sup> In a different approach, California has announced an initiative to produce its own label of generic drugs to be made available to Californians at low cost.<sup>67</sup>

**Implications for Brazil:** Evidence shows that when price regulation in Brazil does not occur, prices are often equivalent to those in the US. For the treatment of spinal muscular atrophy, before the Drug Market Regulation Chamber (*Câmara de Regulação do Mercado de Medicamentos - CMED*) pricing evaluation, the drugs nusinersen (brand name Spinraza) and onasemnogene abeparvovec (brand name Zolgensma) were initially procured by litigation at USD \$135 thousand and USD \$2,1 million, respectively – similar to the prices announced in the US. For onasemnogene abeparvovec the price was reduced by 77% in the first instance, but the manufacturer refused to commercialize the product, which was procured at full price for the following 13 months until the final economic regulation. With economic regulation, the maximum authorized price of these two therapies were reduced by 50% and 46%, respectively.<sup>68,71</sup> The rising prices in the US are reflected in healthcare systems around the world that use the external reference pricing (ERP) mechanism as one of the price regulation tools. The World Health Organization (WHO) recommends ERP to be used in combination with other policies to determine drug pricing, suggesting also that reference countries should be selected according to explicitly stated factors, such as GDP.<sup>69</sup> Moreover, ERP has impacts when not combined with other pricing guidelines: the non-regulated prices in the US may be replicated in other countries, imposing risks that tend to be harder to low- and middle-income economies, especially when the only price published as a comparator for a certain drug is that of the US.<sup>70</sup> This increases the vulnerability of other health care systems beyond the US for two reasons. First, high US prices inflate prices in any country performing ERP that uses the US as part of their reference basket. Although only a few countries such as Brazil, Canada and Japan have US prices regularly included in their ERP calculations, US prices often become part of ERP baskets when the US price is the only global price available.<sup>78,79</sup> It can also indirectly impact other countries that use those countries in their ERP. Second, high US prices may also contribute to delayed access to new technologies in other countries if drug manufacturers opt to delay market launch of new drugs in other countries in order to have the US price as the single global comparator, forcing it to be used as a reference in ERP pricing baskets.<sup>79</sup> Following the US, other countries, including Brazil, are now facing a common challenge of keeping pace with rapid innovations in the pharmaceutical market, resulting in novel treatments at dramatically increased costs.<sup>80</sup> As it strives to promote faster access to new medicines, Brazil has often been the second country after the US to have new drugs approved into its market. When the US is the only country with published prices and its inflated list prices are the only available comparator, a ripple effect can be detrimental to the second country to evaluate drug prices, as this country will use the US as a comparator, and therefore will tend to have the highest or second highest price. In order to ensure early access at fair(er) prices, it is important to have additional mechanisms in place to incorporate value dimensions into pricing negotiations. Health technology assessments (HTA) such as those performed by CMED, can provide a competitive advantage for pricing negotiations in the Brazilian market that is lacking in the US. Currently, however, Brazil does not have additional pricing mechanisms for new molecules entering the market that provide therapeutic gain as compared to existing alternatives but that do not have published prices among the countries in the ERP basket.<sup>79</sup> The market-based US drug pricing system, which by definition does not incorporate HTA, has been insufficient to lower the price of new technologies, especially those without competition, both in the US and in the global market.<sup>7</sup> In Brazil, lower prices have been achieved by the Ministry of Health negotiating the maximum prices defined by the CMED to even lower levels, without hampering the entry of new drugs onto the market. The pharmaceutical industry is going through a reconfiguration with global impacts: the development of cost-effective and broad-spectrum medicines is giving space to personalized medicines that increasingly serve specific populations, with less clinical evidence and ultra-high prices. As a result, spending on conventional drugs is decreasing while spending on orphan and specialty drugs is increasing.<sup>43</sup> Since pharmaceutical trends generally arrive first in the US, this effect is expected to impact the Brazilian healthcare system and population in the near future.

Source: authors' rendering based on information from sources cited in the text.

## Conclusions and future prospects

The US health care system is fragmented and has a distinctively low level of government involvement. Because the US does not regulate drug prices, relying on a market-based pricing system instead, the US health care system faces even bigger sustainability challenges than countries that have drug pricing regulation mechanisms in place. The growing budgetary pressures from higher drug prices and greater health care needs, together with the increasing complexity and ever-growing prices of new therapies threaten the efficiency of the US health care system and access to medicines. Although some drug pricing reforms have been proposed to mitigate high prices in the US, no nationwide initiatives have been successful thus far, and there is continued political debate around policy and regulatory reform. The US high-priced drugs are not only detrimental to Americans – restricting affordability and access to pharmaceuticals, and leaving US patients at greater risk of adverse clinical outcomes – but may also be detrimental to other economies around the world. A change in US drug prices would have ripple effects on other countries and healthcare systems like Brazil, which has often been the second country after the US to have new drugs approved into its market. The US experience underscores the need for global drug pricing mechanisms that support early access to new technologies at fairer prices.

### Collaborators

MPS: conceptualization, writing original draft, writing – review and editing; JAO: conceptualization, writing original draft, writing – review and editing; FG: conceptualization, writing original draft, writing – review and editing; DPK: conceptualization, writing original draft, 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 of interests statement

The authors have no conflict of interests to declare in relation to this manuscript.

### Disclaimer

The views expressed in this article are from its authors, and do not necessarily reflect those of the Johns Hopkins Bloomberg School of Public Health, the International Working Group for Health Systems Strengthening (IWGHSS), the Instituto do Câncer do Estado de São Paulo (ICESP), or the Executive Secretariat of the Drug Market Regulation Chamber (SCMED).

### Series' Guest Editors

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