INTRODUCTION Rethinking Pharmaceutical Policies in Latin America and the Caribbean: An Overview

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Abstract: The demographic and epidemiological transitions are driving pharmaceutical expenditures up in Latin American and the Caribbean, with much of the cost falling on households. The domestic development and manufacturing of biosimilars could make medicines more affordable.

1. Introduction

Medicines account for a growing share of healthcare expenditures in Latin America and the Caribbean. This trend is partly driven by the aging of the population and the shift to non-communicable diseases. Chronic conditions such as diabetes and dementia have become much more prevalent, while cardiovascular ailments and cancers account for an ever-growing number of hospitalizations and deaths. These transformations in the burden of disease result in a greater reliance on pharmaceutical products for treatment.

The pharmaceutical products themselves are also undergoing substantial changes. While many small-molecule drugs are available as generics, and are hence affordable, some of the most innovative medicines are patent-protected biologics, and they can be very expensive. The drugs used to treat cancers and immune diseases most often belong in the latter group, which puts enormous pressure on healthcare budgets.

Moreover, while healthcare coverage is nominally universal across most of Latin America and the Caribbean, medicines are not always available or reimbursed as intended. Many households end up buying them directly from pharmacies, which results in significant out-of-pocket expenditures, especially in the event of catastrophic health shocks.

Given this combination of health transitions, therapeutic innovations and institutional weaknesses, pharmaceutical policies have a critically important role to play in Latin America and the Caribbean. With a sound design, they can facilitate access to medicines at affordable prices, improving the health condition of the population and helping contain healthcare costs.

Sound pharmaceutical policies can also boost the scientific capacity of countries in the region. Unlike small molecules, which can be perfectly cloned, biological products are shaped by their research and manufacturing processes, so that two of them can be therapeutically equivalent without being identical. This greater diversity opens the door to the local production of cheaper biosimilars without infringing on the property rights of the originator.

Designing sound pharmaceutical policies is not straightforward, however. The market for medicines is complex, as there are significant information asymmetries between households, physicians, pharmacies, manufacturers and regulators. Assessing the effectiveness and equivalence of drugs is demanding as well, implying that important decisions end up being

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made in a context of significant uncertainty. And the local production and international trade of medicines involve arcane legal issues related to intellectual property rights, investment protections, government subsidies and public procurement, among others.

And yet, despite their importance, in much of Latin America and the Caribbean pharmaceutical policies have not received the attention they deserve. Countries in the region generally have a policy for generics, and some have tried to bolster their local scientific, technological and productive capacity. However, ministries of health are understandably focused on strengthening healthcare systems, extending their coverage and improving their quality. Ministries of finance care about the budget implications, trying to contain costs without necessarily grasping how markets for pharmaceuticals work. And important policy decisions are at times made as byproducts of international trade and investment agreements, or of court rulings on access to specific medicines and their reimbursement.

Critical to designing better policies is to gain a deeper understanding of the pharmaceutical sector in Latin America and the Caribbean, including their key players, the different types of products involved, and how government policies can shape the outcomes. Such is the goal of the ten papers included in this *JLME* symposium issue and summarized in this overview. The selection of topics the ten papers cover, and the analytical thread that connects them, are informed by a recent, comprehensive stock-taking effort by Vargas, Rama and Singh.[1]

The ten papers can be regrouped into three main blocks. The first one concerns the workings of the pharmaceutical market, starting with a quantification of out-of-pocket (OOP) spending on medicines by households in the region. This is followed by an inventory of the innovative biological products available, identifying which ones are produced locally. The analysis is complemented by an assessment of perceptions on the effectiveness and safety of the latter group of drugs by physicians, pharmacists and the public at large.

The second set of articles is about local scientific, technological and productive capacity in Latin America and the Caribbean, and how it is shaped by government policies. Country-level capacity is benchmarked using indicators that range from resources for research and development (R&D) to publications and patents to innovative products on the market or in the pipeline. This is followed by detailed studies on the policy approaches embraced by each of the three countries with the strongest capacity in the region — namely, Argentina, Brazil and Cuba.

The final block is about the forces that could shape pharmaceutical policies in the coming years. Changes could come from strategic thinking inspired by Asian success stories, illustrated by the diverse approaches chosen by India, Korea and Singapore. Changes could also come from adjustments to current policies, with the European experience in regulating the prices of pharmaceutical products as an important reference. But changes may also happen in unplanned ways, as revealed by the growing judicialization of access to medicines in the region.

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2. The Market for Pharmaceuticals

Health expenditures by households have remained high in Latin America and the Caribbean despite the coverage of healthcare systems being universal across most of the region, and governments generally devoting an ever-growing volume of resources to supporting them. This paradox is partly explained by the demographic and epidemiological transitions, but it also owes to the difficulties households in the region face in accessing affordable medicines.

The article by Cortez, Medici and Singh[2] for this *JLME* symposium issue unpacks the mechanisms at play using evidence from three sources. Cross-country data by the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD) allows an international benchmarking of the region. A systematic literature review of previous studies sheds light on the key correlates of OOP spending on medicines in selected countries.

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And a statistical analysis of household surveys conducted in Costa Rica, Chile and Peru in 2010 and 2020 provides evidence on the distribution of spending across population groups.

The analysis shows that, on average households in Latin America and the Caribbean devote 34 percent of their medical spending to medicines — much higher than the 21 percent OECD average. The share reaches a striking 63 percent in Venezuela and 54 percent in Guatemala, while it stands below 20 percent in Uruguay, Jamaica, Colombia and Argentina — in decreasing order — and is as low as 10 percent in Cuba.

Across the region, most OOP expenditures in medicines are made by the richest segments of the population. But in relative terms the poorest segments devote a larger proportion of their income to drugs. The inequality is particularly acute among households that incur large OOP spending on medicines due to catastrophic health shocks, with their proportion being on average 65 times higher among the poorest income decile than among the richest.

An exception to this highly regressive pattern is provided by Costa Rica, where the share of OOP spending on drugs in total household expenditures is roughly the same for all income quintiles. This remarkable degree of equality can be attributed to the large number of consultations and hospitalizations that are carried out through the public healthcare system.

Elsewhere in the region, large segments of the population seem to deliberately opt out from public healthcare systems. In Argentina, for example, 62.4 percent of households in the poorest quintile rely on it, but the proportion falls by half among the second quintile and to less than 5 percent in the top quintile. In Peru, similarly, 47.6 percent of the population facing a health problem did not seek care, with only 20 percent choosing to visit a public facility.

This secessionist behavior is most likely in response to the significant weaknesses of public healthcare systems in the region, and these in turn have implications for OOP spending on drugs. Presumably, those who do not seek care end up relying on medicines purchased in pharmacies, which they must pay at full price. But even those who visit public healthcare facilities may fail to gain access to affordable medicines. In Brazil, for example, the analysis shows that an encouraging 81.8 percent of those given drug prescriptions had full access to their medications. However, another 10.0 percent received only some of them, and the remaining 8.2 percent got none.

Aggregate spending on medicines provides a useful metric to assess the poverty and equity implications of different pharmaceutical policies. However, the aggregate figure results from a diverse and evolving mix of products and prices, suggesting that much of the action takes place underneath the surface. At the global level, the range of medicines available has expanded considerably in recent years, as small chemical molecules increasingly give way to biological products made from living organisms. But the extent to which these trends are also happening in Latin America and the Caribbean is only partially known.

The article by Ortiz-Prado et al.[3] for this symposium *JLME* issue aims to provide a comprehensive description of the market for biological products in the region. The analysis puts emphasis on a subset of them, called biosimilars. These are medicines that display no clinically significant differences with innovative products approved by the regulator but were developed and produced through different processes, to avoid infringing intellectual property rights. One of the biggest advantages of biosimilars is their lower price, which can lead to substantial savings for healthcare systems and more manageable OOP spending on medicines by households.

The analysis is based on the IQVIA database, which compiles information on the sale of prescription drugs from a worldwide sample of pharmacies and hospitals. In Latin America and the Caribbean, the data can be deemed sufficiently representative in the cases of Argentina, Brazil, Chile, Colombia, the Dominican Republic, Ecuador, Uruguay and Venezuela. Patterns in these countries are studied based on the number of units sold and their individual prices from 2017 to the second quarter of 2022. A comprehensive literature review is conducted to gather information on products and prices in other parts of the region.

In the eight countries with reasonably representative IQVIA data, USD 3.2 billion are spent annually on more than 149 million units of biological products and biosimilars. With 80 products approved, Brazil is by far the region's largest market, followed by Mexico (71), Ecuador (42), Argentina (56) and Chile (53).

The most used biological products and biosimilars are immunosuppressants, antirheumatic agents and tumor inhibitors. The most expensive products, on the other hand, tend to be monoclonal antibodies. There is considerable price variability across countries, however. For example, Bevacizumab costs USD 1,900 per unit in the Dominican Republic and Rituximab USD 1,023, but the same medicines can be purchased for USD 340 in Chile and for USD 157 in Mexico, respectively. Overall, Uruguay, Chile and Colombia — in that order — exhibit more stable and lower average prices. And across Latin America and the Caribbean, bio-

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similars are about a third cheaper than the innovator drugs they mimic.

The analysis also reveals that at least 156 manufacturers of biological and biosimilar products operate in the region. Most of them — including Roche, Novartis, Sanofi and Johnson & Johnson — are multinational companies and their affiliates. However, in a few countries — especially Cuba, Brazil, Mexico and Argentina — domestic companies have made significant strides in the development and manufacturing of these products.

Most countries in Latin America and the Caribbean have adopted policies to encourage the use of generic drugs and biosimilar products, as these can provide cost-effective alternatives to originator products and reduce spending on drugs. Policies include strengthening the national medicine agencies tasked with the approval of generics and biosimilars. They also include the adoption of health technology assessments, to evaluate medical products and procedures and increase public confidence in healthcare systems. And several countries in the region conduct educational and promotional campaigns to boost the utilization of generics and biosimilars by key stakeholders — physicians, pharmacists, patients and the public at large.

In advanced economies, it has been argued that limited knowledge and negative perceptions among stakeholders undermine these efforts and result in an insufficient uptake of generics and biosimilars. However, the available literature reviews and meta-analyses only cover Latin America and the Caribbean very partially, and rarely include studies published in Spanish or Portuguese.

The paper by Aguilera, Peña and Morales[4] for this *JLME* symposium issue tries to fill this gap by conducting a scoping review specifically focused on the region. It does so by searching all the relevant literature indexed in the PubMed and Epistemonikos databases, from inception to October 2022, and then developing a narrative synthesis along three dimensions: knowledge, perceptions and utilization.

After screening 668 studies and removing duplicates, 22 academic articles were deemed relevant and retained for the analysis. Almost all these articles concern the six countries in the region whose frameworks for drug regulation are considered adequate by the WHO. And 17 of them include stakeholders from Brazil, a country that is a policy leader in the region in relation to generics and biosimilars.

The analysis shows that key stakeholders have a relatively good knowledge of generics, and that pharmacists — especially in Brazil — have a positive perception of their quality, safety and efficacy. However, the assessment is more negative among physicians and the general population, and even more so among patients. These unfavorable views are likely to reduce the willingness to prescribe and purchase generics, relative to the more expensive originator products.

Knowledge is more limited, and perceptions more negative, in the case of biosimilars. Patients, in particular, voice strong concerns about their equivalence with originator products, hence about their efficacy. Physicians, in turn, express reluctance to use biosimilars and have a clear preference to rely on the originator products.

However, these findings need to be interpreted with caution. All the reviewed studies on generics were self-funded or tapped public resources. Most studies on biosimilars, on the other hand, were funded by the pharmaceutical industry, including by transnational companies in the biologics market. And indeed, activism by the laboratories behind innovator products could well be one of the reasons behind negative perceptions and limited uptake of biosimilars.

3. Pharmaceutical Policies and Local Capacity

The capacity to develop and manufacture pharmaceuticals domestically is important to improve access to safe and effective medicines at affordable prices, hence containing healthcare costs.

But a higher scientific, technological and productive capacity can translate into innovation at the local level. Because innovative drugs can be patented, they face limited competition during extended periods of time, leading to significant rents. Therefore, the gains for a country are higher if these drugs are developed and manufactured domestically rather than imported. A higher local capacity also strengthens the ability to design and adopt sound health policies, as it became apparent during the COVID-19 pandemic.

Building local capacity and transforming it into innovative products are not straightforward, however. Large government spending on R&D presumably helps innovation, but other aspects not directly controlled by the authorities — from researcher networks to entrepreneurial culture — matter as well. It is thus important to look beyond R&D spending and consider a broader array of indicators, capturing the availability of the necessary skills as well as the effectiveness of research and development and manufacturing processes to make discoveries, create new products, and take them to markets.

The paper by Vargas and Darrow[5] for this *JLME* symposium issue compares scientific capacity and

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pharmaceutical innovation across a sizeable number of countries in Latin America and the Caribbean. It does so by compiling indicators related to inputs (R&D spending), outputs (researchers, publications, and patents), and outcomes (products on the market or in the pipeline). Information comes from a new database of innovative pharmaceutical products and from publicly available sources such as Nature Index, UNESCO, and WIPO.

While R&D spending by the region remained relatively stagnant over the past decade, the number of researchers in life sciences and the number of pharmaceutical patents doubled between 2008 and 2018, and the number of publications on chemistry and natural sciences increased by 60 percent between 2015 and 2021. Remarkably, the top 20 universities in life sciences in Latin America and the Caribbean account for more than half of these publications, their share of patent filings is twice the global average, and most pharmaceutical products in the pipeline involve partnerships with them.

As of April 2023, the region had totally or partially developed 309 new therapeutic products, of which 20 were already on the market. Vaccines and other biologics accounted for more than three quarters of them, the rest being naturally derived products and repurposed small molecules.

The composition of this portfolio is indicative of a high capacity in life sciences and chemistry. Indeed, about a third of vaccines use the latest technolgies such as recombinant vectors, DNA, protein-based virus-like particles and RNA. Similarly, slightly more than half of the 130 biologics were originator products in the pipeline and on the market rather than biosimilars. By the cutoff period for the study, Cuba, Costa Rica, Argentina and Chile had managed to bring new biologics products to the market. But significant capacity exists in Mexico, Brazil and Uruguay as well.

Natural products — the mainstay of pharmacopeia for centuries — are relevant for Latin America and the Caribbean, a region of outstanding biodiversity, which also means chemical diversity. Natural products are the source of about half of modern drugs, and they play an important role in the treatment of cancers, the second leading cause of mortality in the region and a major burden on its healthcare budgets. However, absence of consensus between the Convention on Biolgocial Diversity and the TRIPS Agreement, which governs patening, remain an important obstacle to taking natural products to the market. So far, Brazil is the only country in Latin America and the Caribbean that has succeeded in doing so. Ongoing work in Brazil, Costa Rica, Colombia, Ecuador, Panama and Peru shows promise as well.

With more than USD 1 billion in sales — close to one-third of the broader pharmaceutical market — Argentina's biological sector has rapidly expanded over the last two decades to the point of becoming a key segment of the domestic industry. The country has 71 companies with biotechnological capabilities for research, formulation and, in several cases, production. Only 11 of them are subsidiaries of large foreign pharmaceutical companies. Seen from this perspective, Argentina is a success story and other countries in Latin America and the Caribbean may be keen to understand the reasons for this success.

The paper by Lavarello, Gutman and Pita[6] for this symposium *JLME* issue reviews the strategies and learning trajectories that made this remarkable development of local scientific, technological and productive capacity possible. Building on previous research by the authors, the paper analyzes how a conducive approach to intellectual property at the national level enabled the ascent of "creative imitators". In a context of rapid technological advances at the global level, a window was open for local firms to advance in the development and manufacture of biological drugs that are similar to the originals, but substantially cheaper.

In Argentina's case, this opportunity arose as there was no link between patents and health approval, allowing an approach to intellectual property that enabled local imitative strategies. In parallel, policy instruments such as non-reimbursable contributions and tax credits supported the development of biotechnological platforms for the national production of recombinant proteins. And mechanisms such as government procurement favoring local producers and advance market commitments for vaccines were also introduced along the way.

However, a loose and evolving regulatory framework at the international level also generated high uncertainty, leading to frequent firm entry and exit. By 2020, 34 of the 71 companies with biotechnological capabilities in Argentina were spin-offs from pharmaceutical laboratories, universities, or technological institutes, each exploiting some product niche with low regulatory thresholds.

Despite this fluidity, the analysis reveals three main phases in the development of biosimilars in Argentina. In the early stages, low international regulatory constraints and knowledge thresholds allow imitative local firms to compete in international markets for biosimilars. In the second phase, once the diffusion phase is reached and international markets became more contested, local firms rely on supportive govern-

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ment procurement to build development and production capacities. Finally, as the patents for more complex drugs gradually expire, and knowledge thresholds increase, local firms start developing their own clones, or acquiring clones from international companies — often with support from the national science and technology infrastructure.

A pending question is whether this experience of transient autonomy could gradually come to an end. There is growing pressure from large foreign pharmaceutical companies for Argentina to loosen patenting and approval mechanisms, reorient R&D support to clinical trials and remove R&D requirements from government procurement. These changes may limit opportunities for local firms and eventually weaken the country's scientific capacity.

Brazil's pharmaceutical market is the largest in Latin America and the Caribbean and the 7th largest globally. By 2017, it comprised 214 companies selling more than 6,500 products and earning USD 13.9 billion in revenue. Between 2003 and 2020 the production volume of the sector increased by 37 percent and its employment by 54 percent, while the share of its output sold abroad grew from 4 to 12 percent. Interestingly, during this period the market share of national companies rose substantially, whereas foreign companies drastically reduced their local production and focused on commercializing medicines developed abroad.

How Brazil accomplished these remarkable results is of course of interest to other countries in Latin America and the Caribbean. This is not to say that its experience can be considered a "model", as the very large scale of its domestic market is unique in the region. However, there may still be important lessons in terms of government stewardship, especially because Brazil underwent significant policy swings over the last three decades.

The paper by Paranhos, Hasenclever and Perin[7] for this *JLME* symposium issue discusses how the adoption of radically different policy orientations by alternating government administrations modified the structure of the Brazilian pharmaceutical market. The analysis is based on a survey of secondary public data and a review of relevant scientific literature, newspapers and official documents.

A first policy phase, covering the period 1990-2002, was marked by trade liberalization, the signing of the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the adoption of an intellectual property law going beyond TRIPS obligations, the creation of a national health surveillance agency to steer the sector, and the development of a vibrant market for generics with mandatory bioequivalence.

During this period, the participation of foreign pharmaceutical companies in the Brazilian market grew considerably, with imports gradually replacing the local production of medical products. Prestigious research institutions — such as Butantan and Fiocruz — were central to the production of vaccines and the treatment of tropical diseases, but they were largely disconnected from pharmaceutical production.

The second phase covered the period 2003-2015 and was characterized by a return to policies for science, technology and innovation. An executive group coordinating 14 public institutions was established to improve the capacity of local firms to participate in the global market. Partnerships between universities and firms were encouraged, while R&D initiatives were financially supported through resource grants, tax incentives and subsidized loans. Importantly, public procurement was used to purchase selected pharmaceutical products, mostly from national companies.

As a result of these measures, the ability to develop, manufacture and export medicines by local pharmaceutical companies grew substantially. However, the sector remained highly dependent on foreign technologies and imported Active Pharmaceutical Ingredients (APIs).

A third phase, in 2016-2020, entailed a temporary return to the policy choices of the first one. These dramatic swings reflect the different orientations of the political coalitions in power. In a context of acute polarization, further swings in Brazil's pharmaceutical policy cannot be ruled out, with potentially significant implications for local scientific, technological and productive capacity, and for the roles played by domestic and foreign pharmaceutical companies respectively.

Cuba punches above its weight in the development of innovative biological medicines and vaccines. Its pharmaceutical sector comprises 32 companies that employ more than 20,000 workers to manufacture more than 1,000 drugs. Among them is the well-known Interferon alfa-2b, an antineoplastic used to treat a wide range of infections and cancers. With its exports growing from USD 50 million in 2006 to USD 2.8 billion in 2013, the pharmaceutical sector also became an important source of foreign exchange for the island.

Such success may seem unlikely in a socialist country. To its advantage, Cuba benefits from an abundant and highly qualified labor force at low cost, thanks to the massive training of medical personnel and the centrality of public health that characterize its development strategy. But the market imperfections that have made it difficult for other countries in Latin America

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and the Caribbean to build a strong pharmaceutical sector can be expected to be even more severe in an economy run by central planning, where market institutions are inherently weak.

The paper by Pérez Villanueva and Campos Espiñeira[8] for this *JLME* symposium issue aims to explain this paradox. It does so by unpacking three mechanisms that allowed Cuba to overcome the market failures that are typical of every economy but become even more constraining in a socialist context. The main contribution of this paper is not to uncover new information but rather to reinterpret existing information through the lens of rigorous economic thinking.

The first important mechanism was coordination. In Cuba the industry is vertically integrated, from basic science to clinical trials, production and marketing. This "closed cycle" strategy started with the creation of a biological front including several scientific institutions in 1981 but took off with the establishment of the West Havana Scientific Pole in 1992, and especially with the regrouping of all biotechnological companies under the BioCubaFarma conglomerate in 2012.

Second was the strong focus on incentives. The patent law was revised to take advantage of flexibilities allowed by the TRIPS agreement, and finetuned in the 2011-18 period. Under this regime, the Cuban state leads in the licensing and management of patents for the development of its pharmaceutical sector, but each organization can have its own marketing company and researchers' earnings are linked to the income derived from their inventions.

Finally, rent sharing was used to attract foreign partners who could strategically complement the local industry through financial resources, related patents, and marketing channels. By 2022 BioCubaFarma had more than 2,400 patent registrations abroad. Many of them served as the basis for international joint ventures. Agreements were often set up under the legal regimes of advanced economies such as the United Kingdom or Switzerland, to avoid the uncertainties that reliance on Cuban courts would have created.

However, this combination of mechanisms works well only as long as Cuba can export its pharmaceutical products, because domestic demand is insufficient to internalize the fixed costs of the research and development activity. By preventing sales abroad, the tightening of economic sanctions imposed by the United States since 2017 is thus undermining the main sources of income for Cuban biotechnology and putting its unquestionable success on hold.

4. New Directions in Pharmaceutical Policy

Asia's pharmaceutical sector has experienced remarkable growth over the last two decades, with the region now producing close to half of the global specialty generics, biologicals and APIs. Countries in Latin America and the Caribbean may want to understand how this extraordinary transformation took place, especially because it did not happen spontaneously, nor by replicating the path taken by advanced economies.

The paper by Basak[9] for this *JLME* symposium issue describes the policies and trajectories of India, Korea and Singapore, each a success story on its own. Indeed, India has emerged as the pharmacy of the world, supplying affordable generics, vaccines and other drugs to more than 100 countries. Korea has transformed its biotech sector into a global leader in the industry, with a strong focus on biosimilars. And Singapore has attracted eight of the world's top ten pharmaceutical companies to have a manufacturing presence locally.

Interestingly, the income levels of these three countries span even wider than the entire range observed in Latin America and the Caribbean. But the analysis shows that the critical elements of the strategies they embraced were especially well adapted to their circumstances.

India took advantage of its large domestic market and its vast pool of engineers and technologists to first develop an inward-oriented pharmaceutical industry. In 1970 it ended the recognition of Western-style patents, enabling local manufacturers to embark in reverse engineering. Market liberalization, in 1991, allowed them in turn to enter joint ventures and benefit from the opening of the US and other advanced economies to generic drugs. Standard patent protections were reintroduced in 2005, but their evergreening was substantially restricted. And since 2012, government provided generous, non-refundable support for research in pharmaceuticals.

Korea acquired assets from advanced economies to tap into their capacity and networks. A key milestone, in 2002, was a joint venture between a group of Korean investors and a San Francisco-based biotech company to produce vaccines and recombinant therapeutic proteins. After training its staff with the US partner, the new company built one of the world's largest biotechnology facilities locally. In 2006, the government supported the process through an ambitious plan to invest USD 16.6 billion in biotechnology over ten years. And in 2012, the sector fully integrated globally through the signing of the Korea-US free-trade agreement.

Singapore embraced a development strategy based on pro-business regulation, low corporate tax rates,

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and high legal and compliance standards. While the strategy aimed at creating a level playing field across all sectors, biotechnology companies were supported through significant government investments in industrial parks and laboratory space. Importantly, partnerships with the private sector allowed mid-career professionals from all sectors who wanted to upskill and work on the manufacturing of biologicals and vaccines to undergo on-the-job training for up to 21 months with leading pharmaceutical companies globally.

Given their lower income levels and institutional capacity, most countries in Latin America and the Caribbean may find the Singapore approach out of reach. But insights from the experiences of India and Korea could certainly be considered.

The growing availability of highly specialized medicines with an extremely high price tag - such as gene and cell therapies and drugs for rare diseases — challenges healthcare systems everywhere. Even advanced economies are finding it increasingly difficult to cover the cost of these innovative drugs. This cost burden has made the pricing and reimbursement of medicines and vaccines a hot topic for policymakers around the world.

Few countries in Latin America and the Caribbean have well-established pharmaceutical pricing policies. Brazil and Colombia are among the most advanced, but they are still in preliminary stages. Chile, Mexico and Peru, are also discussing how to regulate medicine prices. And the region has a valuable trajectory in the joint procurement of vaccines through the Pan American Health Organization (PAHO). But overall, it is European countries that have the richest experience, and there may be lessons in it for the region.

The paper by Leopold, Poblete and Vogler[10] for this *JLME* symposium issue discusses the three approaches used to set drug prices in 20 large and mid-sized countries in Europe. The analysis is based on a pragmatic review of academic articles in PubMed and Google Scholar, unpublished data by the Pharmaceutical Pricing and Reimbursement Information (PPRI) network and the websites of the relevant national organizations, as of December 2022.

The approach most commonly used by European countries is external referencing. The underlying principle is to consider price information of the same medicines in other countries. Doing so raises important methodological issues, such as selecting the relevant set of comparator countries and deciding how to deal with missing data. However, the most important limitation of this approach is that discounts tend to be negotiated for high-cost medicines, with the rebates remaining confidential. Relying on benchmark prices may thus result in over-spending.

An alternative is to use value-based pricing. What matters in this case is the estimated contribution a medicine makes to a longer and healthier life. This approach is usually supported by health technology assessments, which review multiple aspects of each new medicine, including their clinical effectiveness, safety and implications for patients and society at large. However, conducting such assessments requires considerable capacity and resources and, so far, there is no general agreement on how to translate them into concrete prices.

European countries also have a long-term experience in the use of generics to contain the price of medicines, and the region is the most advanced in the approval of biosimilar products. The prerequisites for this approach to work are ensuring therapeutical equivalence with the originator products and fostering trust in their effectiveness and safety among physicians and pharmacists. However, doing so can be challenging in the case of biological drugs, which also tend to be the most expensive.

These three approaches are not mutually exclusive, and their design varies across countries. But in trying to adapt them to the local context, countries in Latin America and the Caribbean should keep in mind their capacity constraints, and the fact that in the region medicines are often sold to patients in pharmacies, without the direct involvement of the healthcare system.

With innovative pharmaceutical products being increasingly expensive, and with healthcare systems often not covering their full cost, litigation is becoming an increasingly frequent pathway to gain access to medicines. In no other region of the world is this trend stronger than in Latin America and the Caribbean. Thus, in just a decade, the number of health-related lawsuits increased by 130 percent in Brazil, by 119 percent in Colombia and by 144 percent in Costa Rica. In Uruguay, it multiplied by six in a mere three years.

The paper by Iunes and Guerra[11] for this JLME symposium issue analyzes the drivers and consequences of this growing judicialization of access to medicines. Its information sources are media reports, legal proceedings and cost assessments by the administrators of public healthcare systems. While the resulting data is patchy, it yields important insights.

The main reason why judicialization is becoming so prevalent in the region is that access to health is treated as a human right by the constitutions of many countries in Latin America and the Caribbean. Also, with easy access to judicial protection, an activist civil society and often empathetic judges, courts become a natural ave-

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nue to seek redress when healthcare policies and practices are seen as inadequate, unfair, or discriminatory.

Some of the litigation is triggered by denied access to treatments and drugs that patients are supposedly entitled to but are often unavailable. Thus, 70 percent of health-related court cases in the state of Para (Brazil) involve medicines that are part of the country's essential list. And in Colombia, 74 percent of the lawsuits concern goods and services that are included in the country's benefits package but are not provided, with medicines at the top of the list.

However, litigation also concerns expensive medicines — such as innovative biological drugs — that are not part of standard benefit packages but can effectively treat life-threatening conditions and rare diseases. In this case, judicial rulings create increasingly significant pressures on healthcare spending. Thus, in the state of Santa Catarina (Brazil) the cost of complying with court decisions increased from 1 percent of health expenditures in 2004 to 8 percent in 2016. And in Costa Rica, it grew from 2 percent in 2015 to 11 percent in 2021.

Practical measures can be considered to contain this surge in healthcare expenditures. Improvements in the mechanisms through which medicines are distributed and dispensed can reduce the need for judicialization. Another possible response is to create specialized courts and train judges so that they have the relevant expertise. In Brazil, for example, technical support centers were created in each state to assist magistrates in the resolution of health-related demands.

At a deeper level, however, judicialization creates an institutional tension. Forcing the authorities to comply with approved laws and regulations is a traditional role of the judiciary, but deciding which medicines and treatments to provide at which cost is a typical prerogative of the executive. How to balance human rights and technical considerations, or individual and collective priorities, is an issue for each society to address. The growing availability of lifesaving but unaffordable pharmaceuticals will only make the choices harder over time.

5. Emerging Research and Policy Agendas

A steady change in the types of diseases the Latin America and the Caribbean region faces is underway, and it raises serious financial challenges for both public budgets and OOP expenditures by households. A strong emphasis on promoting access to generic drugs, advocated by international organizations and embraced by governments in the region, has kept the burden from cardiovascular diseases relatively contained. But the increasingly effective biological drugs that are needed to treat cancers and immune diseases are most often under patents by major pharmaceutical companies in the US and Europe, and they tend to be very expensive.

The growing tension between treatment opportunities and resource constraints calls for a rethinking of pharmaceutical policies in the region. The ten articles in this *JLME* symposium issue represent a collective contribution to this discussion. Building on a previous encompassing effort to diagnose the pharmaceutical sector by Vargas, Rama and Singh,[12] these ten articles dig deeper into the structure of the market for medicines in the region, the extent of local capacity and the policies used so far to strengthen it, and the new directions in which the sector could be evolving in the coming years.

Also building on that previous effort, the main research and policy agendas emerging from these ten articles can be regrouped into three distinct categories. First, there are measures that would clearly improve matters and seem relatively uncontroversial; these could lead to immediate action. Second, there are areas in which tradeoffs arise, and the available knowledge on the costs and benefits of the various options is partial; in these areas, more analytical work and policy experimentation are the priority. Finally, some issues touch upon international relations and individual rights, so that they transcend the pharmaceutical sector; these are issues calling for a national debate to forge consensus.

Key among the first group of measures is to **increase the availability of biosimilar products**, which cost substantially less than the originator drugs. As the experience of Argentina, Brazil and Cuba shows, first- and second-generation biologics can be produced locally in competitive terms. And thanks to the growing scientific, technological and productive capacity of the region in natural sciences and chemistry, there are several biosimilars in clinical trials and many drugs in the research and development pipeline. However, proactively moving toward a greater reliance on biosimilars requires strengthening the institutional and regulatory environment at the national level, to ensure the bioequivalence and safety of the new products on the market.

Another uncontroversial response is to **tap the region's rich biodiversity**, which translates into chemical diversity and opens the possibility to develop new drugs. Internationally, approximately half of cancer drugs mimic natural molecules or are natural molecules themselves. Regionally, countries with biodiversity hotspots and a stronger scientific, technological and productive capacity are already showing promising potential in this respect, with Brazil, Costa

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Rica and Panama in the lead. From a policy point of view, a key step in this direction is to incorporate the principles of the Biological Diversity Convention into international trade agreements.

The second category of implications involves significant tradeoffs and only partial clarity on the costs and benefits associated with the various options. How to **gain medical practitioner support** falls in this category. The reluctance by physicians and pharmacists in the region to endorse lower-cost treatment alternatives has led to their underutilization. Going forward, it could undermine efforts to increase the reliance on biosimilars. A stronger institutional and regulatory environment at the national level would help increase trust in the new products. But this is an area where targeted interventions — from communication to subsidization — can be tried and rigorously evaluated, and successful experiences scaled up.

There are also uncertainties on how to **control the price of pharmaceuticals**. Public procurement is an effective tool in this respect, as government agencies can obtain significant discounts from companies producing and distributing medicines. But they could further leverage their purchasing power through adjustments to the scale, composition and design of their tenders — with big data analysis being particularly useful in this respect. As for direct price controls, the European experience calls for some caution. External referencing is difficult because negotiated prices abroad are often confidential, and value-based pricing requires considerable capacity and resources. Here the recommendation would be to pilot health technology assessments in the spirit of those conducted in Europe, and to evaluate their effectiveness.

Another potential direction for improvement — one that gets considerable attention in the public discourse on pharmaceuticals in the region — is to **strengthen cross-country collaboration**. A very valuable precedent in this respect is the joint procurement of vaccines through PAHO. Building on its success, there have been calls for coordination of R&D and regulatory processes in a way that encourages mutual learning. This sounds appealing in principle, but countries in Latin America and the Caribbean have signed numerous regional agreements of questionable effectiveness. Rather than aiming for very ambitious goals from the onset, cross-country collaboration could first focus on concrete goals, such as endorsing the approval of specific medicines — especially biosimilars — by other countries in the region.

Finally, some of the potential directions for improvement are intrinsically debatable, either because they affect foreign policy or because they touch upon individual rights. Chief among the first group are policies to **boost local technological and productive capacity**. Advance purchase commitments, government procurement, tax incentives and research grants can be used to this effect. However, international trade agreements often preclude favoring national firms over their foreign competitors. As a result, measures that may be perceived as industrial policy may generate tension in international relations — with smaller countries being more vulnerable to the ensuing pressures. Useful lessons on how to handle these tensions may be learned from the experience of East Asian countries that successfully managed to develop their pharmaceutical industry — and especially from India and Korea.

Last, but not least, countries in the region — especially those with a higher income — need to **address the judicialization of medicine**. Litigation on accessing and reimbursing high-cost medicines is increasing healthcare costs — sometimes substantially — and encroaching on the role of regulators. The training of judges, the creation of specialized jurisdictions and the strengthening of advisory units with the necessary expertise, can lead to more informed court rulings. However, at a deeper level there is a tension between individual and collective rights, one that is bound to increase as more expensive lifesaving medicines come on the market. And this is a tension that only an informed national debate can help address.

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