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Pharmaceutical Services and comprehensiveness 30 years after the advent of Brazil's Unified Health System

Jorge Antonio Zepeda Bermudez [1]
Angela Esher [1]
Claudia Garcia Serpa Osorio-de-Castro [1]
Daniela Moulin Maciel de Vasconcelos [1]
Gabriela Costa Chaves [1]
Maria Auxiliadora Oliveira [1]
Rondineli Mendes da Silva [1]
Vera Lucia Luiza [1]

Abstract Abstract *This article examines pharmaceutical services and access to essential medicines in Brazil during the 30 years since the advent of Brazil's Unified Health System from a comprehensiveness perspective. The following topics are addressed: the "realignment" of pharmaceutical services; human resources in pharmaceutical services; the essential medicines concept; the rational use of medicines; technological advances and drug manufacturing; and ethical regulation. With a strong regulatory focus and a structural framework centered on the National Medicines Policy, the past three decades represent a mixture of progress and setbacks, considering the national complexities of the healthcare system and the political, economic and social changes that have influenced policy and access to medicines, which is a key concern even in the world's richest countries, as the forums of discussion on global health have demonstrated. We show that major steps forward have been taken, highlighting that the recent fiscal austerity measures imposed by the government threaten to seriously undermine social progress.*

Key words *Pharmaceutical services, National medicines policy, Essential medicines, Comprehensiveness in healthcare, Unified Health System*

[1] Departamento de Política de Medicamentos e Assistência Farmacêutica, Escola Nacional de Saúde Pública Sergio Arouca, Fiocruz. R. Leopoldo Bulhões 1480, Manguinhos. 21041-210 Rio de Janeiro RJ Brasil. jorge.bermudez@fiocruz.br

Introduction

As we contemplate present-day Brazil, with the current political situation threatening to undermine the impressive social progress made by the country, it is important to look back to 1988 and remember what the 30 years that have passed since the creation of the Citizens' Constitution mean for the Unified Health System (*Sistema Único de Saúde* – SUS) and the right to health with universal access to healthcare. The transition from 20 years of military rule to the return to democracy gave rise to the progressive, supra-party health reform movement, which envisaged a fair and equitable country with social justice[1].

This movement included pharmaceutical services, which has undergone major changes during the 30-year period covered by this article (Chart 1). It is within this context that we discuss the main milestones in pharmaceutical services and access to medicines in Brazil focusing on the key guidelines and priorities laid out in the National Medicines Policy (NMP) and one of the guiding principles of the SUS, comprehensiveness.

With regard to World Health Organization (WHO) guidelines, in previous works we highlighted the importance of discussions for influencing and guiding different countries in the implementation of actions directed at ensuring access to essential medicines[2,3]. Recently, based on an extensive review of literature, the WHO highlighted a number of challenges to ensuring access to safe health technologies, various of which are discussed in this article[4].

Commissions of inquiry, decrees and laws, the reorientation of public policies, and technological proposals have failed to echo the idea of a state pharmaceutical industry widely discussed during the military regime. Nonetheless, a series of proposals and initiatives have had a definite impact on pharmaceutical services in the SUS over the last three decades.

Realignment of pharmaceutical services – the comprehensiveness paradigm

This guideline brought together key structural elements for the consolidation of the SUS. The fact that it was entitled "reorientation"(realignment) was innovative in itself, "giving a new orientation or new meaning" to a process that had already begun and was evolving.

Up to that point, the term "pharmaceutical services" was coined from a medicine supply perspective. Although the decree[5] that created the state pharmaceutical company *Central de Medicamentos* (CEME)contained the term pharmaceutical services, a clear definition of its scope, objectives, and activities would only be provided with the creation of the NMP. Thus, the reorientation of pharmaceutical services set out in the NMP represented a proposal for the effective integration of pharmaceutical services into the SUS, paving the way for the promotion of citizenship in line with the constitutional right to health.

The reorientation of pharmaceutical services proposed by the NMP was cross-cutting,

Chart 1. Selected events related to pharmaceutical services in Brazil by 10-year period. Brazil, 1988-2017.

Guidelines*	1988-1997	1998-2007	2008-2017
General aspects	**1990**: Basic Health Law (8080/90), which determines the government's commitment to guarantee comprehensive healthcare, including pharmaceutical services. **1997**: Decree 2283/97: Abolishes the CEME, responsible up until them the supply of medicines in the public health system.	**1998**: Ministerial Order MS/GM 3916/98: The National Medicines Policy(NMP). **2003**: 1st National Medicines and Pharmaceutical services Conference(CNAF, acronym in Portuguese). **2003/2004**: Evaluation of the pharmaceutical situation nursing WHO method. **2004**: NHC Resolution 338/04: Publication of the National Pharmaceutical Services Policy(PNAF, acronym in Portuguese). **2005**: Hospital pharmacy survey carried out in Brazil.	**2011**: Law 12401/11 and Decree7508/11: Important changes made to the organization of the SUS, health planning, healthcare, and inter-federative coordination and integration directly related to pharmaceutical services. **2013-2014**: Ministerial Order MS/GM 2077/12: National Access to and Use of Medicines Survey

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producing direct impacts in the field of public health[6]. The priorities set forth in the guideline are built around three key elements: decentralization, funding, and logistical actions[7]. Moreover, it guided and reinforced commitment to the constituent elements of pharmaceutical services within each of the three management levels of the SUS.

The inherent characteristics of this guideline reflect the social and political context in Brazil, reproducing the developments in the field of health witnessed during each 10-year period (Chart 2).

During the first 10 years of the SUS, pharmaceutical services were characterized by the transition between the abolishment of the CEME and the coming into force of the NMP. During this initial period, the Basic Pharmacy Program was reintroduced, marked by the supply of medicine kits to small municipalities, reflecting the centralized nature of pharmaceutical services and similar problems and criticisms to those observed in the CEME period[8].

Between 1998 and 2007, principles consistent with those of the SUS can be observed, with a focus on the organization of pharmaceutical services based on decentralization and the search for funding to provide access to medicines. Changes were made to tendering methods and more efficient and effective procurement procedures were introduced, which meant that state and local government faced the challenge of strengthening their planning and management capacity.

Two other important events can also be highlighted during this 10-year period. The first involved the restructuring of SUS funding, which was divided into blocks, improving the status of pharmaceutical services which was allocated its own specific block. However, this did not lead to a large increase in resources for pharmaceutical services. Federal government spending figures for the period 2010 to 2016 show an average growth of 21% across the three dispensing components of the block[9], where the basic component was the only to suffer a fall.

Another aspect was the fragmentation of care resulting from the organization of pharmaceutical services according to three medicine dispensing components. Models of organization and management of services that focus on the product rather than service delivery hamper patient care and certainly jeopardize comprehensive care in the SUS[10].

The second event was the introduction of the "Popular Pharmacy Program" (*the Popular Pharmacy Program do Brazil*- PFPB), which underwent various changes throughout its lifetime, relying heavily on the pharmaceutical industry for its consolidation and expansion. This program represented a return to a centralized approach to the provision of medicines. Questions were also raised as to the interface between this program and the public model in the SUS, raising doubts about its complementary or competitive action and its higher costs compared with studied public scenarios[11]. Furthermore, we can question to what extent this model, which emphasizes consumption as a central element of the promotion of access to medicines, is consistent with the principle of comprehensiveness, bearing in mind that the PFPB does not set out actions for promoting the appropriate use of medicines, therapeutic drug monitoring, etc.[11].

Finally, the last 10-year period, from 2008 to the present day, has brought old and new challenges. The strengthening of the primary care model through the expansion of the Family Health Strategy introduced actions directed at organizing pharmaceutical services via family health support centers. This permitted integration between pharmacists and other health professionals, enabling actions to promote the appropriate use of medicines, an example of comprehensive care and one of the underlying principles of the SUS.

Other recent events jeopardize the future of the SUS, such as the constitutional amendment that freezes government spending, which certainly undermines the right to health[12].

The abolishment of funding blocks without increasing resources is likely to weaken internal areas of the public health system, such as pharmaceutical services, as they are forced to compete with each other for resources. Although it is still too early to assess the full impact, we propose the following questions: (1) what will be the role of the Ministry of Health in inducing, formulating and regulating policy? (2) what will be management capacity and funding implications for local government? (3) to what extent will installed capacity with hard technology drain resources from other sectors? (4) how should striking regional disparities be addressed?

During the 30 years since the creation of the SUS and 20 years since the advent of the NMP, the primary focus of pharmaceutical services has been supply and logistics oriented towards supporting health actions and services, with limited focus on the social practices of care and provision of pharmaceutical services directed at the correct

Chart 2. Selected events related to the reorientation of pharmaceutical services, human resources development and capacity building in Brazil by 10-year period. Brazil, 1988-2018.

Guidelines*	Priorities*	1988-1997	1998-2007	2008-2018
Reorientation of pharmaceutical services	*Guarantee resources for the 3 spheres of government for direct or decentralized distribution* *Full decentralization of the purchase and distribution of medicines* *Specific funding for primary care medicines* *Special attention given to high-cost medicine*s	**1997**: Basic Pharmacy Program aimed at ensuring access to medicines in small municipalities in the period between the abolishment of the CEME.	**1999**: Ministerial Order MS/GM 176/99: Decentralization of pharmaceutical services. **2000**: Decree3555/00 –Regulates the*Pregão*, a new tendering format designedto streamline the tendering process, having a significant impact on medicine purchases. **2004**: Ministerial Order MS/GM 1651/04: Creation of the Popular Pharmacy Program, with expansion to the private network in 2006. **2006**: National *Planejar é Preciso* (planning is necessary) project aimed at promoting the effective planning of pharmaceutical services at municipal level. **2007**: Ministerial Order MS/GM 204/07: defines SUS funding blocks; three blocks created for medicines, in addition to funding for infrastructure.	**2008**: Ministerial Order154/2008: created Family Health Support Centers (NASF, acronym in Portuguese), establishing expected actions in the realm of pharmaceutical services. **2011**: determined that three therapeutic groups shall be provided free of charge to the Popular Pharmacy Program through the program *Saúde Não Tem Preço* (Health is Priceless). **2016**: Constitutional Amendment 95 of 15/12/2016, which freezes government spending over the next 20 years. **2017**: Ministerial Order MS/GM 3992/17: deep changes to the funding of the SUS, including pharmaceutical services and abolishment of blocks.
Human resources development and capacity building	*HR training (management of health and information systems; standard therapeutic guides; pharmaco vigilance WHO)*		**1999-2000**: Series of training workshops provided by the Ministry of Health across the country for local government pharmaceutical services managers aimed at promoting the effective decentralizationof pharmaceutical services. **2001 to 2002**: Courses provided under the Sentinel Project, beginning in2002, focusing on the management of pharmaceutical services, pharmacovigilance and URM. Important initiative for the consolidation of a network of sentinel hospitals with adequate capacity for health risk management. **2005**: Creation of a professional Master's program in Pharmaceutical Services Management as part of a cooperation agreement between the Department of Pharmaceutical servicesand the Rio Grande do Sul Pharmacy Faculty; 31 Master's graduates in 2005 to 2007. **2007**: Ministerial Order MS/GM 204/09: Establishes that 15% of funding from the pharmaceutical services basic component allocated to local and state governments can be used forstructuring and activities linked to continuing education.	**2008**: Ministerial Order MS/GM 362/08: Inclusion of pharmacy course in the Pro Health Program to build the capacities of student and qualified pharmacists and meet the needs of the Brazilian population and operate the SUS. Including the approval of financial incentives for projects to promote the physical restructuring of public services and capacity building. **2008**: Various courses provided by the Department of Pharmaceutical Services (professional Master's program at UFRGS, specialization in management, *Sistema Hórus* distance learning course, course with realistic simulation in Hospital Pharmacy) **2012**:Ministerial Order MS/GM 1214/12: Program created designed to enhance the quality of pharmaceutical services, with education as one of it four core areas **2013**: Training course in primary care provide across Latin America. **2017**: Ministry of Education Resolution 06/17 defining syllabus guidelines for pharmacy courses.

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use of medicines. This challenges us to think of reorientation as a continuous and living movement that brings about a positive transformation of reality rather than an end in itself.

The breadth of activities and actions involved means that, in likeness to comprehensiveness, 'pharmaceutical services' has become a polysemous term. That is why it is necessary to incorporate concrete actions into the care practices of professionals and into the organization of pharmaceutical services and government responses that are sensitive to health needs and the perspective that defends this doctrinal value[9,13].

Human resources in pharmaceutical services

Human resources are a critical element of health systems and services. Appropriate human resources in terms of both quantity and quality are necessary to operate health policies. Both the WHO and Pan American Health Organization consider human resources to be one of the key components of a NMP[14,15].

One of the guidelines of Brazil's NMP deals with human resources development, providing that the three levels of government (federal, state and local) are responsible for ensuring that there are enough trained personnel available to implement the policy (Chart 2) and stating that there is a need for capacity-building in specific areas, such as the promotion of the rational use of medicines, technological development, pharmaceutical services, and health surveillance[16].

With respect to the implementation of the NMP, Azeredo[16] shows that the guideline in question has relatively few normative instruments. According to the author, possible explanations for this situation include the lack of importance given to this guideline and coordination difficulties with the Ministry of Education in proposing the necessary changes[16]. The situation seems to have improved with the introduction of the following measures: the creation of the Department of Work and Education Management; the expansion of the *programa Pró-Saúde* (Pro Health program)to include pharmaceutical services; the publication of Ministerial Order Nº 2.981/2009[17], which sets a specific percentage for the allocation of financial resources to the basic component of pharmaceutical services for structuring and activities linked to continuing education; and the creation of the *programa Qualifar-SUS*, which aims to promote continuing education by offering face-to-face and distance learning courses[18].

Despite the above situation, it is important to recognize the importance of and the efforts made by the Ministry of Health over the last the 20 years since the publication of the NMP. Chart 2 shows the different initiatives taken by this body to strengthen pharmaceutical services through promoting staff capacity building, mainly pharmacists[19,20], including the first national course on teaching the rational use of medicines directed at physicians in 2002, which focused on medicines prescribing, and local and regional capacity-building programs.

However, despite these efforts, a number of challenges remain, including the concentration of pharmacists in state capitals[21], inadequate structure of pharmaceutical services, and lack of trained personnel[22] and difficulties in prioritizing capacity building given the work demands of pharmacists[23]. Furthermore, other barriers exist that cannot be overcome only with capacity building.

Essential medicines – efficacy, cost-effectiveness, quality, and safety

The path taken by essential medicines in Brazil between 1988 and 2018 is closely tied to that of the NMP (Chart 3).

The principle of comprehensiveness evolved during the lead-up to the creation of the SUS. In the 1980s and 1990s, comprehensiveness was viewed as the identification of and response to the health needs of the population[24]. Under this umbrella, essential medicines were conceived as those which satisfy health needs[25]. This concept predominated in the NMP, with the adoption and continuing review of the National List of Essential Medicines (Rename, acronym in Portuguese).

A national list of medicines and ingredients had existed since 1964. During the time of the CEME, the Rename served as a basis for the selection of medicines which were purchased and distributed in a centralized manner. In 1996, within the scope of the drafting of the NMP, the first evidence-based list of essential medicines was born, ushering in an intense process of consecutive reviews[26].

In 2002, the WHO defined essential medicines as those that satisfy the priority health care needs of the population[27], showing that the concepts of 'essentiality' and 'priority' were complementary. In Brazil, the responsibility for reviewing the list was transferred to the Multidisciplinary Commission for Updating the National

Chart 3. Selected events related to selection and appropriate use of medicines in Brazil by 10-year period. Brazil, 1988-2018.

Guidelines*	Priorities*	1988-1997	1998-2007	2008-2017
Adoption of the list of essential medicines	*Regular review*	**1997**: Adoption of the evidence-based paradigm with a view to modernizing the RENAME updating process.	**2002 and 2006**: Two updates of the RENAME produced. **2006**: National Medicinal Plants and Herbal Medicines Program; herbal medicines included in the RENAME.	**2009 to 2017**: Five updates of the RENAME are published along with two national formularies. **2011**: Law 12401/11: the responsibility for updating the RENAME is transferred to from the COMARE to the CONITEC, which fuses the RENAME into the context of health technologies.
Promotion of the rational use of medicines	*Educational campaigns* *Registration and use of generic medicines* *National Formulary* *Pharmaco epidemiology and pharmaco vigilance*	**1989**: Publication of the 2nd edition of the therapeutic memento of the CEME. **1999**: ANVISA Resolution 328/99 establishing requirements for dispensing health products in pharmacies and drugstores.	**2007**: Ministerial Order MS/GM 1555/07 creating the National Committee for the Promotion of the Rational Use of Medicines. **2001**: Brazil joins the WHO's Pharmaco vigilance Program	**2008**: ANVISA Resolution 96/08 updating regulations governing marketing, advertising, information and other practices aimed at promoting commercial medicines. **2009**:ANVISA Resolution 44/09 establishing Good Pharmaceutical Practices for dispensing and selling products and the provision of pharmaceutical services in pharmacies and drugstores. **2009**: ANVISA Resolution 47/09 establishing uniform standards for the content of patient information leaflets and rules for elaboration, updating, and publication, and differentiating patient information leaflet and information leaflets for health professionals. **2011**: ANVISA Resolution 20/11 establishing regulations governing the control of prescribing and selling antimicrobial drugs.

List of Essential Medicines (COMARE, acronym in Portuguese), which had its own rules of procedure and explicit criteria for the inclusion and exclusion ofmedicines[28]. The concept of essential medicines as those that satisfy the priority health care needs was institutionalized at local and state level with the creation of municipal and state lists of essential medicines. Comprehensiveness therefore depended upon the effective implementation of a hierarchical system in which the local and state selection of essential medicines complemented the needs guided by the Rename. The notion of 'essentiality' – medicines selected on the basis of efficacy, safety, quality, and affordability – reflected comprehensiveness. Two reviews of the list were conducted up to 2006[26].

In the 2000s, divergences began to appear between the above concept of essential medicines and that which governed the national list. Pressure to innovate within the SUS intensified. With the supply and adoption of new technologies, the objective was to guide service users through levels of care in a 'regulated' manner. Needs should be met, but within lines of care that determined supply within the system[17]. At the same time, the funding for organization of pharmaceutical services began to determine provision of essential medicines, placing pressure on selection. The Rename became vulnerable to the supply capacity of municipal governments. Weaknesses of in local government management began to be felt after the decentralization of pharmaceutical

services[29]. Although ministerial orders that tied funding of essential medicines to their presence on the Rename[30] were unable to prevent the application of evidence-based selection, they weakened the hierarchical process that integrated local and national lists[27,31], leading to serious gaps and fragmented provision of essential medicines in the SUS.

Difficulties in ensuring comprehensiveness became evident with an increase in the health litigation for access to essential medicines since 2007. The litigation for access represents an important milestone in the attainment of the right to health as a fundamental human right[32]. However, fragmented funding has had an enormous impact on the provision of essential medicines and 'grey' areas not covered by funding have grown, impelling users to seek access through the courts.

Between 2008 and 2010, two editions of the National Formulary (*Formulário Terapêutico Nacional* – FTN) were produced – one referring to the 2006 Rename and the other to the 2008 RENAME. The FTN is an important complement to the list of essential medicines since it contains a wide spectrum of information and advice on prescribing.

The adoption of the concept of essential medicines also implies regulatory actions, such as 'cleaning up' the market by restricting the registration of medicines of doubtful therapeutic value[31,33,34], training of prescribers in the rational use of medicines, and monitoring medicines introduced onto the market to curb abuse and misuse and to assess their effectiveness and safety in the real world. However, Brazil has not taken the restriction and monitoring path. Clinical protocol and therapeutic guidelines were introduced in 1997 and their development has been notable since 2002[33]. Protocols are a crucial strategy for the establishment of acceptable use standards, since they are based on best evidence. However, their implementation has been relaxed and their application in the SUS has been feebler than expected[35].

Six updated versions of the Rename were produced up to 2012 (of which only the first five were published). However, Law 12.401[36] had negative consequences, transferring the responsibility to incorporate new technologies into the SUS and to review and update the Rename to the newly created National Commission for the Incorporation of Technologies (Conitec, acronym in Portuguese). The list published in 2012, compiled by the Ministry of Health based on all the lists and supply of medicines in the SUS was recognized as a list of all SUS-funded medicine products[37], rather than a list of essential medicines. Paradoxically, all cancer and ophthalmology medicines were excluded from the list. Through the lens of the national list, comprehensiveness came to be understood as 'everything'[38,39] provided through the funding components, except those products funded by the APAC. It thus became a positive list for the system, relegating the concept of essential medicines and comprehensiveness based on need.

In 2013, the rules and regulations governing the registration[40] of medicines and expanded access and compassionate use of drugs[41] were relaxed, shortening the time it takes for a product to access the Brazilian market. This is an international trend resulting from pressure for innovation and funding[42], leading to an unprecedented growth in health litigation and jeopardizing the public provision of medicines. In this respect, in 2016, spending on the provision of medicines across the three levels of care of the SUS amounted to R$13 billion, while spending on medicines provided as a result of judicial decisions was R$8 billion[43].

Uneven progress has been made in the public provision of medicines over the 20 years since the NMP came into force: excellent access to particular medicines in certain primary healthcare niches can be seen[44], while enormous difficulties are faced by patients who need specialtydrugs[9,45]. However, the regular review of the Rename and the adoption of the concept of essential medicines, regarded as core elements of the policy that guide provision and all pharmaceutical services activities, have been jeopardized over time. The adoption of the idea of essentiality is a key factor for the successful implementation of the SUS and is in full consonance with the principle of comprehensiveness. It makes sense within the idea of care networks as a strategy to overcome fragmented care[46].

Rational use of medicines

Together with access to quality medicines, the rational use of medicines is seen as a central goal of any national medicines policy. Since the landmark Nairobi Conference on the Rational Use of Drugs[47], it has been widely recognized that the benefits of access are not concretized, and may even be lost, if medicines are not used properly.

There is a current trend to use the term "the appropriate use of medicines" instead of the "ra-

tional use", since misuse may be supported by spurious rationalities.

Strategies to promote the appropriate use of medicines have been classified as regulatory, management-based, and educational[48].The main milestones in the promotion of the appropriate use of medicines in Brazil are summarized in Chart 3.

Few actions directed at the promotion of the appropriate use of medicines were developed in Brazil up to the end of the 1980s. One of the few national actions was the publication of the therapeutic mementos of the CEME, which provided advice and information on the characteristics, use and care that should be taken with medicines contained in the Rename. The last memento was published in 1989[49].

At the end of the 1990s,a number of independent professional and user associations emerged whose prime aim was to promote the appropriate use of medicines. Also at that time, partnerships were established with international organizations representing different continents. Although the Pharmaceutical Services Center at the Oswaldo Cruz Foundation, created in 1998, and the PAHO/WHO Collaborating Center state that the main focus of their work is pharmaceutical policy, these centers have worked on various themes related to the appropriate use of medicines.

Given that regulatory measures are a core component of the promotion of the appropriate use of medicines, Brazil's regulatory body has always played an important role in this area. In this respect, it is important to highlight the development of good dispensing practices -which have a direct impact on the appropriate use of medicines - byBrazil's National Health Surveillance Agency (Anvisa, acronym in Portuguese)in the period 1988 to 1997[50].

One of the highlights of the period 1998to 2007 was the creation of the National Committee for the Promotion of the Rational Use of Medicines[51], which was redefined in 2013[52]. This committee is comprised of various organizations and has developed a number of actions, including the organization of events – the most notable of which was the Brazilian Congress on the Rational Use of Medicines – and the production of educational material, recommendations on regulatory actions, and the promotion of campaigns. During the same period, Brazil created the National Pharmaco vigilance System within ANVISA, strongly induced by the PAHO and national groups that advocated for the appropriate use of medicines[53]. Brazil gained important recognition when it was included as the 62nd member of the International Drug Monitoring Program Brazil[53].

Finally, the period 2008 to 2018 has witnessed a larger number of initiatives, such as the updating of drug marketing and advertising regulations in 2008[54], the development of good pharmacy practices, including the provision of pharmaceutical services in pharmacies and drugstores[55],the definition of uniform standards for the content of patient information leaflets[56], and the establishment of regulations for prescribing and selling antimicrobial drugs[57].

The progress made by these initiatives involves controversies. With respect to drug marketing and advertising, during the time of the public hearing which resulted in the regulatory instrument, a large group of researchers, professionals, and activists made an emphatic pronouncement criticizing the document, particularly the failure to adopt prior inspection. The group argued that in the case of subsequent detection of an infringement, the small size of the fine does not act as a deterrent because risks are more than compensated by the sales during the period in which marketing piece are broadcast. Indeed, studies have shown a low level of compliance with the legislation governing marketing pieces directed at both professionals and users[58,59].

With respect to pharmaceutical services, the Federal Pharmacy Council established regulations for prescribing drugs[60], a topic that lacks consensus even among pharmacy professionals[61]. Anvisa made efforts to strengthen actions related to patient information leaflets, such as the *bulário eletrônico*[62], an online system providing information about medicines to the public and professionals alike.

Finally, with respect to antimicrobial drugs, the regulations have led to an initial decrease in consumption[63].

The promotion of the appropriate use of medicines is firmly situated in the field of health promotion and disease prevention, be it primary, secondary, tertiary or quaternary care, and is therefore intertwined with the healthcare process. It could be said, therefore, that actions in this area satisfy the principle of comprehensiveness. The promotion of the appropriate use of medicines involves numerous challenges, given that it has a significant impact on the consumption of medicines, and therefore sales, requiring changes in the behavior of professionals, managers, and consumers.

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Technological development and manufacturing

The technological dependence of Brazil within the pharmaceutical industry was evident throughout the twentieth century and the government responded to this situation in various moments. Brazil was considered a "peripheral" country within an industry consolidated mainly in European countries and the United States and whose base depended on launching new innovations onto the market and sales growth[64].

At the beginning of the 1970s, the domestic production of medicines was related to pharmaceutical services. With the creation of a public market, which ensured constant demand, the CEME adopted other instruments to stimulate public sector production and the development of active pharmaceutical ingredients (APIs)[65]. The CEME was abolished in 1997 amidst claims of irregularities because it did not meet any of its initial goals (Chart 4)[8].

The first ten years of existence of the SUS therefore came to end with a long-term perspective stemming from the publication of the NMP in 1998. Aspects related to industrial policy were recognized, with the inclusion of specific guidelines for scientific and technological development and the promotion of pharmaceutical production[16].

These guidelines led to the development of concrete initiatives directed at the national pharmaceutical industry, including Brazil's Generic Medicines Policy (Law 9.787/99), which, using financing provided by the National Bank for Economic and Social Development, stimulated the growth of the private national pharmaceutical industry[66], and the *Projeto Guarda Chuva* (the Umbrella Project), which ensured financing for government pharmaceutical manufacturers (LFOs, acronym in Portuguese), focusing on the production of antiretroviral drugs in the context of the HIV/AIDS epidemic[67]. Lessons learned from these experiences show that LFOs play an important role in production cost estimation and in the strategic development of products under monopoly, contributing to government efforts in the negotiation of prices with transnational companies.

The 1st National Medicines and Pharmaceutical Services Conference sought to align pharmaceutical services with other policies related to manufacturing and science and technology recognized by the National Pharmaceutical Services Policy (PNAF, acronym in Portuguese).

With respect to health science and technology, one of the main milestones is the National Science, Technology and Innovation Policy (PNCTI, acronym in Portuguese), approved in 2004 during the 2nd National Health Science and Technology Conference and published in 2008, which incorporates the principles of scientific merit and social relevance[68].

In the second ten years of existence of the SUS, the scope of pharmaceutical industry development extended beyond the health sector with the approval of the Industrial, Technological and Foreign Trade Policy (PITCE, acronym in Portuguese), which encompassed the pharmaceutical industry, aiming to reduce national vulnerability caused by external dependence in technology-intensive areas.

In 2007, with the compulsory licensing of patents of the antiretroviral drug efavirenz, local production became an option once again for the implementation of the measure, resulting in the creation of a consortium for the production of the active pharmaceutical ingredient, meaning that a domestically produced generic drug became available in 2009,generating considerable public spending savings.

In 2008, during the third 10-year period since the creation of the SUS, the Industrial Health Complex (*Complexo Industrial da Saúde*- CIS) was created as one of the key areas of the federal government's strategic plan for the health sector[69], resulting in the approval of a series of regulatory instruments that changed the face of pharmaceutical industry policy, emphasizing the revival of the national industry and strengthening of LFOs[70]. In 2009, Production Development Partnerships were established as technology transfer arrangements to strengthen these two segments, considering that the purchase of products by the SUS provided the prospect of sustained demand without competition.

A recent assessment of LFOs shows that little progress has been made in relation to technological capacity and capacity to contribute to improved access to medicines[70], suggesting that the government has limited ability to address pharmaceutical services deficiencies in the SUS. The selection of appropriate technologies for domestic production and industry development should be considered in the light of comprehensiveness, which in this case would require an analysis of market dynamics to prioritize those areas where there is a risk of shortage, treatment gaps, and high-cost products with a view to subsidizing and regulating prices.

Chart 4. Selected events related to scientific and technological development and the promotion of the production of medicines in Brazil by 10-year period. Brazil, 1988-2018.

Guidelines*	Priorities*	1988-1997	1998-2007	2008-2018
Scientific and technological development	-	**1996**: Law 9279/96: New industrial property law approved defining rights and obligations relative to industrial property. Major changes made to the old law, aiming to meet the requirements of the TRIPS agreement.	**2000**: INOVAR project created with funding from FINEP aimed at boosting the creation and development of technology-based companies, including pharmaceutical companies, through the promotion of venture capital investment. **2003 – 2006**: Forum for Competitiveness in the Pharmaceutical Production Chain created aimed at strengthening the pharmaceutical production chain. **2004**: Guidelines of the Industrial, Technological and Foreign Trade Policy (PITCE) published, emphasizing the need to tackle external vulnerability focusing on technology-intensive sectors such as the pharmaceutical and pharmochemical industry, aimed at improving the efficiency of domestic production and innovative capacity, and the expansion of exports. **2004**: Law 10973/04 regulating incentives to stimulate innovation and technological research in productive environments, emphasizing the involvement of the Scientific, Technological and Innovation Institution in the innovation process and partnership with business. **2005**: Call for Proposals CNPQ 054/05 in support of research on pharmaceutical services.	**2009**: Ministerial Order MS/ GM 2690/09 –National Health Technologies Management Policy. **2015**: Law 13123/15 updating legislation on access to genetic heritage, broadening its scope and simplifying procedures, and creating the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SISGEN, acronym in Portuguese). **2017**: Decree9245/17creating the National Health Technology Inovation Policy.
Promotion of the production of medicines	-		**2001**: Pharmaceutical Production Stimulation Project aimed at strengthening public laboratories; Ministry of Health developed an investment program to modernize 10 institutions (umbrella). **2003**: Production Development Policy. **2004**: Creation of the Pharmaceutical Production Chain Support Program (PRoFaRMa). **2005**: Ministerial Order MS/GM 843/05 creating the Public Pharmaceutical Laboratory Network aimed at strengthening the domestic industry**.**	**2008**: production development policy published, aimed at strengthening the competitiveness of Brazilian companies; one of the challenges is to improve innovation capacity. **2008**: Ministerial Order374/2008 creating the Public Production and Innovation Support Program in the Industrial Health Complex, establishing objectives and guidelines for modernizing and strengthening the technological capacity of public laboratories. **2009**: Development of the Industrial-Economic Health Complex (CEIS, acronym in Portuguese) through Production Development Partnerships. **2011**: The *Plano Brazil Maior* (the bigger Brazil plan) is launched, establishing a series of measures and goals for strengthening industrial competitiveness. *Plano Brazil Maior2011/2014. Inovar para competir. Competir para crescer* (the bigger Brazil plan: innovate to compete; compete to grow).

Chart 5. Selected events related to the regulation of medicines and ethical regulation and medicine safety, efficacy and quality inBrazil by 10-year period. Brazil, 1988-2018.

Guidelines*	Priorities*	1988-1997	1998-2007	2008-2018
Regulation of medicines and ethical regulation	*Revitalization and relaxation of procedures and pursuit of greater technical and scientific consistency Elaboration of systematized operational procedures Training*	**1988**: NHC Resolution 01/88: first resolution regulating health research in the country. **1993**: Decree793/93 dealing with definition of generic medicines. **1994**: Ministerial Order MS/GM 1565/94 establishing guidelines for the National Health Surveillance System (SNVS, acronym in Portuguese), encompassing the roles of the three spheres of government. **1996**: NHC Resolution 196/96 updating the guidelines on research ethics and creates the CEP/CONEP system.	**1999**: Parliamentary Inquiry Commission created to investigate the counterfeit medicines scandal identifies numerous problems, resulting in various regulatory proposals. **1999**: Law 9782/99 creates Brazil's National Health Surveillance Agency (ANVISA) as an autonomous body. **1999**: Law 9787/99 (the Generic Medicines Law), regulating various aspects, such as quality and substitution. **2000**: ANVISA becomes the executive secretary of the Chamber of Medicines (CaMed, acronym in Portuguese), leading to a series of interventions to regulate the price of medicines.	**2008**: Ministerial Order ANVISA 422/208 creates the Regulation Improvement Program (PMR, acronym in Portuguese). **2012**: CEMED Resolution 02/12 dealing with the pricing of medicines by the CEMED. **2012**: NHC Resolution 466/12 updating guidelines for ethics in research. **2013**: Decree 8077/13 relaxing the rules and regulations for the registration of medicines.
Medicine safety, efficacy and quality	-	**1988**: Decree 96607/88: updated version of the Brazilian Pharmacopoeia published.	**1999**: The Medicines Parliamentary Inquiry Commission identifies numerous irregularities in relation to the quality and safety of medicines, especially related to the counterfeiting of medicines.	**2012**: ANVISA Resolution 12/12 creates the Brazilian Analytical Health Laboratory Network (REBLAS, acronym in Portuguese). **2010**: ANVISA Resolution 49/10: updated version of the Brazilian Pharmacopoeia published. **2017**: Homeopathy Formulary of the Brazilian Pharmacopoeia 1st Edition published.

Ethical regulations, research and medicines

The regulation of ethics in pharmaceutical research is governed by the National Health Council (NHC), which involves the Ministry of Health in some of its functions[71].

The first resolution regulating health research in Brazil was the NHC Resolution 01/88. Low levels of adherence to these regulations among the scientific community resulted in the need for a new resolution that was more comprehensive in relation to ethical considerations in research. In 1995, headed by the NHC, a commission was created to elaborate a new resolution. Published in 1996[72,73], Resolution 196/96 updated guidelines and provided for the creation of a centralized ethical review system comprised of the National Research Ethics Commission (CONEP, acronym in Portuguese) "an independent advisory, deliberative, regulatory, and educational collegial body attached to the NHC" and research ethics committees (RECs), defined as "interdisciplinary and independent advisory, deliberative, and educational collegial bodies, with 'public *munus*', creat-

ed to defend the interests of research participants in their integrity and dignity and to contribute to the development of research in accordance with ethical standards"[74]. This resolution was revoked in 2012 with the publication of NHC Resolution 466/12,which brought a number of advances, including instructions on the use of placebos and the requirement that sponsors provide participants free indefinite access to the best provenly effective prophylactic, diagnostic and therapeutic methods at the end of the study[75].

The following resolutions are important instruments in the ethical review process in Brazil: NHC Resolution 506/16 "establishes criteria for the accreditation of RECs in the CEP/CONEP system in public and private institutions" to promote the decentralization of the system and strengthening the autonomy of research to act on a regionalized basis; and Resolution 510/16, which establishes rules and regulations for research in the field of human and social sciences and other fields that use methods specific to these areas, seeking to promote an analysis that is more suited to the specificities of this type of research. This instrument also creates a new area in the *Plataforma Brazil* for the submission of projects and establishes new flows for the assessment of studies in accordance with the risks involved[76].

Bill 7082/17, which has already been approved by the Senate (Bill 200/15) and is currently under consideration by the Chamber of Representatives seeks to provide greater judicial legitimacy and swiftness to clinical trials and proposes limits to the mandatory provision of post-study medicines guaranteed by Resolution 466/12. The bill also proposes the creation of a new ethical regulation system for clinical trials connected to the Ministry of Health. In our view, this proposal is inconsistent considering the primary function of the NHC, which is a participatory and deliberative body attached to the Ministry of Health that plays an important role in formulating and overseeing the implementation of the country's health policy and has taken important steps in guaranteeing the protection of research participants in Brazil.

Final considerations

Thirty years is a long time. The country is huge, unequal and complex and has gone through various political, economic and social changes throughout the period. The theme of essential medicines and pharmaceutical services is broad, central and cross-cutting. Thus, to tell this story it is necessary to break it down into parts and make choices.

Selecting the events was no easy task. We focused principally, but not exclusively, on regulatory instruments, which express an implementation effort. However, this does not necessarily guarantee that they have been fully or successfully implemented, given that this paper is not intended to be an evaluation of achievements. On the other hand, we consider it necessary to warn of the consequences of current policies and the dismantling of solid structures that represent significant social advances. Let's defend the SUS!

Collaborations

JAZ Bermudez, A Esher, CGSO Castro, DMM Vasconcelos, GC Chaves, Oliveira Oliveira, RM Silva and VL Luiza also participated in the design, design, editing, editing and revision of the article, under the coordination of JAZ Bermudez, and all authors approved the final version.

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