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Analysis of new drugs registered in Brazil in view of the Unified Health System and the disease burden

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Abstract *The most important aspect of a new drug in terms of public health is its therapeutic value and benefit it provides for the patient and for the society. The aim of this study was to analyze new drugs registered in Brazil between 2003 and 2013 with respect to Pharmaceutical Assistance programs within the Brazilian health system and to the disease burden in the country. In our retrospective cohort study, new drugs registered in Brazil were identified through document analysis of databases and publicly available documents from National Health Surveillance Agency. The data on disease burden in Brazil was obtained from the Global Burden of Disease Study 2012, published by the World Health Organization. The level of therapeutic innovation was determined using the Motola algorithm. Although a total of 159 new medicines were used in the cohort, only 28 (17.6%) were classified as important therapeutic innovations. There is a disproportionate relationship between the percentage of new drugs and the burden of disease, with an under-representation of drugs for infectious respiratory diseases, heart disease, and digestive diseases. Incentive strategies for research and development of medicines should be prioritized to reduce the disparity regarding the burden of disease and to help develop innovative medicines necessary to improve health throughout the country.*

Key words *Unified Health System, Burden diseases, Innovation, New drugs*

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Introduction

Medicines significantly contribute to the improvement of population health and patient survival[1]. Measures to improve public health are directed towards the prevention, inhibition, and modification of the natural course of diseases, as well as reduction of symptoms, these features are strongly influenced by access to and rational use of suitable drugs[1-3].

The ongoing demographic and epidemiological transitions in Brazil and in several other countries have resulted in a higher prevalence of chronic non-communicable diseases (CNCD), which cover health conditions wherein pharmacotherapy is an important therapeutic approach and prevention measure[1,4].

The pharmaceutical market is one of the most valuable and profitable in the world. Transnational corporations invest considerable resources in scientific drug production due to the high value of innovative medicines and the marketing monopoly guaranteed by patents[5].

For public health, the importance of a new drug is in the therapeutic value and the benefit that it provides for the patient and for society in terms of years of life saved and improved quality of life[6,7]. The therapeutic value should be considered in a broader dimension that goes beyond chemical innovation, based on a wider view of clinical benefit[6].

The benefit of a drug includes its ability to improve population health. Assessment of the impact of pharmacotherapy on population health can be performed by taking into consideration: the burden of the disease treated or prevented by medication; the theoretical interference on mortality, morbidity and quality of life; and the applicability and level of scientific evidence available[8].

Burden of disease is recommended by the World Health Organization (WHO) to define priority drugs for health systems, and various methodologies are used to measure it. The most described methodology employs the DALY (disability-adjusted life year) indicator, a simultaneous measure of mortality and disability of a particular disease or health condition[2,9-12]. In Brazil, this indicator of disease burden was used to analyze the essential drugs selection system[13], however research related to new drugs has not been published to date.

Analyses of new drugs launched in developing countries are uncommon. Studies conducted in Brazil covering the 2000-2004 period identified a small number of drugs with therapeutic advances, and indicated that the pharmaceutical market was not oriented to public health needs[14,15].

Given the above, the objective of this study is to analyze the new drugs registered in Brazil from 2003 to 2013 with regards to the Pharmaceutical Assistance programs of the Unified Health System (SUS), considering the country's burden of disease.

Methods

Design and data collection

We performed a retrospective cohort study that analyzed new drugs registered in Brazil from January 1, 2003 to December 31, 2013 and their relationship with the country's burden of disease. Information sources on medicines were collected by consulting public access documents available on the internet and in specialized literature, which do not require the approval of a Research Ethics Committee.

The Brazilian site of the National Health Surveillance Agency (Anvisa) does not present new drug query functionality. Thus, it was necessary to first identify new drugs launched in the US by obtaining information from the Drugs@FDA database in the Food and Drug Administration (FDA) website, and then search for publications regarding the registration of these drugs using *Diário Oficial da União* (or "Official Gazette of the Union"), a Brazilian government site wherein Anvisa publishes its drug registration decisions. As shown in Figure 1, drugs registered in other countries were identified in the review articles published each year in the *To Market, To Market* chapter of the *Annual Reports of Medicinal Chemistry*[16-26]. Over- the- counter drugs and drugs registered as a new dosage form, new route of administration, new combination or new indication were excluded from the study. Nutritional supplements, radiopharmaceuticals, vaccines and diagnostic agents were also excluded. Finally, the registration of drugs launched overseas in Brazil was verified using Anvisa. Drugs were surveyed by drug name, adopting the common Brazilian denomination.

Information for each product included in the cohort was collected from documents available on the FDA website and from information available in the "*To Market, To Market*" chapters of the *Annual Reports of Medicinal Chemistry*. The fol-

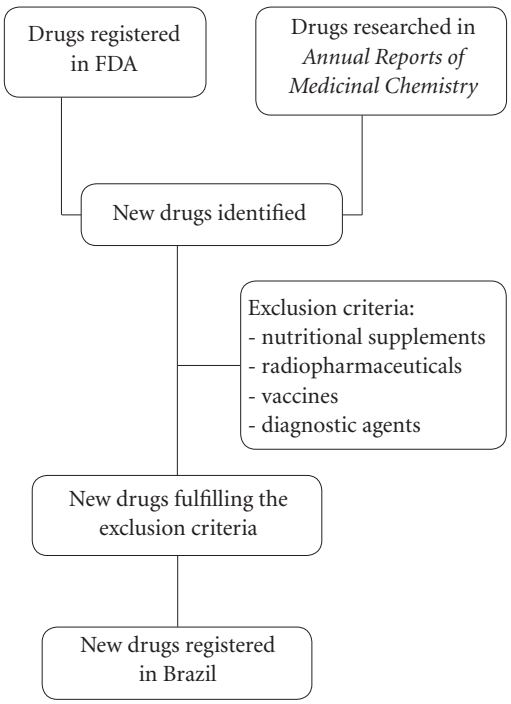


Figure 1. Fluxogram of the identification process for news drugs registered in Brazil between 2003 and 2013. New drugs identified via Anvisa publications and with registration between January 2003 and December 2013 constitute the cohort being investigated.

lowing FDA documents were consulted: *Medical Review*, *Chemistry Review*, *Pharmacology Review* and *Approval Letter,* available in sections *Approval History*, *Letters*, *Reviews*, and *Related Documents*. The following information was collected: year of approval, drug name, orphan drug, *first in class*, primary indication, registration location and nature of the drug production process (chemical or biological).

In this study, the following definitions were used:

- New drug: drug registered by the drug regulatory agency, corresponding to a new molecular entity or new active ingredient of synthetic, semi-synthetic or biological nature, registered for the first time in the country[6,27].
- Orphan drug: drug indicated for the treatment, prevention or diagnosis of rare diseases, therefore being used by a smaller population in contrast to other drugs. These medications are often intended to treat severe or chronic diseases, for which no adequate treatment is previously approved[28].
- First in class: refers to the first drug with action on a particular molecular target without prior registration in the market[29].
- Therapeutic innovation: also called therapeutic value, indicates the additional benefit to the patient of a new treatment when compared to the available options, incorporating the interrelationship of efficacy, safety and convenience[30].

The drugs were classified according to the first and third levels of the Anatomical Therapeutic Chemical (ATC) Classification of WHO. Information on new drug introduction was collected from the website of the National Commission for Technology Incorporation on the National Health System (CONITEC) and the National List of Essential Medicines (RENAME), 2013, available on the Ministry of Health website.

Evaluation of therapeutic innovation was carried out by considering the information from the clinical studies presented on the drug registration process with the FDA and the information contained in the chapters of *To Market, To Market*. The analysis was conducted by two researchers independently and disagreements were resolved by consensus. To assess the level of therapeutic innovation of new drugs the algorithm of Motola et al.[31] was used. The algorithm graded the drugs as: important, moderate, modest, pharmacological, or technological innovations.

The main indication of new drugs was classified according to the International Classification of Diseases (ICD-10), using the first three characters of ICD-10. Drug indications were related with the disease categories defined in the *Global Burden of Disease Study* of 2012[32,33]. This study was developed by WHO to quantify the disease burden in the population and to obtain information on the prevalence, incidence, severity, disability and mortality of more than 100 disease causes. The DALY of different categories of diseases for the Brazilian population was collected in this step[33].

Statistical Analysis

All of the information collected was entered into an EpiData software database (version 3.1, EpiData Assoc, Denmark), wherein double data entry was performed.

A descriptive analysis with frequency and proportion calculations for categorical variables was performed. For the quantitative variables, measures of central tendency and variability

were calculated. Normality was analyzed with the Kolmogorov-Smirnov and Shapiro Wilk tests, considering p-values < 0.05. The association between the number of new drugs and the DALY indicator was verified by non-parametric correlation using the Spearman coefficient, considering p-values < 0.05. The *Statistical Package for Social Sciences* (SPSS for Windows, version 21.0, SPSS Inc., Chicago, IL) was used to perform the statistical analysis.

Results

We identified 331 medicines registered with the FDA which met the inclusion criteria of the study and 260 drugs in the *To Market, To Market* chapters, totaling 591 drugs. Of these, duplicates between the two sources of data collection were withdrawn, totaling 407 drugs. After applying the exclusion criteria, the number of drugs was reduced to 311. Of the 311 drugs, it was found that 249 were registered with the FDA and 62 were identified in the *To Market, To Market* chapters. The study cohort consisted of 159 drugs registered by Anvisa between January 01, 2003, and December 31, 2013.

With respect to the nature of the production process, of the 159 cohort drugs, 118 (74.2%) were chemical drugs and 41 (25.8%) were biological. The number classified as orphan drugs was 23 (14.5%) and 51 (32.1%) were first in class. The main characteristics of the drugs are shown in Table 1.

Regarding the level of innovation according to the algorithm of Motola et al.[31], of the 159 drugs, 28 (17.6%) were classified as important innovations, 34 (21.4%) as moderate, 24 (15.1%) as modest, 66 (41.5%) as pharmacological and 7 (4.4%) as technological (Table 1). As to the degree of innovation of the 51 first in class drugs, 10 (19.6%) were classified as important innovations, 15 (29.4%) as moderate, 10 (19.6%) as modest, and 16 (31.4%) as pharmacological.

According to first level ATC classification, the most common groups were: L-anti-neoplastic and immunomodulating agents (28.9%); A-alimentary tract and metabolism (17%); J-anti-infectives for systemic use (12.6%); and B-blood and blood forming organs, G-genitourinary system and sex hormones, and N-nervous system, at 6.9% each (Table 2). Considering the third level ATC classification, in group A, the frequency of drugs that reduce blood sugar, excluding insulins (A10B), stands out, as it does in group J the frequency of direct action anti-viral drugs (J05A) and in group L the frequency of immunosuppressants (L04A) and other anti-neoplastic agents (L01X). It is important to note the high frequency of anti-thrombotic agents (B01A) in group B (Table 2).

Of all the drugs, 22 (13.8%) were included in the RENAME, eight (5.0%) in the strategic component and 14 (8.8%) in the specialized component. From the perspective of therapeutic care and technological innovation in health, in the context of SUS, 12 (7.6%) drugs had their introduction approved by CONITEC and for 15 (9.4%) introduction was not approved (Table 1).

Table 3 shows the number of drugs launched in Brazil, the disease burden in the country and the ICD-10 corresponding to the indications. The main indications of the drugs were malignant neoplasms (17.0%), endocrine and blood disorders (11.9%), infectious and parasitic diseases (11.3%), neuropsychiatric conditions (10.1%), heart disease (8.2%), diabetes mellitus (6.9%) and musculoskeletal diseases (6.9%). Of the new drugs included in the cohort, 88.1% were identified as NCDs. Analyzing the total DALYs relating to the indications of these drugs, 88.7% of the disease burden was ascribed to non-communicable diseases and 11.3% to communicable diseases.

The correlation between the disease burden and the number of new drugs launched in Brazil was positive and statistically non-significant ($\rho = 0.475$; p-value = 0.073). Graphic 1 shows a disproportionate relationship between the percentage of new drugs launched and the percentage of DALY by disease category. The largest disproportion is evident for endocrine and blood disorders, infectious and parasitic diseases, and skin diseases, showing an over-representation in relation to the disease burden that these categories generate. On the other hand, infectious diseases, heart diseases and digestive diseases are under-represented.

Analyzing the over-represented diseases, it was found that in the category of blood and endocrine disorders, 10 of the 19 drugs were indicated as metabolism-related diseases, and five were classified as orphan drugs. In the category of infectious and parasitic diseases, only four indication groups and 18 drugs were identified, eight drugs for acquired immunodeficiency syndrome (HIV/AIDS), five for viral hepatitis, three for candidiasis and two for bacterial diseases. For skin diseases, eight drugs were registered, and this category included five indications, of which three drugs were for psoriasis.

Table 1. Characteristics of the 159 new drugs registered in Brazil from 2003 to 2013.

Caracteristics	Number of Drugs	%
Chemical drug	118	74.2
Biological drug	41	25.8
First in class	51	32.1
Level of innovation		
Pharmacological	66	41.5
Moderate	34	21.4
Important	28	17.6
Modest	24	15.1
Technological	7	4.4
First level ATC classification		
L – Antineoplastic and immunomodulating agents	46	28.9
A – Alimentary tract and metabolism	27	17.0
J – Anti-infectives for systemic use	20	12.6
B – Blood and blood forming organs	11	6.9
G – Genitourinary system and sex hormones	11	6.9
N – Nervous system	11	6.9
C – Cardiovascular system	9	5.7
Others	24	15.1
Orphan drug	23	14.5
FDA registration	140	88.1
Drug Policy		
RENAME*		
Inclusion in the strategic component	8	5.0
Inclusion in the specialized component	14	8.8
CONITEC** Evaluation		
Introduction in analysis	8	5.0
Approved introduction	12	7.6
Introduction not approved	15	9.4
Drugs not presented for analysis	124	78.0

* National List of Essential Drugs; ** National Committee for Incorporation of Technology on the National Health System.

For under-represented diseases, it was observed that in the category of infectious respiratory diseases, only one medication was registered, which was indicated for the treatment of influenza. In the heart disease category, 13 drugs were identified: four for atrial fibrillation, three for ischemic heart disease, two for hypertension, two for venous thrombosis and two for pulmonary hypertension. For digestive diseases three drugs were registered, one for gastroesophageal reflux, one for Crohn's disease and one for the common cold.

WHO's disease burden study included DALY for eight neglected diseases. The highest values are for diarrheal diseases (404.3), tuberculosis (314.4), Chagas disease (229.3) and dengue (103). The other mentioned diseases are leishmaniasis, malaria, leprosy and lymphatic filariasis. During the study period, there were no new drugs registered for neglected diseases in Brazil. It is also noteworthy that, during this time, a drug for tuberculosis and another for diarrheal diseases were released abroad. Also, no drugs for neonatal conditions, nutritional deficiencies and oral conditions were identified.

Discussion

The analysis of new medicines registered by Anvisa from 2003 to 2013 showed that, in Brazil, the introduction of drugs in the pharmaceutical market is higher for certain disease categories, particularly the anti-neoplasm, anti-diabetic and anti-viral therapeutic classes. A positive correlation without statistical significance between the DALY of the main categories of disease and the number of new drugs was also observed.

The public health perspective has not been fully considered in the process of drug registration in the country, since there is an imbalance between health demands and the interests of the pharmaceutical industry. This scenario was described in a study using DALY measurements, which investigated drugs registered from 1995 to 2009 in the European Union from the viewpoint of the health system[2]. In 2004, the gap between drug development and the country's health priorities was reported in a study comparing the indications of drugs registered from 2000 to 2004 in Brazil with the most prevalent diseases according to data obtained from the information system of the Department of Informatics of the Unified Health System, the DATASUS[15].

The higher proportion of anti-cancer, immunosuppressants and anti-diabetic drugs among the pharmacological groups of new drugs in the cohort, is in line with the criteria for research priorities, drug release and the epidemiological transition underway in Brazil. NCDs strongly represent the vast majority of diseases affecting the Brazilian population today. Among these are

Table 2. First and third level Anatomical Therapeutic Chemical Classification of the 159 new drugs registered in Brazil from 2003 to 2013.

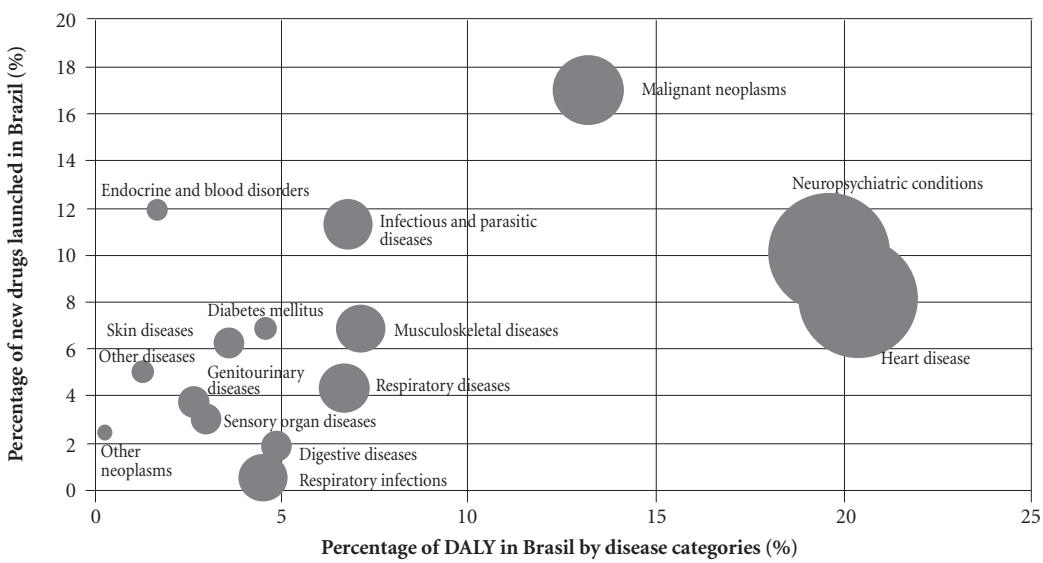
ATC Classification*		n	%
Anti-neoplastic and Immunomodulating agents		**46**	**28.9**
L01B	Anti-metabolites	2	1.3
L01C	Plant alkaloids and other natural products	2	1.3
L01X	Other anti-neoplastic agents	25	15.7
L02B	Hormone antagonists and related agents	1	0.6
L03A	Immunostimulants	2	1.3
L04A	Immunosuppressants	14	8.8
Alimentary Tract and Metabolism		**27**	**17.0**
A02B	Drugs for peptic ulcer and gastrooesophageal reflux disease	1	0.6
A04A	Anti-emetics and anti-nauseants	3	1.9
A06A	Drugs for constipation	2	1.3
A08A	Anti-obesity preparations, excluding diet products	1	0.6
A10A	Insulins and analogues	2	1.3
A10B	Blood glucose lowering drugs, excluding insulins	9	5.7
A16A	Other alimentary tract and metabolism products	9	5.7
Anti-infectives for Systemic Use		**20**	**12.6**
J01A	Tetracyclines	1	0.6
J01D	Other beta-lactam anti-bacterials	1	0.6
J01M	Quinolone anti-bacterials	1	0.6
J01X	Other anti-bacterials	1	0.6
J02A	Anti-mycotics for systemic use	3	1.9
J05A	Direct acting anti-virals	13	8.2
Blood and Blood Forming Organs		**11**	**6.9**
B01A	Anti-thrombotic agents	7	4.4
B02B	Vitamin K and other hemostatics	2	1.3
B03X	Other anti-anemic preparations	1	0.6
B06A	Other hematological agents	1	0.6
Genitourinary System and Sex Hormones		**11**	**6.9**
G03A	Contraceptive hormones for systemic use	2	1.3
G03G	Gonadotropins and other ovulation stimulants	1	0.6
G04C	Drugs used in benign prostatic hypertrophy	1	0.6
G04B	Urologicals	7	4.4
Nervous System		**11**	**6.9**
N03A	Anti-epileptics	2	1.3
N05A	Anti-psychotics	2	1.3
N06A	Anti-depressants	3	1.9
N06B	Psychostimulants, agents used for ADHD and nootropics	2	1.3
N07B	Drugs used in addictive disorders	1	0.6
N07X	Other nervous system drugs	1	0.6
Cardiovascular System		**9**	**5.7**
C01B	Anti-arrhythmics class I and III	2	1.3
C01E	Other cardiac preparations	2	1.3
C02K	Other anti-hypertensives	1	0.6
C07A	Beta blocking agents	1	0.6
C09X	Other agents acting on the renin-angiotensin system	1	0.6
C10A	Lipid modifying agents	2	1.3
Others		**24**	**15.1**
Total		**159**	**100**

* ATC/DDD Index 2015 available in http://www.whocc.no/atc_ddd_index/.

Table 3. Number of new drugs registered in Brazil from 2003 to 2013 and DALY number according to ICD-10 indication.

Indications	Number of drugs	%	DALY number x1000*	%	Disease ICD-10
Communicable diseases	**19**	**11.9**	**5456.8**	**11.3**	
Infectious and parasitic diseases	18	11.3	3276.7	6.8	A48, B18, B23, B24, B37
Respiratory infections	1	0.6	2180.1	4.5	J09
Noncommunicable diseases	**140**	**88.1**	**42956.3**	**88.7**	
Malign neoplasms	27	17.0	6383.8	13.2	C18, C34, C43, C45, C46, C50, C61, C64, C73, C76, C78, C84, C85, C90, C92, C94
Endocrine, immunological and blood diseases	19	11.9	816.5	1.7	D63, D69, D84, E21, E22, E24, E66, E70, E72, E74, E75, E76, E78
Neuropsychiatric conditions	16	10.1	9494.1	19.6	F17, F20, F32, F52, F90, G10, G24, G35, G40, G47
Heart diseases	13	8.2	9855	20.4	I10, I20, I24, I27, I48, I80, I82
Diabetes mellitus	11	6.9	2216.6	4.6	E10, E11
Musculoskeletal diseases	11	6.9	3433.4	7.1	M05, M06, M32, M79, M81
Skin diseases	8	5.0	624	1.3	L01, L08, L40, L50, L57
Respiratory diseases	7	4.4	3224.8	6.7	J30, J44, J45
Genitourinary diseases	6	3.8	1289.4	2.7	N18, N32, N40, N97
Sensory organ diseases	5	3.1	1437.2	3.0	H10, H35
Other neoplasms	4	2.5	140.4	0.3	D01, D37, D46
Digestive diseases	3	1.9	2338.8	4.8	K21, K50, K59
All other diseases	10	6.3	1702.3	3.5	Q25, R11, T47, Z30, Z51, Z94
Total	**159**	**100**	**48413.1**	**100**	

*Disability adjusted life of years.



Graphic 1. Representation of the relationship between the number of new drugs and the disease burden in Brazil.

cardiovascular diseases, diabetes, cancer, chronic respiratory diseases and kidney disease, together which accounted for 72% of deaths in 2007[34]. Given the burden of these diseases, it is understandable that most of the new drugs in the cohort studied are aimed at NCDs.

Despite a considerable reduction in the number of deaths from infectious diseases in the past six decades, they remain a public health problem in Brazil. The distribution of causes of death from infectious diseases in Brazil moved towards a pattern closer to that observed in developed countries. This result is attributed to the success of efficient public policies directed at determining factors and increased access to prevention and treatment resources[35].

The Department of Sexually Transmitted Diseases, AIDS and Viral Hepatitis of the Ministry of Health coordinates the anti-retroviral treatment access policy, which provides drug distribution free of charge to the entire population and has a large diversity of therapeutic alternatives[9,36]. There is a continuing need of identification of anti-retroviral therapy drugs due to the rapid mutation of the HIV genome and the development of resistance to existent anti-retroviral drugs[9,37].

The over-representation of drugs for infectious and parasitic diseases can be attributed to the reduction of the burden of these diseases in the country, coupled with the access guarantees to anti-retroviral drugs in the country and the need for drugs to address resistance to existing anti-retroviral drugs, leading to pharmaceutical companies having a great interest in registering new drugs in Brazil, which can raise the representation. Anti-virals are among the main therapeutic classes of the cohort studied, including anti-retroviral agents and drugs for hepatitis. Viral hepatitis is currently a public health concern and the drug access program has been expanded through the specialized component of pharmaceutical assistance[38].

Brazil has shown sustained advances in biomedical, clinical and epidemiological research on issues involving the prevention and treatment of infectious diseases[35]. These academic achievements should be converted into products and policies that benefit the entire Brazilian population, including new drugs for neglected diseases, especially those that the health system has been unable to control. Meeting the challenges of treatment adherence and transmission of pathogens resistant to treatment for tuberculosis and HIV/AIDS is also a research priority[35,37].

The principle of social solidarity to prioritize health research applies to diseases for which there are currently no incentive to develop new drugs, among which stand out neglected diseases[9]. Between 2003 and 2013, there was no record of any new medicine for neglected diseases in Brazil, despite the prevalence of these diseases in the country, highlighting the challenge of facing the problem of a lack of therapeutic alternatives. Given the above, health priorities should be established to guide research and development efforts in order to produce new drugs to treat neglected diseases still common in Brazil, such as tuberculosis, malaria, leprosy, leishmaniasis, schistosomiasis, Chagas disease and dengue[9,15,35]. However, there are some barriers to investments, such as limited interest, low market value of these products and lack of funding[9,39]. Therefore, there must be a public commitment to develop an approach focused on the global needs of the health agenda in the research and development for neglected diseases, and create appropriate mechanisms, incentives and monitoring to enable the effective implementation of that agenda[9].

The therapeutic category of endocrine and blood disorders showed over-representation, due to the high number of new medicines launched for this class, which represents only 1.7% of DALY in Brazil. However, it is noteworthy that 23.6% of these drugs are indicated for rare diseases related to disorders in lipid, carbohydrate and protein metabolism. The release of drugs for rare diseases also complies with the principle of social solidarity recommended by WHO for health system priority drugs[9]. It is important to introduce legislation similar to that already existing in the United States, to encourage the introduction of new drugs on the market, by protecting the investments on research and development of pioneering drugs for rare or orphan diseases[40].

While there was an over-representation of infectious and parasitic diseases, endocrine and blood disorders as well as skin diseases, we also observed an under-representation for infectious respiratory diseases, with only one registered drug, indicated for the treatment of influenza. The decline in the discovery of new anti-bacterial drugs, especially those active against Gram-negative bacteria, is a growing concern considering the emergence of microbial resistance[9]. Actions to encourage the search for new antibiotics to provide therapeutic alternatives for treatment of pneumonia and other infections are a global priority[9,35].

Cardiovascular diseases are the leading cause of death in Brazil and generate the largest hos-

pitalization costs in the national health system[34]. The low number of new drugs, when the burden of these diseases is taken into account, requires an analysis from the perspective of the strategies for treatment, prevention and control. Ischemic heart disease and cerebrovascular disease contribute with significant portions to the burden of heart disease in Brazil. For these diseases, effective drugs that reduce the incidence of heart attacks and brain stroke are available[41]. The pharmacotherapeutic profile of cardiovascular drugs in our cohort shows the permanent absence of therapeutic innovation regarding drugs for dyslipidemia. On the other hand, a significant number of pharmacological innovations on oral anti-coagulants for use in the prophylaxis of thromboembolic events in atrial fibrillation-suffering patients and other profiles was identified, which was not observed for ischemic heart disease and hypertension. The high number of new anti-coagulants and anti-platelet agents is another example of niche market discovery by the pharmaceutical industry. The introduction of dabigatran, an ATC B01A group drug, in clinical practice was analyzed by pharmacoepidemiologists and health economics researchers as an example of the need to optimize the use of new drugs in health systems[42].

The category of neuropsychiatric disorders presented a number of drugs proportional to its burden of disease, which reflects the prevalence of depression, psychoses and disorders attributable to excessive alcohol use, and, more recently, dementia. However, drug indications do not reflect this health situation. In the category of "lifestyle" drugs, the high number of drugs for sexual dysfunction not caused by organic disorder or disease (ICD-10 - F52) had a noteworthy representation, with high profit potential for the pharmaceutical industry.

From the health system perspective, the registration of new drugs for depression is expected, particularly for the treatment of adolescents and elderly as well as for Alzheimer's disease. However, there are still challenges to be overcome by researchers in organic synthesis and medicinal chemistry to synthesize drugs that ensure significant therapeutic advances in this area[44,45]. Despite recent advances in Alzheimer's disease research, there are still major scientific gaps in understanding the pathophysiology and on effective therapeutic interventions relevant to the design of new drugs. Another challenge is the elucidation of the role of biomarkers in drug development and its contribution to efficiency determination[45].

The decision to introduce new drugs, in particular biological ones, in the health systems of countries with different levels of economic development is a challenge due to high costs, and requires economic analysis of the introduction of health technologies to guide the decision-making process[1]. The increasing trend of participation of new drugs in the therapeutic arsenal is evident in the studied cohort, whose share of biopharmaceuticals accounted for a quarter of drugs.

Brazil has already adopted a strategy of economic evaluation of health technologies, as for the financing of a drug by the SUS an evaluation by CONITEC is required. The latter, when evaluating a new drug introduction request, proved to be accurate and showed concern about the cost-effectiveness of drugs to be financed by SUS, as only a small percentage of the drugs analyzed was introduced.

In the 2013 RENAME, the largest introduction of new drugs in the studied cohort was in the specialized component and there was no release of drugs with applicability in primary care. The process of developing new technologies in healthcare, particularly drugs, is long, costly, subject to failure and driven by commercial perspectives[12,41]. The drugs used in primary care are indicated for the prevention and control of major diseases from an epidemiological point of view, however their cost is not high when compared to the specialized component[36]. Specialized component drugs have a significant budget impact due to high unit value and treatment chronicity[5,36]. Health innovation reflects all the factors that influence the return on investment, and the burden of disease is just one of the factors[12,41]. The absence of new drugs for use in primary care can be explained by economic and market determinants that influence the pharmaceutical industry at the expense of national health priorities[12,39,41,44].

Important measures to optimize the use of new health system-funded drugs include therapeutic clinical guidelines, restriction criteria for prescriptions, effectiveness, and security monitoring[1,3]. Some of these measures are already incorporated by the SUS for the medicinal products of the specialized component, the HIV/AIDS program and others from the strategic component[46].

The classification of Motola et al.[31], adopted in the present study to determine the therapeutic value of drugs, considers the interrelationship between treatment availability and the therapeutic effect, addressing three areas of pharmaceutical innovation[4,47]: use context (including alternative

therapies), drug novelty (chemical, pharmacological and pharmaceutical) and impact (efficacy, safety). However, like other concepts available in the literature, the Motola algorithm does not consider the impact on public health and health services (disease severity, affected population size and possibility of introduction).

Regarding drug development, there are researchers who warn of a decline in the innovation pace in the pharmaceutical industry, however there are groups who dispute this claim. This controversy arises because different methods of defining pharmaceutical innovation are used[1,6,7,48]. A systematic review with the objective of identifying the methods used in determining pharmaceutical innovation trends developed a taxonomy of the strategies employed in the studies. These strategies were classified into four categories: number of approved drugs, therapeutic value determination, economic results and published patents[48].

Studies based on the number of approved drugs have shown positive and negative innovation trends depending on the definition used, the country and the period studied. Investigations analyzing economic results and published patents have failed to establish conclusions about the degree of innovation. However, studies published in the last decade that measured the therapeutic value reported a negative trend in the innovation of new drugs. A reduced number of drugs with important innovations was detected in all studies included in the systematic review, regardless of the method used for measuring the therapeutic value[48].

This study analyzes innovation in the perspective of the therapeutic value measurement. The number of drugs with important and moderate innovation, launched in 2003-2013 Brazil, was not high, and the same happened for the first in class, reflecting the international declining trend in the launch of innovative medicines identified in the UK, Canada, USA and other countries[6,48]. Among the first in class, a larger number of moderate and pharmacological innovations was found compared to important innovations, which highlights the relevance of employing broader concepts and not considering just the chemical innovation to define the clinical benefit of a drug[6,7].

The reduced number of drugs with important innovation in this study points to the need for Anvisa to reevaluate the criteria that guides the registration of new drugs in Brazil and to implement intersectoral actions to encourage translational research in public and private institutions and also measures that contribute to the encouragement of research productivity in the pharmaceutical field and reduce the complexity of the drug development process[6].

This study provides an overview of new drugs launched in Brazil in the last decade and an analysis from the health system perspective, presenting data important for national pharmaceutical care policy. A limitation of the research is the identification system of new drug registrations in the Official Gazette of the Union, which may have caused failures in the identification of drug registrations in Brazil. Greater accuracy would be attained if the Anvisa portal had the features presented on the FDA website.

Conclusions

New drugs launched in Brazil in the 2003-2013 period reflect the process of epidemiological and demographic transition underway in the country, with a predominance of drugs for NCDs. However, there is an imbalance between the disease burden and the number of new drugs registered, with an under-representation of drugs for cardiovascular, digestive and infectious respiratory diseases.

Research and production of drugs for neglected diseases should be encouraged by the Health System, due to their importance and health impact. The same is true for essential anti-microbials for the treatment of community and nosocomial infections, given the scenario of increasing microbial resistance.

Health policy makers, together with the pharmaceutical industry representatives, should analyze the consequences of the imbalance presented in this work to establish a list of priority medicines and strategies that will encourage the research and development of new drugs in the SUS perspective. The number of drugs with significant therapeutic innovation level was low. It is also essential to promote actions in the science and technology field that contribute to expanding the development of innovative medicines necessary for the health situation of Brazil.

Perspectives for future research, including the safety of new drugs registered in the country and the introduction of new drugs in hospitals and other health services are important to improve knowledge and contribute to pharmaceutical assistance.

Collaboration

SF Botelho has contributed to project design, data collection, analysis and interpretation, writing and critical review relevant to the content of the article, as well as being responsible for all aspects of the work in ensuring the accuracy and completeness of any part of the article. MAP Martins contributed with the design of the project, critical review and final approval of the version to be published. AMM Reis has contributed to project design, data collection, analysis and interpretation, writing and critical review relevant to the content of the article, and to follow all steps of the work in ensuring the accuracy and integrity of any part of the article.

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References

1. Godman B, Malmström RE, Diogene E, Gray A, Jayathissa S, Timoney A, Acurcio F, Alkan A, Brzezinska A, Bucsics A, Campbell SM, Czeczot J, de Bruyn W, Eriksson I, Yusof FA, Finlayson AE, Fürst J, Garuoliene K, Guerra Júnior A, Gulbinovič J, Jan S, Joppi R, Kalaba M, Magnisson E, McCullagh L, Miikkulainen K, Ofierska-Sujkowska G, Pedersen HB, Selke G, Sermet C, Spillane S, Supian A, Truter I, Vlahović-Palčevski V, Vien LE, Vural EH, Wale J, Władysiuk M, Zeng W, Gustafsson LL. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? *Expert Rev Clin Pharmacol* 2015; 8(1):77-94.
2. Catalá-Lopez F, García-Altés A, Alvarez-Martín E, Gènova-Maleras R, Morant-Ginestar C. Does the development of new medicinal products in the European Union address global and regional health concerns? *Population Health Metrics* 2010; 8:1-10.
3. Campbell SM, Godman B, Diogene E, Fürst J, Gustafsson LL, MacBride-Stewart S, Malmström RE, Pedersen H, Selke G, Vlahović-Palčevski V, van Woerkom M, Wong-Rieger D, Wettermark B. Quality indicators as a tool in improving the introduction of new medicines. *Basic Clin Pharmacol Toxicol* 2015; 116(2):146-157.
4. Godman B, Paterson K, Malmström RE, Selke G, Fagot JP, Mrak J. Improving the managed entry of new medicines: sharing experiences across Europe. *Expert Rev Pharmacoecon Outcomes Res* 2012; 12(4):439-441.
5. Guerra Júnior AA, Acurcio FA. Políticas de Medicamentos e Assistência Farmacêutica. In: Acurcio FA, organizador. *Medicamentos: políticas, assistência farmacêutica, farmacoepidemiologia e farmacoeconomia*. Belo Horizonte: COOPMED; 2013. p.13-73.
6. Ward DJ, Slade A, Genus T, Martino OI, Stevens AJ. How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012. *BMJ* 2014; 4(10):e006235.
7. Vitry AI, Shin NH, Vitre P. Assessment of the therapeutic value of new medicines marketed in Australia. *J Pharm Policy Pract* 2013; 6:1-2.
8. Maison P, Zanetti L, Solesse A, Bouvenot G, Massol J; ISPEP group of the French National Authority for Health. The public health benefit of medicines: how it has been assessed in France? The principles and results of five years' experience. *Health Policy* 2013; 112(3):273-284.
9. World Health Organization (WHO). *Priority Medicines for Europe and the World 2013 Update*. Geneva: WHO; 2013.
10. Schramm JMA, Oliveira AF, Leite IC, Valente JG, Gadelha AMJ, Portela MG, Campos MR. Transição epidemiológica e o estudo de carga de doença no Brasil. *Cien Saude Colet* 2004; 9(4):897-908.
11. Daems R, Maes E, Mehra M, Carroll B, Thomas A. Pharmaceutical portfolio management: global disease burden and corporate performance metrics. *Value Health* 2014; 17(6):732-738.
12. Martino OI, Ward DJ, Packer C, Simpson S, Stevens A. Innovation and the burden of disease: retrospective observational study of new and emerging health technologies reported by the EuroScan Network from 2000 to 2009. *Value Health* 2012; 15(2):376-380.

13. Figueiredo TA, Schramm JMA, Pepe VLE. Seleção de medicamentos essenciais e a carga de doença no Brasil. *Cad Saude Publica* 2014; 30(11):2344-2356.
14. Gava CM, Bermudez JAZ, Pepe VLE, Reis ALA. Novos medicamentos registrados no Brasil: podem ser considerados como avanço terapêutico? *Cien Saude Colet* 2010; 15(3):3403-3412.
15. Vidotti CCF, Castro LL, Calil SS. New drugs in Brazil: do they meet Brazilian public health needs? *Rev Panam Salud Publica* 2008; 24(1):36-45.
16. Hegde S, Schmidt M. To Market, To Market – 2003. *Annuals Reports of Medicinal Chemistry* 2004; 39:337-369.
17. Hegde S, Schmidt M. To Market, To Market – 2004. *Annuals Reports of Medicinal Chemistry* 2005; 40:443-473.
18. Hegde S, Schmidt M. To Market, To Market – 2005. *Annuals Reports of Medicinal Chemistry* 2006; 41:440-477
19. Hegde S, Schmidt M. To Market, To Market – 2006. *Annuals Reports of Medicinal Chemistry* 2007; 42:505-554.
20. Hegde S, Schmidt M. To Market, To Market – 2007. *Annuals Reports of Medicinal Chemistry* 2008; 43:455-497.
21. Hegde S, Schmidt M. To Market, To Market – 2008. *Annuals Reports of Medicinal Chemistry* 2009; 44:577-632.
22. Hegde S, Schmidt M. To Market, To Market – 2009. *Annuals Reports of Medicinal Chemistry* 2010; 45:467-537.
23. Hegde S, Schmidt M. To Market, To Market – 2010. *Annuals Reports of Medicinal Chemistry* 2011; 46:433-502.
24. Hegde S, Schmidt M. To Market, To Market – 2011. *Annuals Reports of Medicinal Chemistry* 2012; 47:499-569.
25. Hegde S, Schmidt M. To Market, To Market – 2012. *Annuals Reports of Medicinal Chemistry* 2013; 48:472-546.
26. Hegde S, Schmidt M. To Market, To Market – 2013. *Annuals Reports of Medicinal Chemistry* 2014; 49:437-508.
27. Eichler HG, Aronsson B, Abadie E, Salmonson T. New drug approval success rate in Europe in 2009. *Nat Rev Drug Discov* 2010; 9(5):355-356.
28. Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, Vrueh RL, Leufkens HG. Safety-Related Regulatory Actions for Orphan Drugs in the US and EU.A Cohort Study. *Drug Saf* 2010; 33(2):127-137.
29. Buckle DR, Erhardt PW, Ganellin CR, Kobayashi T, Perun TJ, Proudfoot J, Senn-Bilfinger J. Glossary of terms used in medicinal chemistry. Part II (IUPAC Recommendations 2013). *Pure Appl. Chem* 2013; 85(8):1725-1758.
30. Lexchin J. Postmarket safety in Canada: are significant therapeutic advances and biologics less safe than other drugs? A cohort study. *BMJ Open* 2014; 4:1-6.
31. Motola D, De Ponti F, Rossi P, Martini N, Montanaro N. Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. *Br J Clin Pharmacol* 2004; 59(4):475-478.
32. World Health Organization (WHO). *WHO methods and data sources for global burden of disease estimates 2000-2011*. Geneva: Department of Health Statistics and Information Systems WHO; 2013.
33. World Health Organization (WHO). Health statistics and information systems. Disease Burden. *DALY estimatives, 2002-2012*. WHO Member States, 2012 [internet]. 2012 [acessado 2015 jan 24]. Disponível em: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html.
34. Schmidt MI, Duncan BB, Azevedo e Silva G, Menezes AM, Monteiro CA, Barreto SM, Chor D, Menezes PR. Chronic non-communicable diseases in Brazil: burden and current challenges. *Lancet* 2011; 377(9781):1949-1961.
35. Barreto ML, Teixeira MG, Bastos FI, Ximenes RAA, Barata RB, Rodrigues LC. Sucessos e fracassos no controle de doenças infecciosas no Brasil: o contexto social e ambiental, políticas, intervenções e necessidades de pesquisa. *Lancet Saúde no Brasil* 2011; 6736(11):47-60.
36. Vieira FS. Gasto do Ministério da Saúde com medicamentos: tendência dos programas de 2002 a 2007. *Rev Saude Publica* 2009; 43(4):674-681.
37. Kinch MS, Patridge E. An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. *Drug Discov Today* 2014; 19(10):1510-1513.
38. Blatt CR, Santos ME, Benzaken A, Corrêa RG, Cattapan E, Sereno LS, Naveira MC. An Estimate of the Cost of Hepatitis C Treatment for the Brazilian Health System. *Value in Health JCR* 2012; 16(1):129-135.
39. Pedrique B, Strub-Wourgaft N, Some C, Olliaro P, Trouiller P, Ford N, Pécoul B, Bradol JH. The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment. *Lancet Glob Health* 2013; 1(6):371-379.
40. Milne C, Kaitin K, Ronchi E. *Orphan Drug Laws in Europe and the US: incentives for the Research and Development of Medicines for the Diseases of Poverty*. Geneva: Commission on Macroeconomics and Health; 2001. CMH Working Paper Series, Paper No. WG2: 9.
41. Fordyce CB, Roe MT, Ahmad T, Libby P, Borer JS, Hiatt WR, Bristow MR, Packer M, Wasserman SM, Braunstein N, Pitt B, DeMets DL, Cooper-Arnold K, Armstrong PW, Berkowitz SD, Scott R, Prats J, Galis ZS, Stockbridge N, Peterson ED, Califf RM. Cardiovascular drug development: is it dead or just hibernating? *Am Coll Cardiol* 2015; 65(15):1567-1582.
42. Godman B, Malmström RE, Diogene E, Jayathissa S, McTaggart S, Cars T, Alvarez-Madrazo S, Baumgärtel C, Brzezinska A, Bucsics A, Campbell S, Eriksson I, Finlayson A, Fürst J, Garuoliene K, Gutiérrez-Ibarluzea I, Hviding K, Herholz H, Joppi R, Kalaba M, Laius O, Malinowska K, Pedersen HB, Markovic-Pekovic V, Piessnegger J, Selke G, Sermet C, Spillane S, Tomek D, Vončina L, Vlahović-Palčevski V, Wale J, Wladysiuk M, van Woerkom M, Zara C, Gustafsson LL. Dabigatran - a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs. *Front Pharmacol* 2014; 5:1-11.
43. Rahman SZ, Gupta V, Sukhlecha A, Khunte Y. Lifestyle drugs: concept and impact on society. *Indian J Pharm Sci* 2010; 72(4):409-413.
44. Bradley P, Akehurst R, Ballard C, Banerjee S, Blennow K, Bremner J, Broich K, Cummings J, Dening K, Dubois B, Klipper W, Leibman C, Mantua V, Molinuevo JL, Morgan S, Muscolo LA, Nicolas F, Pani L, Robinson L, Siviero P, van Dam J, Van Emelen J, Wimo A, Wortmann M, Goh L. Taking stock: A multistakeholder perspective on improving the delivery of care and the development of treatments for Alzheimer's disease. *Alzheimers Dement* 2015; 11(4):455-461.

45. Haas M, Mantua V, Haberkamp M, Pani L, Isaac M, Butlen-Ducuing F, Vamvakas S, Broich K. The European Medicines Agency's strategies to meet the challenges of Alzheimer disease. *Nat Rev Drug Discov.* 2015; 14(4):221-222.
46. Picon PD, Beltrame A, Banta D. National guidelines for high-cost drugs in Brazil: achievements and constraints of an innovative national evidence-based public health policy. *Int J Technol Assess Health Care* 2013; 29(2):198-206.
47. Iordatii M, Venot A, Duclos C. Designing concept maps for a precise and objective description of pharmaceutical innovations. *BMC Med Inform Decis Mak* 2013; 13:1-8.
48. Kesselheim AS, Wang B, Avorn J. Defining "Innovativeness" in Drug Development: A Systematic Review. *Clin Pharmacol Ther* 2013; 94(3):336-349.

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