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Market authorization scenario for synthetic and semisynthetic drug products in Brazil

Painel de registro de medicamentos sintéticos e semissintéticos no Brasil

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ABSTRACT

Introduction: Market authorization is the government approval needed for drug product commercialization in Brazil. The requirements for market authorization were reorganized in 1999, when the Brazilian Health Regulatory Agency (Anvisa) was created and, also, when the National Police for Generic Drugs was implemented. **Objective:** About 20 year after the implementation of the Police and the creation of Anvisa, this work aimed to describe the current scenario of market authorization for synthetic and semisynthetic drug products. This scenario aims to aid the decision-making process of regulators and regulated. **Method:** We used the System of Product and Services under Health Surveilance (Datavisa) to perform the data survey regarding valid market authorizations. Access to this database is exclusive to Anvisa's employees. **Results:** We found 6,454 valid market authorizations, accounting for 7,721 different drug products. More than 80.0% of the market authorizations are for generic and similar drug products. The national companies play an important role in the Brazilian pharmaceutical market, but we still identified some difficulty related to innovation. Among the main approved categories, we could find several over-the-counter drug products and, also, antibacterials for systemic use, drug products with action in the central nervous system, antineoplasic agents, and drug product for management of metabolic syndrome. The diseases treated by these drugs are highly prevalent in Brazil. **Conclusions:** The data showed the effectiveness of the adopted policies and can be used in the formulation of new policies related to the regularization of drug product in Brazil.

KEYWORDS: Market Authorization; Generic Drug Products; Similar Drug Products; New Drug Application; National Police for Generic Drugs; Anvisa

RESUMO

Introdução: O registro sanitário é a autorização governamental necessária para que um medicamento possa ser comercializado no Brasil. As exigências relacionadas ao registro sanitário foram reestruturadas a partir de 1999 com a criação da Agência Nacional de Vigilância Sanitária (Anvisa) e com a instituição da Política Nacional de Medicamentos Genéricos. **Objetivo:** Cerca de 20 anos após a implementação desta política e a criação da Anvisa, este trabalho objetivou descrever o cenário atual de registro de medicamentos sintéticos e semissintéticos, a fim de fornecer subsídios para a tomada de decisão dos agentes reguladores e regulados. **Método:** Para realizar o levantamento dos dados referentes aos produtos registrados, foi utilizado o Sistema de Produtos e Serviços sob a Vigilância Sanitária (Datavisa), que é de acesso exclusivo aos servidores da Anvisa. **Resultados:** Foram localizados 6.454 processos de registros de medicamentos sintéticos e semissintéticos válidos, que correspondem a 7.721 produtos diferentes. Mais de 80,0% dos produtos registrados são genéricos ou similares. As empresas nacionais desempenham papel importante no mercado farmacêutico brasileiro, porém ainda é possível identificar dificuldades relacionadas à inovação. Dentre as principais categorias

registradas, estão os medicamentos isentos de prescrição médica, os antibacterianos de uso sistêmico, os medicamentos que atuam no sistema nervoso central, os agentes antineoplásicos e os medicamentos para tratamento de síndrome metabólica. As doenças tratadas por esses medicamentos possuem alta prevalência na população brasileira. **Conclusões:** Os dados apresentados demonstram a efetividade das políticas adotadas e podem ser utilizados na elaboração de novas políticas relacionadas à regularização de medicamentos no Brasil.

PALAVRAS-CHAVE: Registro; Medicamentos Genéricos; Medicamentos Similares; Medicamento Novos; Política Nacional de Medicamento Genéricos; Anvisa

INTRODUCTION

The Brazilian pharmaceutical market occupies a prominent position in the world drug products trade, possible reaching fifth place in the world ranking by 2023. This year, this market is expected to move between US$39 billion and US$43 billion, with the sale of 238 million units[1].

For these products to be marketed, it is necessary to obtain a sanitary market authorization. According to Law No. 6,360, of September 23, 1976[2], the market authorization is an "entry, in a proper book after the concessive order of the director of the Ministry of Health, under order number, of the products referred to in this Law, indicating the name, manufacturer, origin, purpose, and other elements that characterize them". In other words, the market authorization of a drug products is the authorization by a specialized government agency for a product to be manufactured and marketed[3]. Although the obligation to apply for market authorization predates the Brazilian Health Regulatory Agency (Anvisa), this process has been improved since its creation, through Law No. 9,782, of January 26, 1999[4].

Also in 1999, the generic drug policy was implemented in Brazil[5]. This policy aimed to stimulate commercial competition, improve the quality of medicines, and facilitate the population's access to drug treatment[6] and was incorporated by Anvisa through several internal regulatory acts. In 2004, the normative acts referring to the market authorization of medicines were redefined through the Medicinal Products Regulation policy in Brazil, which brought stricter rules and greater requirements for the market authorization of medicines. Among other points, this policy is based on the recognition of three main categories for the market authorization of synthetic drugs, namely: new, generic, and similar drugs[7]. Subsequently, new drugs were reclassified as new and innovative. The definitions of these four categories of products are currently found in the Resolution of the Collegiate Board of Directors (RDC) No. 200, of December 26, 2017[8], and are described below:

> XXVI - generic drug - drug similar to a reference or innovative product [reference listed drug], which is intended to be interchangeable with it, generally produced after the expiration or waiver of patent protection or other exclusivity rights, proven its effectiveness, safety, and quality, and designated by the DCB or, in its absence, by the DCI;
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> XXVII - similar drug - one that contains the same active ingredients, has the same strength, pharmaceutical dosage form, route of administration, dosage, and therapeutic indication, and which is equivalent to the reference listed drug approved by the federal agency responsible for health surveillance. It may differ only in characteristics related to the size and shape of the product, expiration date, packaging, labeling, excipients, and vehicles, and must always be identified by trade name or brand (Provisional Measure No. 2,190-34, of 2001);
>
> XXVIII - new drug - drug with a new Active Pharmaceutical Ingredient - API in the country;
>
> XXIX - innovative drug - drug with incremental innovation, with development of improvements in relation to a drug already approved in the country, including new salts, isomers or mixture of isomers, esters, or ethers of molecules previously approved [...]

Within the scope of definitions, it is also important to include "clone" drugs, which were created through RDC No. 31, of May 29, 2014[9]. This Resolution instituted the simplified procedure for market authorization, post-approval evaluation and market authorization renewal requests. Is also defined that the "clone" drug is one whose technical and clinical reports are linked to those presented in a "matrix" application process and may differ from this exclusively regarding the brand name, packaging layout, and legal information present in the package insert and labeling.

Still on drug market authorization issue, it is important to note that, is Brazil, the approval is granted for a defined period, which can be three or ten years, as established in RDC No. 317, of October 22, 2019[10]. Companies holding drug market authorization must frequently request renewals of them to update their validity. The market authorization renewal request has a term stipulated in Law No. 6.360/1976[2] and, also, in RDC No. 317/2019[10]. If a market authorization holder does not request renewal in a timely manner, the market authorization is considered lapsed and cancelled. In addition, other facts may lead to the withdrawal of the drug market authorization , such as: i) sanitary infractions on the part of the holder of the market authorization or the manufacturer of the drug product; ii) Anvisa's disapproval of the market authorization renewal request for technical reasons or assessment that the drug no

longer has a therapeutic benefit that outweighs the health risk - for example, due to new findings related to its effectiveness, safety, or quality that were not known at the time the market authorization was granted; iii) request from the holding company. Thus, it can be said that medicines have a "life cycle", which begins with the granting of their market authorization, goes through several post-approval changes, and ends with their withdrawal.

In this context, about 20 years after the creation of Anvisa and the generics policy and after the improvement of drug regulation in the country, the objective of this work was to present an overview of synthetic drugs market authorization in Brazil in the categories of new/innovative, generics, and similar, in order to provide transparency to companies and society about the Agency's work and to provide subsidies for the decision-making of regulatory and regulated agents.

METHOD

To conduct the survey of data referring to authorized drug products, the System of Products and Services under the Health Surveillance (Datavisa) was used. Datavisa is Anvisa's internal information system, which gathers data on the market authorization of products and companies, in addition to controlling the processing and archiving of documents at the Agency[11]. Although the information obtained from the system and presented in this work is publicly accessible, through Anvisa's website, the database that consolidates the information is exclusively accessible to Anvisa's servers[11].

For this work, valid market authorization were considered. So, products that filed a Product Change History (HMP) in the last two consecutive years were examined. This strategy was adopted because, to obtain the number of valid market authorization, it is necessary to consider those products that have been granted and those that are, in fact, active – that is, those ones that have not been canceled or expired. The effective withdrawal may take some time to materialize, so that a direct listing of "non-canceled" records may present an overestimated result by considering records already in the cancellation phase or already expired. On the other hand, RDC No. 73, of April 7, 2016[12], determines that the HMP must be submitted annually, in the product's anniversary month, for all active approved products. The HMP lists all changes made throughout the year or declares that there were no post-approval change in this same period[12]. Thus, an efficient way of estimating the number of valid market authorizations in a year is to list all HMPs filed in that year, since their protocol is mandatory annually for active drugs and that there will be no HMP protocol for drugs in the withdrawal phase or with an expired market authorization, even if the effective withdrawal has not yet been published by Anvisa. In this work, the HMP listing of two consecutive years was used to make it possible to double check the data, reducing errors resulting from the lack of document protocol in a specific year and avoiding the loss of products that eventually, for some reason, have been delayed in sending the HMP by one year.

Drugs classified as "clones" were excluded because they are directly linked to a matrix, thus not characterizing the variability of drugs available on the market. Then, the data were processed to include products approved in the last year, exclude medicines withdrawal in the last year, and change the market authorization holders of products that requested transfer of ownership in the last year. This update was performed on April 8, 2020.

After the initial survey, the records considered valid were reviewed for separation by pharmaceutical dosage form. The applications that contained more than one pharmaceutical dosage form were divided into two or more products, depending on the number of pharmaceutical dosage forms present. The reason for dividing products into different dosage forms was to equalize the data, since applications requested after January 11, 2015 are individualized by dosage form as requested by in RDC No. 60, of October 10, 2014[13]. It means to say that if the division was not done, the products before this date would be divided differently from the ones after.

Products with a valid market authorization were then reassessed for inclusion in the therapeutic class, according to the Anatomical Therapeutic Chemical (ATC) classification system.

The data extracted from the database were organized and processed using Microsoft Excel® version 2002 software.

RESULTS

6,454 valid synthetic drugs market authorization were located, corresponding to 7,721 different drug products. The distribution of products among the categories of new/innovative, generic, and similar is shown in Table 1. The database did not allow the market authorizations of new and innovative medicines to be separated from each other. As can be seen, more than 80.0% of the approved products are copies of other drugs that were previously on the market.

The distribution of market authorization by company is shown in Table 2. We can see that about 60.0% of the active market authorization (4,112; 63.7%) are concentrated in 30 companies. Most of these companies (17) are nationally owned.

Table 1. Market authorizations number of synthetic and semi-synthetic drugs by regulatory category.

Category	Number of market authorizations	%
Generic	2,819	43.7%
Similar	2,457	38.1%
New/Innovative	1,178	18.3%
Total	6,454	100.0%

Source: Elaborated by the authors, 2020.

Table 2. Distribution of the market authorizations for active synthetic and semi-synthetic drugs by company.

Category	Number of market authorizations	Percentage
Company 1 (National)	380	5.9%
Company 2 (National)	276	4.3%
Company 3 (National)	265	4.1%
Company 4 (National)	234	3.6%
Company 5 (National)	227	3.5%
Company 6 (National)	209	3.2%
Company 7 (National)	193	3.0%
Company 8 (National)	185	2.9%
Company 9 (National)	183	2.8%
Company 10 (National)	175	2.7%
Company 11 (National)	172	2.7%
Company 12 (National)	166	2.6%
Company 13 (National)	122	1.9%
Company 14 (Multinational)	122	1.9%
Company 15 (Multinational)	100	1.5%
Company 16 (Multinational)	96	1.5%
Company 17 (Multinational)	87	1.3%
Company 18 (Multinational)	84	1.3%
Company 19 (National)	83	1.3%
Company 20 (National)	82	1.3%
Company 21 (National)	81	1.3%
Company 22 (Multinational)	78	1.2%
Company 23 (National)	73	1.1%
Company 24 (Multinational)	70	1.1%
Company 25 (Multinational)	67	1.0%
Company 26 (Multinational)	64	1.0%
Company 27 (National)	61	0.9%
Company 28 (Multinational)	61	0.9%
Company 29 (Multinational)	59	0.9%
Company 30 (Multinational)	57	0.9%
Other companies	**2,342**	**36.3%**

Source: Elaborated by the authors, 2020.

The distribution of market authorization products by pharmaceutical dosage form is shown in Figure 1. As can be seen in Figure 1, the most frequently approved pharmaceutical dosage forms are those for oral use, especially coated tablets (1,678; 21.7%) and plain tablets (1,336; 17.3%). Other pharmaceutical dosage forms, not represented in this figure, add up to 562 products (7.3%).

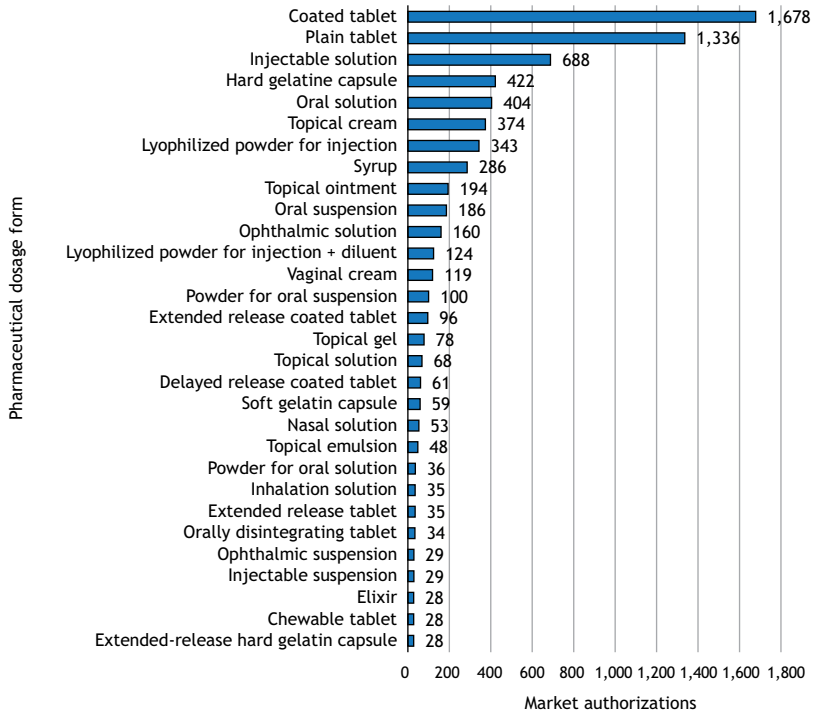
The main therapeutic classifications identified for the market authorization synthetic products are presented in Table 3. In addition to drugs normally classified as over-the-counter, such as analgesics (377; 4.9%), mostly pyrazolones (124) and anilides (116); antiinflammatory and antirheumatic drugs (370; 4.8%); antifungals for dermatological use (279; 3.6%), antihistamines for systemic use (251; 3.3%), and cough and cold preparations (224; 2.9%), is noteworthy the following numbers: antibacterials for systemic use (732; 9.5%), especially fluoroquinolones (117) and broad-spectrum penicillins (80); psychoanaleptics (343; 4.4%), especially selective serotonin reuptake inhibitors (155), and psycholeptics (299; 3.9%), with emphasis on benzodiazepine derivatives (89). We can still highlight antineoplastic agents (298; 3.9%) and products for the treatment of metabolic syndrome (ACE inhibitors, plain (223; 2.9%), diuretics (133; 1.7%), lipid-modifying agents (132; 1.7%), beta blocking agents (124; 1.6%), drugs used in diabetes (113; 1.5%), and cardiac therapy (93; 1.2%)).

The main isolated API and the main fixed-dose combination are shown, respectively, in Figures 2 and 3. We found 6,374 products (82.6%) containing isolated API and 1,347 fixed-dose combination (17.4%). A total of 886 different isolated API and 371 different fixed-dose combinations were identified. In both cases, there is a predominance of sporadic drugs, especially analgesics, antipyretics, and antimicrobials.

DISCUSSION

The granting of market authorization for medicines for human use is one of Anvisa's attributions, established in Law No. 9,782/1999[4]. According to the administrative procedures established by Anvisa, medicines can be classified into different regulatory categories, including new/innovative, generic, similar, specific, herbal medicine, dynamized, medicinal gases, biological products, radiopharmaceuticals, and low-risk medicines subject to simplified notification. New/innovative, generic, and similar drugs comprise products whose active pharmaceutical ingredients are of synthetic or semi-synthetic origin and correspond to the majority of medicines regulated by Anvisa[14,15]. Products in this category are regulated by RDC No. 200/2017[8] and RDC No. 73/2016[12].

By enabling the exchange of a reference listed drug for their generics, the National Generic Drug Policy has brought greater competitiveness to the pharmaceutical market, having been effective in regulating the price of medicines and favoring the consumer's right to choose[6]. It cannot be denied that, by encouraging competition for products with expired patents, the National Generic Drug Policy was a major driver of the national industry[16,17]. As we can see in Table 2, most companies that hold market authorization in Brazil are nationally owned and many are part of large economic groups, which were not listed in this study to prevent companies from being identified. The growth of national companies, however, did not change the structure of the Brazilian pharmaceutical market, characterized as a differentiated oligopoly[16]. The data



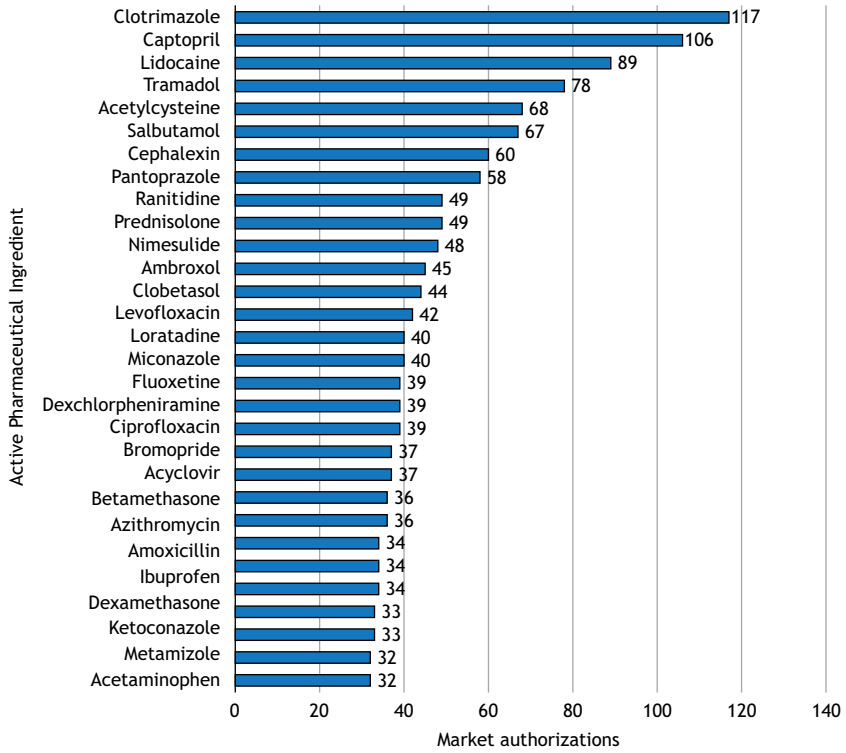
Source: Elaborated by the authors, 2020.

Figure 1. Number of synthetic and semi-synthetic market authorizations by pharmaceutical dosage form.

Table 3. Major Anatomical Therapeutic Chemical (ATC) classifications of market authorizations in the synthetic drug categories.

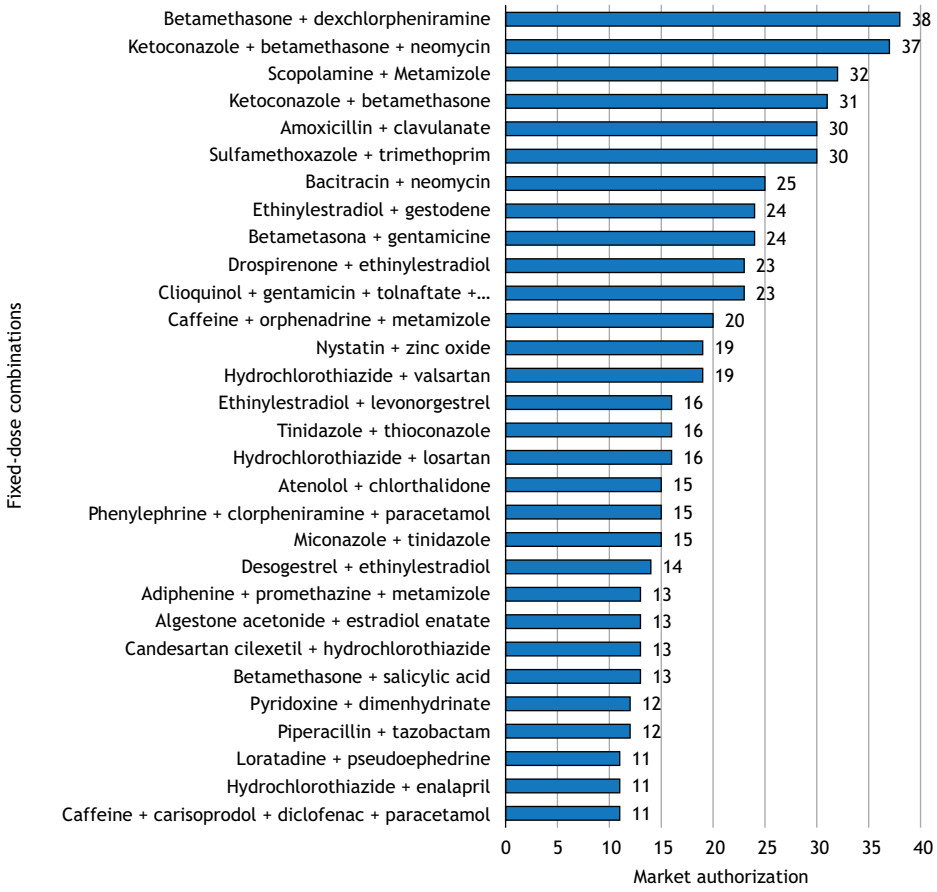
ATC code	ATC classification	No. of market authorizations	%
J01	Antibacterials for systemic use	732	9.5%
N02	Analgesics	377	4.9%
M01	Antiinflammatory and antirheumatic products	370	4.8%
N06	Psychoanaleptics	343	4.4%
N05	Psycholeptics	299	3.9%
L01	Antineoplastic agents	298	3.9%
D01	Antifungals for dermatological use	279	3.6%
G03	Sex hormones and modulators of the genital system	252	3.3%
R06	Antihistamines for systemic use	251	3.3%
N03	Antiepileptics	230	3.0%
D07	Corticosteroids, dermatological preparations	229	3.0%
R05	Cough and cold preparations	224	2.9%
C09	ACE inhibitors, plain	223	2.9%
S01	Ophthalmologicals	218	2.8%
R03	Drugs for obstructive airway diseases	181	2.3%
A03	Drugs for functional gastrointestinal disorders	178	2.3%
A02	Drugs for acidity-related disorders	164	2.1%
H02	Corticosteroids for systemic use	159	2.1%
C03	Diuretics	133	1.7%
C10	Lipid modifying agents	132	1.7%
G01	Gynecological antiinfectives and antiseptics	132	1.7%
J05	Antivirals for systemic use	130	1.7%
C07	Beta blocking agents	124	1.6%
G04	Urologicals	117	1.5%
A10	Drugs used in diabetes	113	1.5%
D06	Antibiotics and chemotherapeutics for dermatological use	97	1.3%
J02	Antimycotics for systemic use	96	1.2%
C01	Cardiac therapy	93	1.2%
Other classifications		1,547	20.0%
Total		**7,721**	**100.0%**

Source: Elaborated by the authors, 2020.



Source: Elaborated by the authors, 2020.

Figure 2. Main Active Pharmaceutical Ingredients (API) isolated approved.



Source: Elaborated by the authors, 2020.

Figure 3. Main fixed-dose combinations approved.

from the present study show that more than half of the active market authorization are concentrated in 30 companies. Such data corroborate those published by the Drug Market Regulation Chamber (CMED) on the market concentration index, which indicate that 78% of the commercialized therapeutic subclasses were classified as highly concentrated[18,19].

Although it was effective in strengthening the national pharmaceutical industry, this policy did not generate great incentives for innovation in the country. Data observed in Table 1 indicate a high number of market authorization in the form of copies. The difficulty of innovation is also expressed in the authorized pharmaceutical dosage forms, as indicated by the data presented in Figure 1. Pharmaceutical dosage forms that require greater technology for their development, such as prolonged and delayed release tablets and capsules containing or not microgranules; orally disintegrating tablets; transdermal patches; chewable tablets and chewing gum; aerosol solutions and suspensions; inhalation powder; implants, intrauterine device (IUD), and colloidal dispersion, correspond to 4.1% (313 products) of the authorized pharmaceutical dosage forms. If the prolonged and delayed release tablets and capsules are removed, only 189 products (2.4%) are found. These data reinforce the lack of stimulus to innovation in the Brazilian pharmaceutical market. The development of pharmaceutical dosage forms that reduce the dosage regimen or that facilitate administration is a positive strategy for increasing patient adherence to the prescribed treatment[20]. Even so, the pharmaceutical dosage forms mentioned would no longer be considered modern in view of what is already discussed in relation to personalized medicine, such as the printing of 3D tablets or capsules containing electronic devices[21].

In Figure 1, we can also observe the main pharmaceutical dosage forms approved in Brazil. Due to the ease of administration and its amenities, oral dosage forms are the ones that stand out the most. Next, we can identify injectable drugs, which are mainly used in a hospital environment and, although they do not have all the comforts of oral products, they are sometimes the most appropriate alternative, as they have a higher speed of action, greater bioavailability, and less susceptibility to initial hepatic metabolism (first pass effect). Thirdly, there are topical medications, which are mostly used for local release of actives.

Regarding the most approved therapeutic categories in the country (Table 3), the antibacterials for systemic use stands out in the first place, mainly fluoroquinolones and broad-spectrum penicillins. Consumption data demonstrate consonance with the market authorization of such classes of antimicrobials. In a survey carried out by the World Health Organization (WHO), Brazil has an average use of antibacterials for systemic use (ATC J01) corresponding to 22.75 doses per day, higher than the average in Europe and other American countries. Penicillins were the most frequently consumed group of antibiotics, representing 53% of total consumption, while quinolones represent 12% of total consumption of these products[22]. Antimicrobials for systemic use are also listed among the main approved assets, as can be seen in Figures 2 and 3. Although they are prescription drugs, until 2011 these products could be purchased in pharmacies without a prescription. The data presented here indicate the high availability of this type of medication on the market and reinforce the need for policies to control the use of antimicrobials, such as RDC No. 20, of May 5, 2011[23], as a strategy to prevent antimicrobial resistance.

Other prominent categories are drugs for the treatment of the central nervous system – psychoanaleptics and psycholeptics occupy the fourth and fifth positions respectively in Table 3, with emphasis on fluoxetine in Figure 2. This data are in agreement with the information presented by the WHO, which indicates a high prevalence of psychiatric disorders in the Brazilian population. According to the institution, Brazil leads the world ranking in the prevalence of anxiety disorder (9.3%) and is fifth in the prevalence of depression (5.8%)[24,25]. Another therapeutic class worth mentioning are antineoplastic agents, the sixth most approved therapeutic category in the country. The data corroborate the information found in the literature that cancer is one of the main causes of death in Brazil[26] and in the world[27,28]. Also, it is worth mentioning the market authorization of products of therapeutic classes related to the treatment of metabolic syndrome (antilipemics, antihypertensives, and drugs for the treatment of diabetes), with emphasis on the associations of hydrochlorothiazide with other antihypertensives (Figure 3), justified by the high prevalence of this syndrome in the population (from 12.3% to 44.6% in South America, depending on the criterion used)[29].

Both in Table 3 and in Figures 2 and 3, we can identify the presence of different classes of products and active principles commonly categorized as over-the-counter drugs (OTC). We highlight the presence of analgesics, such as paracetamol and metamizole, anti-inflammatory drugs, such as ibuprofen, and antifungals for topical use, such as ketoconazole and miconazole. These medications are used to treat symptoms common to various diseases, such as fever, inflammation, headache, and general pain. According to IQVIA data, OTCs represent 31% of the Brazilian pharmaceutical market[30]. In this scenario, there are initiatives being taken to simplify the market authorization of these drugs. The main one is the inclusion of some of these products (paracetamol-based drugs – solution, suspension, and tablets, miconazole nitrate – all authorized pharmaceutical dosage forms –, and ketoconazole – cream) in the list of low-risk products, subject to simplified notification, as suggested in Public Consultation No. 819, of June 1, 2020[31]. As previously described, these API are on the list of products with a high number of market authorization application. This simplification of the process should not be seen as a simple stimulus to new application or even as a justification for reducing the quality of the products. It is, in fact, a rationalization of work processes, in which the workforce available at Anvisa will be allocated to the assessment of more complex applications and greater health risk products. It is important to clarify that products subject to simplified notification must comply with the same quality requirements established for drug products submitted via market authorization application process.

Among the limitations of this study, we can highlight the difficulty in obtaining accurate data regarding valid market authorization. Since an automatic database is not available, several manual treatments were performed to obtain the data. It is understood that the availability of a database with more accurate data on the market authorization would be beneficial to facilitate research such as the one presented in this work and to ensure greater transparency of the data produced by the Agency for the productive sector and for society.

CONCLUSIONS

The data presented allowed us to outline the current scenario of market authorization in Brazil, which was directly influenced by the National Generic Drug Policy, presents national companies as protagonists, and demonstrates Anvisa's effective work in making medicines available to the Brazilian population. The scenario outlined can be used by regulatory and regulated agents to propose new policies to improve the market authorization process in Brazil.

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Author's Contributions

Franca JR – Conception, planning (study design), data acquisition, analysis and interpretation and writing of the work. Carmo ACM – Data analysis and interpretation and writing of the work. Pereira RS – Data collection. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.

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