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Analysis of sanitary legislation to subsidize the obtainment and adaptation of registration of medicines destined to neglected diseases

Análise da legislação sanitária para auxiliar na obtenção e na adequação do registro de medicamentos destinados às doenças negligenciadas no Brasil

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ABSTRACT

Introduction: The sanitary registration is a precondition for the commercialization of a medicine in the national market. **Objective:** This manuscript makes a critical analysis of Brazilian sanitary legislation to subsidize the obtainment and adaptation of registration of medicines destined to neglected diseases. **Method:** The development of this article was based on a critical analysis of the legislation available on the website of the National Agency of Sanitary Surveillance (Anvisa). This analysis was compared with international guidelines, in addition to the daily practice of the Regulatory Affairs Sector of an Official Pharmaceutical Laboratory. **Results:** The data obtained showed that there is no specific legislation for registration and post-registration of medicines for neglected diseases. Thus, there are gaps in the legislation applicable to these drugs. The absence of reference drugs in Brazil, and the lack of active ingredient suppliers that comply with current legislation, impairing the adequacy of these registries and obtaining new record are examples of the existing gaps. **Conclusions:** Nowadays, keeping a record of this class of medicine at Anvisa becomes a significant challenge, and each registry must be explicitly treated with the regulatory agency.

KEYWORDS: Health Legislation; Drugs; Neglected Diseases

RESUMO

Introdução: O registro sanitário é um pré-requisito para a comercialização do medicamento no mercado nacional. **Objetivo:** Este manuscrito faz uma análise da legislação sanitária brasileira para auxiliar na obtenção e na adequação do registro de medicamentos destinados às doenças negligenciadas, verificando se as dúvidas e dificuldades, no momento de se montar o dossiê para esta categoria de medicamentos, são dirimidas. **Método:** O desenvolvimento deste artigo baseou-se numa análise crítica das legislações disponíveis no sítio eletrônico da Agência Nacional de Vigilância Sanitária, além de compará-las com guias internacionais, somada à prática diária do Setor de Assuntos Regulatórios de um Laboratório Farmacêutico Oficial. **Resultados:** Os dados obtidos demonstraram que não há uma legislação específica para registro e pós-registro de medicamentos destinados às doenças negligenciadas. Assim, percebe-se que há lacunas na legislação aplicável a estes medicamentos, como por exemplo: a ausência de medicamentos de referência no Brasil e a falta de fornecedores de insumos ativos que atendam à legislação vigente, prejudicando a adequação destes registros e a obtenção de novos registros. **Conclusões:** Manter um registro desta classe de medicamento na Anvisa nos dias atuais torna-se um grande desafio, tendo que cada registro ser tratado especificamente junto à agência reguladora.

PALAVRAS-CHAVE: Legislação Sanitária; Medicamentos; Doenças Negligenciadas

INTRODUCTION

In 1999, the Brazilian National Health Surveillance System (SNVS) was transferred to the National Health Surveillance Agency (Anvisa), which was regulated by Law n. 9.782 of January 26 that year. This legislation assigns Anvisa the institutional role of promoting the protection of the health of the population through the sanitary control of the production and marketing of products and services subject to health surveillance, through sanitary control of the production and marketing of products and services that, either directly or indirectly, relate to health, including all stages and processes, from production to consumption, as well as the control of ports, airports and borders[1].

Prior to the creation of Anvisa and generics, drugs were limited to two categories: innovative drugs with new molecules and similar drugs, which are copies of innovative drugs without patent protection[2]. Thus, not only did generics make up a new category of products for Anvisa, since they set a new standard for the development and marketing authorization of drugs in Brazil[3], they also paved the way for the selectivity of specific categories that have specific requirements, like biological products, plant-based drugs, among others.

Since 2003, Anvisa has equated similar drugs with generic drugs by requiring bioequivalence tests for the marketing authorization of these branded drugs. This had an impact on the work of the Official Pharmaceutical Laboratories (OPL), which faced challenges to achieve compliance with the requirement to conduct bioequivalence studies for the marketing authorization of generic and similar drugs, including those already registered. That situation is worsened by the bidding process for the acquisition of active pharmaceutical ingredients[4]. Drugs for neglected diseases have been directly impacted by such a regulatory measure for the adequacy of their marketing authorizations, since these drugs can be registered as new, generic and similar, depending on their therapeutic features, their active pharmaceutical ingredient and their pharmaceutical form. Today, in 2018, the legislation that establishes the criteria for granting and renewing the marketing authorization of drugs with synthetic and semi-synthetic active ingredients classified as new, generic and similar is Resolution of the Board of Directors (RDC) n. 200, of 26 December, 2017[5]. RDC n. 73, of April 17, 2016[6], is the regulation that regulates post-authorization changes, cancellation of marketing authorization of drugs with synthetic and semi-synthetic active ingredients. At present, these laws generally provide for the marketing authorization and post-authorization of drugs for neglected diseases in Brazil.

Neglected diseases, according to the World Health Organization (WHO), are designated as neglected to a greater or lesser degree, because of their following inherent peculiarities: the affected persons usually live in remote rural areas; incipient investment in research and development; lack of appropriate control tools; the burden of the disease is poorly recorded and managing diagnosis, treatment and follow-up is difficult[7]. However, considering a more modern concept, we should think of a "neglected population" rather than a "neglected disease", after all, the issue of access to medicines is no longer restricted to low-income countries or to a limited scope of diseases[8].

One of the actions of the Brazilian government in healthcare is the promotion of the public production of medicines by treating the OPL as a national asset. This highlights the importance of technological sovereignty in order to minimize Brazil's foreign dependence and thus ensure national security. OPLs act not only in manufacturing, but strategically as inducers of research, innovation, development of formulations and new drugs, as well as regulators of prices in the domestic market[9]. The OPL's main mission is the production of drugs from the National Drug List to meet the demands of the Single Health Service (SUS)[9].

On the other hand, the National Medicines Policy, as an essential part of the National Health Policy that aims to guarantee access to essential drugs, is a prerequisite for the effective implementation of actions that are capable of improving the conditions of the health care given to the population, considering the principles and guidelines of SUS. This policy defines guidelines and priorities related to the inspection, quality control and assurance legislation, selection, acquisition and distribution, rational use of drugs, human resource development and scientific and technological development[10].

Therefore, the Strategic Component of Pharmaceutical Assistance (CESAF) intends to ensure access to drugs and supplies for the prevention, diagnosis, treatment and control of specific diseases and conditions addressed by SUS strategic healthcare programs. CESAF provides medicines for people suffering from tuberculosis, leprosy, malaria, leishmaniosis, Chagas' disease, cholera, schistosomiasis, filariasis, meningitis, onchocerciasis, plague, trachoma, systemic mycoses and other diseases that are related to and perpetuate poverty[11].

However, the neglected diseases that affect 90% of the population receive about 10% of the investment destined for research and development in health. This is a mismatch caused by the pharmaceutical industry, which neglects research and development of drugs for diseases that are related to poor living conditions[12].

In this scenario, researchers in the area of neglected diseases are engaged in modeling scenarios aimed at eliminating these diseases, considering not only the demands for new therapies, but also the treatments and tools that already exist, with the massive application of preventive therapies, improvement of existing technologies, implementation of vector control actions and education[13].

The main objective of this study was to analyze the Brazilian sanitary legislation to inform the procedures for obtaining and adjusting the marketing authorization of drugs for neglected diseases, checking whether there are answers to the questions and obstacles found in the routine of the Regulatory Affairs Sector, mainly at the moment of preparing the dossier for this category of drugs. Furthermore, we wrote a topic on the advantages of the marketing authorization of this class of drugs in Brazil and a brief presentation of the main international regulations on the marketing authorization of drugs for neglected diseases.

METHOD

We researched the Anvisa database on www.portal.anvisa.gov.br. The following keywords were used in the search on Anvisa's site: "*registro de medicamentos*" (marketing authorization); "*pós-registro*" (post-authorization); "*doenças negligenciadas*" (neglected diseases).

The bibliographic search was done in June 2018. The documents dated from 1999 to June 2018 were analyzed critically, i.e. documents referring to neglected disease drugs, in addition to the legislation currently in force for marketing authorization and post-authorization, were read and analyzed in their entirety. We checked whether there were answers for the questions and obstacles found in the preparation of dossiers for the marketing authorization and post-authorization of this class of medicines in Anvisa. Other documents that did not deal specifically with neglected diseases but were found using the "*registro de medicamentos*" and "*pós-registro*" keywords had only their abstracts analyzed. The results were presented and discussed in the topic of "Marketing authorization and post-authorization of drugs for neglected diseases in the Brazilian context". We also assessed the analysis prioritization mechanism for this category of drugs, as well as other measures adopted by Anvisa to expedite marketing authorization and post-authorization analysis, as presented in the topic "Advantages of the marketing authorization of drugs for neglected diseases in the Brazilian context". To prepare this item, we analyzed the legislation on the topic of prioritization of analysis, extracted from the Anvisa website as previously described.

Finally, we studied the main literature on this type of medicine in the international context. To achieve this objective, we searched the official documents published by the Food and Drug Administration (FDA) of the United States and the European Medicines Agency (EMA) of the European Union on their respective websites: www.fda.gov and www.ema.europa.eu. In these websites, we searched for "neglected diseases" keyword. This bibliographic search was carried out in June 2018, and the documents from January 2005 to December 2014 were analyzed. These results were addressed in the topic of "Marketing authorization of drugs for neglected diseases in the international context". It is worth noting that the personal contributions of the authors of this article have increased the complexity of this study, since they work in the Regulatory Affairs Sector of a large OPL, which has a large portfolio of drugs for neglected diseases, and routinely participate in meetings and discussions with Anvisa.

RESULTS AND DISCUSSION

Marketing authorization and post-authorization of drugs for neglected diseases in the Brazilian context

We found 324 records with the "*registro de medicamentos*" expression on Anvisa's website. We read all the abstracts of these 324 documents. Therefore, we can state that in Brazil there is no specific regulation that guides the marketing authorization of drugs destined to the treatment of neglected diseases. In this scenario, after the results found in this research and the experience acquired in the Regulatory Affairs Sector, we verified that in today's regulatory framework edited by Anvisa, there is enforcement of the legislation that regulates the criteria for marketing authorization and authorization renewal of new, generic and similar drugs, RDC n. 200/2017, for the marketing authorization of drugs for neglected diseases. However, because this legislation is not specific for drugs for neglected diseases, it has significant gaps and is not fully adequate to the various situations inherent in this category of drugs. Consequently, in the routine of the Regulatory Affairs Sector within a pharmaceutical company, there are some challenges and questions when it comes to preparing a dossier for the marketing authorization of drugs for neglected diseases. One of the challenges faced in the new drug category lies in the conduction a clinical study without an international reference drug chosen to subsidize the evaluation by the national regulatory bodies, which hinders the suppression of new complete clinical trials with the drug in question.

On the other hand, the drugs already authorized for neglected diseases in Brazil are categorized, for the most part, as similar. One of the regulatory requirements in RDC n. 200/2017 for the marketing authorization of similar drugs is the submission of bioequivalence studies. This test is also required for some post-authorization changes. However, the lack of reference drugs in Brazil often leads to non-compliance with this regulatory requirement, that is, the non-presentation of relative bioavailability, which is another recurring question in regulatory practice. In this context, the bioequivalence study is not feasible, due to the lack of a drug of choice for comparison, either for marketing authorization or for post-authorization purposes, which hampers the process of technological evolution of the product itself. For example, by undergoing incremental innovation as a result of improvement in its technological process, in order to guarantee greater safety and efficacy to the population, this drug generates a barrier due to the non-existence of the reference comparison product for relative bioavailability or biowaiver studies. Unfortunately, this is not provided for by any health-related document. It is therefore necessary to request a meeting with Anvisa, in most cases, to deal specifically with each change related to this class of drugs, which causes delays in dossier submission.

A feasible alternative would be recognition by Anvisa of the drugs on the lists of reference drugs of international organizations, such as WHO, FDA and EMA.

From the application of the international reference drugs as comparison, the problem of the absence of relative bioavailability studies for most of these drugs in Brazil would be remedied. Furthermore, in view of the satisfactory results of these studies, drugs authorized in Brazil could be eligible to be part of the national reference drugs list. This action would expedite the post-authorization process of these products, making national references available to the national market, encouraging other companies to register the same product in Brazil.

With the "*pós-registro de medicamentos*" keyword, we found 58 records, none of which is specific for post-authorization of drugs for neglected diseases. Now using the "*doenças negligenciadas*" term, six records were found. They were read in their entirety and only two of them are in force: RDC n. 204, of December 27, 2017, which provides for the classification in the priority category of authorization requests, post-authorization requests and prior consent in clinical research, and RDC n. 57, of November 17, 2009, which provides for the authorization of active pharmaceutical ingredients.

In order to make the marketing authorization process more adequate, it is important to highlight the current legislation. RDC n. 73/2016 provides for post-authorization changes, cancellation of authorization of drugs with synthetic and semi-synthetic active ingredient. Since there is no specific legislation, as previously mentioned, this legislation is also used for post-authorization of drugs for neglected diseases.

When analyzing RDC n. 73/2016, we can state that some important changes were implemented after its publication. Among the new regulatory requirements listed by this regulation and aiming at continuous improvement, Anvisa assigned shared responsibility to the regulated sector, as well as the need for a critical and multidisciplinary evaluation of the changes. The diversification of categories of amendments and requests provided for by RDC n. 73/2016 defined a greater number of types of amendments as having immediate implementation. This means that these do not require prior approval by Anvisa before their implementation and are classified as low sanitary risk. This enables Anvisa to optimize its flow of responses and the focus on the on the requests with greater complexity and sanitary risk.

With the knowledge acquired in the Regulatory Affairs Sector, we noticed that Anvisa has issued some revisions of existing legislation and expanded its regulations for new categories of drugs. This can be observed in the proposal of special procedures for marketing authorization of new drugs for treatment, diagnosis or prevention of rare diseases. Another example involves proposals for the revision of the resolutions that deal with the establishment of procedures used in the cases of reference drugs that are not available in the domestic market and for their classification in the priority category, marketing authorization requests, post-authorization and prior consent in clinical research.

Initiatives to review the legislation on reference drugs and to include new categories to be considered are a great opportunity to discuss alternatives to include the requirements of drugs for neglected diseases.

Another challenge that pharmaceutical companies face to get a drug's marketing authorization is that - due to the low cost of drugs for neglected diseases and the continuous revision of drug regulations, especially with regard to active pharmaceutical ingredients - it is more difficult to qualify companies that are capable of offering these ingredients at such low cost with the quality required by Brazilian legislation. Added to this fact, OPLs, in the condition of public laboratories that produce according to the demand of the Public Health Programs of the Ministry of Health, are faced with an additional impasse: to negotiate the quality of active pharmaceutical ingredients with no guarantee of purchase.

The cases not covered by any of the situations provided for in the legislation could be treated as a priority by Anvisa and integrated with the Ministry of Health and its programs, through collaborative participation of the companies responsible for the development, production and marketing of these products, which are so relevant to public health in Brazil.

On the other hand, Anvisa adopted a different procedure in the case of the submission of products under development from the Partnerships for Productive Development, published by Resolution n. 02 of July 1, 2011, which could be extended, for example, to the development of drugs for neglected diseases, since it provides for the possibility of submitting marketing authorization dossiers to Anvisa in stages, thus allowing a closer follow-up by Anvisa, as well as obtaining support and alignment among Anvisa's team and the company responsible for product development.

In view of this discussion, the maintenance of the authorization for drugs destined to neglected diseases in the Brazilian market, with an up-to-date technology, is a big and continuous responsibility, since investment of national or foreign capital for the development and redevelopment of these products is scarce, leaving the Brazilian government alone to fill this gap. For this reason, the Brazilian government has its OPLs play a crucial and challenging role in keeping the authorizations of drugs for neglected diseases compliant with new legislation, even if the new regulations are not specific for these drugs, as demonstrated in this topic. Moreover, it is important that OPLs have proposals for incremental innovation and work on the development of new therapies to be used in the fight against neglected diseases.

After analyzing the documents that support this topic, we verified the existence of a mechanism of prioritization of analysis for drugs for neglected diseases. Therefore, we conducted a survey on the "prioritization of analysis" mechanism allowed by Anvisa for this category of drugs, the results of which are described below.

Advantages for the marketing authorization of drugs for neglected diseases in the Brazilian context

Among the six documents found when using the term "neglected diseases", five referred to the prioritization of request analysis, namely: Resolution n. 28 of April 4, 2007, Resolution n. 16 of March 13, 2008, Resolution n. 57 of December 20, 2013, Resolution n. 37 of June 16, 2014, and Resolution n. 204/2017. Considering this legislation, there is an advantage for neglected disease drugs, which will be discussed next.

As has been reported, ever since its creation, in 1999, Anvisa has not issued any specific regulations to guide the marketing

authorization of drugs for the treatment of neglected diseases. However, as a result of the increase in the number of companies regulated by Anvisa and an increase in sanitary legislation, there has also been an increase in the number of processes submitted to the evaluation of this agency. Therefore, Anvisa created an instrument of analysis prioritization in 2007, addressed in RDC n. 28/2007. Based on the segmentation of drug categories, like those intended for the treatment of neglected diseases and attribution of the prerogative of some categories, they receive the analysis prioritization within a stipulated period of 90 days[14].

The granting of analysis prioritization to the marketing authorization processes and authorization changes in this category constitutes the only piece of legislation of Anvisa to conceptualize neglected diseases. They are conceptualized as those that do not present economic appeal for the development of drugs or that mainly affect the population of developing countries. That is the only Anvisa instrument that is specific about the regulation of drugs for neglected diseases. RDC n. 28/2007, which is currently repealed, assumed the need to promote the rational use of drugs in order to guarantee the population's access to essential drugs for health, adopting a measure with the objective of expediting the analysis of the requests that fit into one of the conditions presented in the Figure, through validation by the technical committee of Anvisa's general drug management.

Over time, Anvisa has enacted new legislation on this subject, for example, RDC n. 37/2014 and RDC n. 57/2013. RDC n. 37/2014 revoked RDC n. 57/2013, which preceded it, on the definition of criteria for the prioritization of technical analysis, maintaining the requirements defined by RDC n. 57/2013 and, at the same time, promoting their expansion and enabling the framework to obtain prioritization in situations like incremental and radical innovation, unprecedented generic or similar authorization, and several requests for post-authorization[15].

Recently, in 2017, Resolution n. 204 replaced RDC n. 37/2014, making available to the regulated sector new criteria for framing the priority category, for verification of concepts and compliance with Law n. 13.411, of December 28, 2016, which amended Law n. 6.360, of September 23, 1976, and addresses, among other topics, deadlines established for final decision on marketing authorization processes and post-registration changes, as well as the criteria established for transparency and predictability to the process of granting marketing authorization of drugs and post-authorization changes.

RDC n. 204/2017, on the one hand, inserted new categories of drugs in the priority classification, which may enjoy the prerogatives of the analysis period provided for in Law n. 13.411/2016. The regulation provides that in the application for marketing authorization or post-authorization, the applicant company must select the option of ordinary or priority request and, if it is a priority, it must present a justification based on the framework criteria established by RDC n. 204/2017. However, unlike other resolutions issued by Anvisa on this subject, RDC n. 204/2017 limited the granting of prioritization of post-authorization of drugs for neglected diseases only to cases of new therapeutic indication or expansion of use. Other cases should respect the deadlines of the ordinary request[16].

It is important to emphasize that Anvisa's analysis prioritization aims to rationalize the process of analysis of marketing authorization and post-authorization dossiers subject to the priority category, in addition to improving access to pharmaceutical assistance. The fact that the analysis prioritization comprises the drugs for neglected diseases denotes that Anvisa recognizes the importance of these drugs for public health.

Over time, Anvisa adopted other measures to expedite the approval of new authorizations and the implementation of changes to existing authorizations for drugs for neglected diseases, as highlighted in the Chart, which was based on the evaluation of all the legislation read in this article and the experiences acquired in the routine of the Regulatory Affairs Sector. In this framework are compiled the measures adopted from 2007 to 2017, with the purpose of reducing the time of analysis by Anvisa.

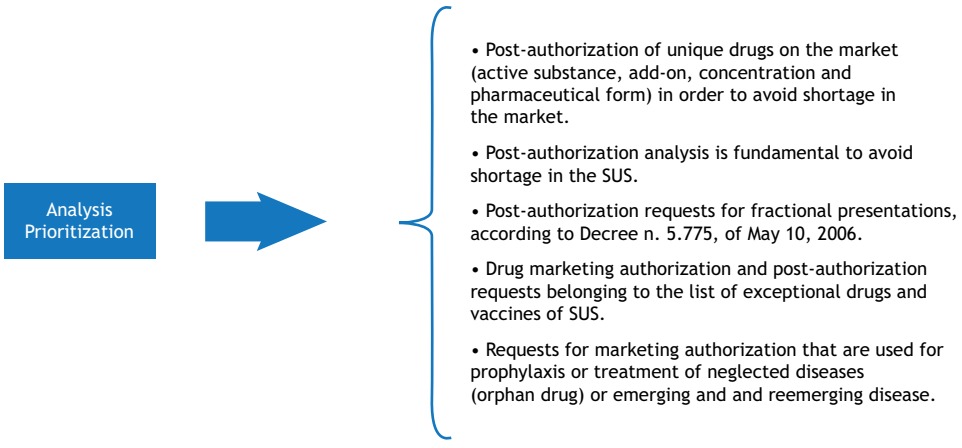

Figure. Criteria for analysis prioritization according to RDC n. 28/2007.

Chart. Measures adopted by Anvisa to reduce the time taken to analyze drugs for neglected diseases.

MEASURES ADOPTED TO REDUCE TIME OF ANALYSIS	
Resolutions n. 28/2007; n. 57/2013; n. 37/2014 and n. 204/2017	· Prioritization of analysis (marketing authorization and post-authorization) · Criteria for prioritization: first generic; national immunization program; rare, neglected or emerging disease; PPD; shortage or radical innovation in the country.
Resolution n. 73/2016	· Post-authorization Immediate implementation for minor and expected changes to Product Change History
Resolution n. 31/2014	· Simplification of clone requests
Actions to reduce the number of requirements	· Publication of regulatory guides · Publication of questions and answers (FAQ) · Assistance to companies in discussion sessions · Workshops with the regulated sector

Marketing authorization of drugs for neglected diseases in the international context

We found some documents in international databases, as described in the method. However, because of the importance of treating neglected diseases, we chose two papers that were presented and discussed briefly: the American guide *Guidance for Industry Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention* from the FDA and European standard EMEA/CHMP/5579/04.

It has been found that the development of drugs for treatment or prevention of neglected tropical diseases in developing countries is the topic of this FDA-specific guide for the industry. It determines actions to drive a drug development program aimed at treatment or prevention of neglected diseases[17]. This guideline clarifies that FDA's commitment to enabling access to indicated therapies for neglected diseases that are likely to reduce the mortality and morbidity associated with these diseases through the exercise of its regulatory authority can approve drugs for the treatment of neglected diseases that are not endemic in the United States or those whose clinical development has occurred outside the United States. However, the regulatory criteria for endemic drug approval are the same for the steps of approval of a neglected disease drug[17].

In the United States and in developed countries, neglected diseases are rare or non-existent, on the other hand, they are widespread in developing countries. Therapies for neglected diseases may benefit the population globally, including the United States in the case of tuberculosis, but mainly developing countries, where there is no incentive to the development of these drugs[18].

FDA guidelines emphasize that in the United States there is a prerogative of prioritizing the analysis of drugs for neglected disease and the submission immediately afterward, regardless of the therapeutic class of the drug, establishing the necessary requirements for the preparation of a dossier of marketing authorization of a medicinal product intended for the treatment of neglected diseases. Thus, if the company requests marketing authorization of a neglected disease drug and, after that, of a generic drug, the company will have its analysis prioritized in both submissions[17]. If we draw a comparison with the Brazilian legislation, we can see that Anvisa grants the prioritization of analysis of drugs for neglected diseases, however, the Brazilian agency will not prioritize other requests submitted right afterward.

In Europe, European Union health regulations have legislation to stimulate the launching of rare disease products in this region, offering prerogatives to pharmaceutical companies in terms of speed of approval and market exclusivity. However, it is limited to rare diseases, which affect no more than 5 out of 10,000 people in the European Union and includes market exclusivity for 10 years[18]. Neglected diseases in the European Union are rare diseases, given their low incidence in Europe.

At the same time, the EMA, through its *Committee for Medicinal Products for Human Use* (CHMP), in the framework of its cooperation with the WHO, has developed in 2005 a regulation for the evaluation of drugs intended exclusively for markets outside the European Community, with the purpose of providing scientific assistance to non-member countries and at the same time expediting the access of these countries to new pharmaceuticals[19]. EMEA/CHMP/5579/04 ruling plays a supportive role for WHO by using its regulatory rigor to harmonize the intended products in markets outside the European Community with its seal. The final opinion of the CHMP for the evaluated products should present favorable conclusions that support quality, safety and efficacy, taking into account the risk/benefit relationship under the conditions of use documented by clinical data[19].

This cooperation mechanism allows the EMA to assist in the evaluation, for example, of processes for obtaining the marketing authorization of neglected diseases, in compliance with the regulatory rigor provided by the CHMP.

EMEA/CHMP/5579/04 emphasizes the need to respond to the protection of public health through assistance to non-member countries, i.e. CHMP's scientific advice is directed to markets outside the European Community, in order to prevent or treat diseases of relevant public interest. Applicant companies have the opportunity to discuss with EMA experts all matters of legal and regulatory procedures related to the proposed submission, including the prerogative of pre-submission meetings.

This EMA support system for these products is not foreseen by Anvisa, since Brazilian legislation does not provide for specialized support for these relevant products in the field of public health. Anvisa is restricted to scheduling technical hearings to discuss one-off issues, and the marketing authorization dossier is treated within broad categories that do not consider its relevance of public health.

CONCLUSIONS

Current Brazilian health legislation cannot answer some of the questions that arise in regulatory practice, especially when it

comes to preparing dossiers for obtaining marketing authorization and post-authorization of drugs for neglected diseases, causing delays in the submission of these documents to Anvisa.

In view of this fact, the gaps evidenced in the health legislation on drug marketing authorization have led to the conclusion that it is extremely urgent for Anvisa to harmonize the marketing authorization and post-authorization requirements to be applied for neglected diseases in a consolidated and official manner by the available means. This is particularly urgent for those that do not have a reference drug in the country and do not fit as new drugs either.

If the regulatory legislation is specific and provides for systematic mechanisms for the marketing authorization and post-authorization of drugs for neglected diseases, difficulties such as the lack of suppliers of active ingredients that conform to the Brazilian legislation will decrease. Furthermore, by promoting the standardization of drugs for neglected diseases offered to the Brazilian population, this could encourage companies to improve existing formulations, generating incremental innovation to these products. This is the only way we can prevent shortages and encourage the production of these drugs using newer manufacturing technologies.

In this context, among other actions to facilitate the marketing authorization and post-authorization of drugs for neglected diseases, we suggest that Anvisa begin to officially recognize international reference drugs whenever there is no Brazilian reference for comparison to be used in studies of bioequivalence, in addition to allowing a differentiated submission for the marketing authorization of this class of drugs, as is already done for drugs resulting from the Partnership for Productive Development.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.