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Analysis of the regulatory scenario for the renewal of registration of generic and similar drugs at the National Health Surveillance Agency: subsidy to the health regulation of post-registration of drugs

Análise do cenário regulatório da renovação de registro de medicamentos genéricos e similares na Agência Nacional de Vigilância Sanitária: subsídio à regulação sanitária do pós-registro de medicamentos

Henrique Mansano Rosa Oliveira*

Agência Nacional de Vigilância Sanitária (Anvisa), Brasília, DF, Brasil

* **E-mail:** henrique.mansano@anvisa.gov.br

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ABSTRACT

Introduction: The publication of the Resolution of the Collegiate Directorate of the Brazilian Health Regulatory Agency (Anvisa) No. 200, of December 26, 2017, made the analysis of petitions for renewing the registration of medicines would become a lesser activity complexity. However, the number of automatic registration revalidations remains expressive. In addition, rejections of these petitions continue to occur. **Objective:** Characterize the outcomes of the analyzes of these renewals and quantify the number of automatic renewals of registration of generic and similar drugs. **Method:** Retrospective analysis of requests for renewal of registration of generic drugs and similar procedures processed by the General Office of Medicines and Biological Products (GGMED) Anvisa, from January 2017 to August 2018. The information was obtained in the system Datavisa, from Anvisa, after GGMED and the Coordination of Institutional Security (CSEGI) authorized access. **Results:** In the period from January 2017 to August 2018 processed through GGMED 1,450 requests for renewal of medication registration generics and the like. A considerable percentage of automatic revalidations was observed medication registration, since 378 (26.0%) petitions among those processed by GGMED in the study period were automatically revalidated. An expressive portion was found of medicinal products belonging to the similar category, 247 petitions, corresponding to 65.0% of the 378 petitions renewed automatically. In the set of analyzed and rejected petitions, the main reasons for rejections were related with technical-administrative reasons (36 petitions, out of 51 rejected). **Conclusions:** The automatic registration revalidations, which should be an exception possibly if became the rule. Fact that brings concern from the health point of view.

KEYWORDS: Renewal of Registration; Health Legislation; Automatic revalidation; Product Registration; Medicines; Brazilian Health Regulatory Agency

RESUMO

Introdução: A publicação da Resolução da Diretoria Colegiada da Agência Nacional de Vigilância Sanitária (Anvisa) nº 200, de 26 de dezembro de 2017, fez com que a análise das petições de renovação de registro de medicamentos se tornasse atividade de menor complexidade. Contudo, o número de revalidações automáticas de registro continua expressivo. Além disso, continuam a ocorrer indeferimentos dessas petições. **Objetivo:** Caracterizar os desfechos das análises dessas renovações e quantificar o número de renovações automáticas de registro de medicamentos genéricos e similares. **Método:** Análise retrospectiva das petições de renovação de registro de medicamentos genéricos e similares tramitadas pela Gerência-geral de Medicamentos e Produtos Biológicos (GGMED) da Anvisa, de janeiro de 2017 a agosto de 2018. As informações foram obtidas no sistema Datavisa, da Anvisa, após o acesso ter sido autorizado pela GGMED e pela Coordenação de Segurança

Institucional (CSEGI). **Resultados:** No período de janeiro de 2017 a agosto de 2018 tramitaram pela GGMED 1.450 petições de renovação de registro de medicamentos genéricos e similares. Observou-se percentual considerável de revalidações automáticas de registro de medicamentos, pois 378 (26,0%) petições dentre as tramitadas pela GGMED no período do estudo foram revalidadas automaticamente. Foi encontrada parcela expressiva de produtos medicamentosos pertencentes à categoria dos similares, 247 petições, correspondendo a 65,0% das 378 petições renovadas automaticamente. No conjunto das petições analisadas e indeferidas, os principais motivos de indeferimentos relacionaram-se com razões técnico-administrativas (36 petições, das 51 indeferidas). **Conclusões:** As revalidações automáticas de registro, que deveriam ser uma exceção possivelmente se tornaram regra. Fato que traz preocupação do ponto de vista sanitário.

PALAVRAS-CHAVE: Renovação de Registro; Legislação Sanitária; Revalidação Automática; Registro de Produtos; Medicamentos; Agência Nacional de Vigilância Sanitária

INTRODUCTION

The Brazilian National Health Surveillance Agency (Anvisa) was created by Law n. 9.782, of January 26, 1999, with the purpose of coordinating the National Health Surveillance System, designed to eliminate, reduce or prevent health risks. Anvisa was created after a major health crisis in Brazil in the late 1990s, caused, among other factors, by the growing number of counterfeit medicines, a fact that demonstrated the country's need for a regulatory body in the health sector[1].

Anvisa's mission is to promote the protection of the population's health, carrying out, for this purpose, the health control of the production and marketing of products subject to health surveillance[2]. In this context, the importance of regulating the marketing authorization and renewal of the marketing authorization of drugs stands out, in view of the health risk related to the use of medicines.

Law n. 6.360, of September 23, 1976[3], regulated by Decree n. 8.077, of August 14, 2013[4], determines, as defined in Art. 12, § 6, that in the first half of the last year of the five-year period of validity, companies that hold a drug marketing authorization must submit a request for renewal of that authorization to Anvisa. This legislation establishes that Anvisa must analyze the renewal requests before the end of the five-year validity period of the authorization. If this deadline is not met, the authorization is automatically revalidated.

The General Management of Medicines and Biological Products (GGMED) is the technical area of Anvisa in charge of authorizing the drugs, as well as carrying out the renewal of these marketing authorizations. Activities carried done by its subordinate areas: Management of Quality Evaluation of Synthetic Medicines (GQMED), under the I terms of Art. 137; and Coordination of Less Complex Post-Market Authorization (CPMEC), as recommended in item I of art. 141, of Resolution of the Collegiate Board (RDC) n. 255, of December 10, 2018[5], which deals with Anvisa's Internal Regulations.

The GQMED performs the analysis of pharmaceutical technology for marketing authorization renewals. The CPMEC, on the other hand, analyzes marketing authorization renewals filed under the scope of RDC n. 200, of December 26, 2017[6]. This analysis is considered technical-administrative, since the CPMEC verifies only whether the company holding the authorization submitted the invoices that prove the marketing of the object of the renewal request. No other technical aspect of the drug is assessed.

To do its work, Anvisa uses the System of Products and Services under Health Surveillance (Datavisa), which consists of a database with information about the product, such as applicant for marketing authorization, formula and approval or disapproval opinions reports about the marketing authorization renewals.

Therefore, RDC n. 200/2017[6], which is being revised and revoked RDC n. 60, of October 10, 2014[7], by Anvisa, establishes the criteria for the granting and renewal of marketing authorization of synthetic and semi-synthetic drugs classified as new, generic and similar. This RDC also determines the legal instruments of health surveillance and the documents that companies holding marketing authorizations must submit for the analysis of these renewals. This set of documents is considered technical and administrative and of low complexity. Nevertheless, some of these requests are eventually rejected. This fact has an impact on GGMED's analysis routine, since each rejection can lead to an appeal analysis and, sometimes, the cancellation of publications, as recommended by RDC n. 266, of February 8, 2019[8].

The objective of this study was to identify, based on a survey of the documentation status for marketing authorization renewals at Datavisa, the reasons for the rejections of marketing authorization renewals of generic and similar drugs. We also sought to get an overview of the outcomes of the analysis of renewals and quantify the number of automatic revalidations of similar drugs in the period, in order to subsidize the health regulation of drug marketing authorization renewal in Brazil.

METHOD

We did a retrospective analysis of the requests for renewal of the marketing authorization of generic and similar drugs processed by the GGMED from January 2017 to August 2018, in addition to a quantitative summary of the number of automatic revalidations that occurred in the period.

The documentary data obtained on the requests analyzed in the period above were compared with the details of the reasons for

the rejections. This information was obtained from Datavisa. Access to the study data was authorized by the GGMED and by the Institutional Security Coordination (CSEGI). The latter is the organizational unit responsible for monitoring and evaluating the effectiveness of activities conducted within the scope of Anvisa, aiming at the protection of workers and sensitive knowledge, as well as proposing, whenever necessary, corrective measures, as recommended by item III, of Article 69, of Anvisa's Internal Regulations.

The collected data were organized quantitatively and analyzed with the support of statistical inference, as well as health legislation, extracted from ministerial ordinances and Anvisa resolutions, and the scientific literature on the topic.

The bibliography of the study was obtained in surveys of scientific journals on Google search. Anvisa's website was also used as a research source because it has all the Resolutions and Laws applied to the health regulation of medicines. In addition, books and other printed publications stored in physical library collections were consulted. Electronic papers were extracted from the internet using the following descriptors: "*renovação de registro de medicamentos*"; "*registro de medicamentos na Anvisa*"; "*leis da vigilância sanitária*" (renewal of drug marketing authorization; drug marketing authorization at Anvisa; health surveillance laws).

RESULTS

From January 2017 to August 2018, 1,450 files were processed by the GGMED with requests for marketing authorization renewal of generic and similar drugs, categories selected as the object of this study. Of this total, 378 (26.0%) drugs were automatically revalidated (Figure) and, of them, 247 (65.0%) were in the category of similar drugs.

Additionally, we found that 538 files (37.0% of the total) had been analyzed by the GQMED and the CPMEC in the period from January 2017 to August 2018 (Figure). In turn, among the analyzed files, 51 (9.5%) requests were rejected. Of the marketing authorization renewals that were not analyzed, 534 (37.0%) remained in the request queue waiting analysis (see Figure).

Technical-administrative reasons were the most prevalent among the rejected requests, since 36 (72.0%) of the rejections we analyzed had been rejected by Anvisa with this justification. As for technical reasons, these appeared in nine (16.0%) rejections. The rejections that occurred after the analysis of the appeals by Anvisa's Collegiate Board (Dicol) accounted for six (12.0%) of the requests rejected during the study period, as shown in the Chart.

In the group of technical reasons for request rejection there were arguments related to the quality, safety and efficacy of the drug, including impurities, incomplete analytical reports, dissolution profile, stability studies, among others.

In the category of technical-administrative reasons, the justifications for the rejections were the absence of the protocol of the Periodic Pharmacovigilance Report (RPF), as well as the non-submission of the product's commercial invoice, as determined by Art. 12, § 8, item II of Law n. 6.360/1976[3]. Another technical-administrative reason for rejection was the protocol for the request for marketing authorization renewal after the deadline established by Art. 12, § 6 of Law n. 6.360/1976[3]. This provision establishes that the request for marketing authorization renewal must be made in the first half of the last five years of validity of the marketing authorization.

DISCUSSION

For the purpose of analysis, the reasons for rejection were sorted into three categories: technical reasons, reanalysis due to the judgement of appeals by Dicol and reasons of a technical-administrative nature (Table).

Regarding the technical reasons for rejection of requests, the rejection data were considered on the same list and computed together, because for the purpose of this study it is not relevant to consider these data in a stratified manner.

Automatic revalidations (n = 378, 26%), in turn, are provided for in the legislation, both in Law n. 6.360/1976[3] and in Decree n. 8.077/2013[4], which regulate the conditions for the operation of companies subject to health licensing, and the marketing authorization, control and monitoring of products subject to health surveillance. These laws determine that, if Anvisa does

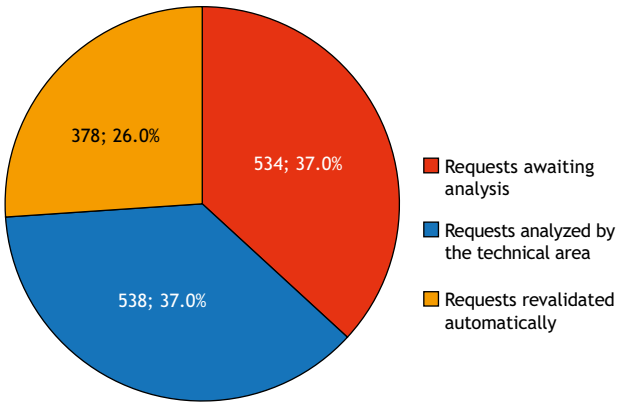

Figure. Status of marketing authorization renewal requests processed at the GGMED between January 2017 and August 2018 (n = 1,450).

Chart. Reasons for rejections of marketing authorization renewal requests of generic and similar drugs submitted to the GGMED, from August 2017 to January 2018 (n = 51 rejected requests).

Reason for rejection	Request (n./%)
Rejections for technical reasons	9/16.0%
Rejections after re-analysis due to the granting of appeals by Anvisa's Collegiate Board	6/12.0%
Rejections for technical-administrative reasons — failure to submit the periodic manufacturing report (RPF), as well as invoices for proof of manufacture of the drug within the last five years of validity of the authorization.	36/72.0%

not analyze the requests until the last day of validity of the marketing authorization, the drug will be automatically revalidated, without any analysis. The occurrence of 378 renewals of generic and similar drugs, of the 1,450 requests processed by the GGMED during the study period (Figure), demonstrates that automatic revalidations occurred in a substantial and worrying number, and not as exceptions, as recommended by the aforementioned legislation.

This situation is not in compliance with the recommendations presented by the Federal Audit Court (TCU) in Report TC n. 006.516/2016-5[9]. In an audit carried out at Anvisa's GGMED, the external control body concluded that there was, at that time, a high number of automatic renewals. In the data analyzed by the TCU, 3,092 requests were audited, from 2014 to 2016. Of these, 2,212 (71.5%) were automatically renewed. Although the data analyzed by the TCU include the category of new drugs, the results of the audit, when compared with the data from the analysis of this study, point out that Anvisa has used automatic marketing authorization renewals as a routine procedure, and not as an exception, as recommended by Law n. 6.360/1976[3].

Also, according to the TCU report, significant health risk was found in this large number of automatic revalidations, since similar products are among the revalidated products. Drugs in this category must be adjusted according to what is recommended by RDC n. 134, of May 29, 2003[10], of Anvisa. Art. 7 of said RDC determines that the holders of marketing authorizations of prescription-only similar medicines and not exempt from proof of relative bioavailability must submit the results of these tests in the second marketing authorization renewal as of the publication date of the RDC (June 2, 2003). Therefore, similar drugs on the market had until 2014 to submit bioequivalence and bioavailability tests to Anvisa[11].

The determination contained in RDC n. 134/2003[10] is recommended and takes the following aspects into account: drugs in the similar category were initially authorized without the presentation of evidence of bioavailability and bioequivalence in the application for marketing authorization, unlike generic drugs, in which bioequivalence and bioavailability were proven in the product marketing authorization[11].

This regulatory situation occurs mainly in drugs authorized before the publication of RDC n. 17, of March 5, 2007[12], since, after this regulation, these studies became a mandatory requirement for granting the marketing authorization. Most of the similar drugs that obtained marketing authorization before RDC n. 17/2007[12] fulfilled the requirements of RDC n. 134/2003[10] and presented technical documentation. However, bioequivalence and bioavailability studies may not have been analyzed in combination with pharmaceutical technology parameters for all similar drugs authorized in Brazil. An evidence of this is the fact that Anvisa publishes the list of interchangeable similar drugs on its portal. This list, which is updated periodically, contains only similar drugs that comply with RDC n. 134/2003[10]. Thus, the significant percentage of automatic renewals of marketing authorization for similar drugs is worrisome from the health point of view. Additionally, in a survey carried out in Anvisa's database on December 2, 2019, it was observed that 483 similar drugs had not yet had their studies related to the proof of RDC n. 134/2003[10] analyzed. That said, these drugs continue to be revalidated automatically, even without the proof established by this Resolution[10].

The analysis of requests for marketing authorization renewal of similar drugs is fundamental for Anvisa to determine whether the requirements of efficacy, safety, and quality, as recommended by the National Medicines Policy[13], have been achieved. Such requirements have been endorsed and referenced by the other public policies related to the pharmaceutical field, enforced in Brazil with the purpose of complying with the regulation of the health measures established in the 1988 Federal Constitution[14] and in the Organic Law of Health[15], especially the National Pharmaceutical Assistance Policy[16].

According to Lucchesi[17], this prerogative of the State to decide on the efficacy and safety of a drug cannot be overlooked, because, according to the author: "Products of uncertain safety or efficacy or products that are unnecessary from a therapeutic point of view should not have access to the market because they expose the population to unnecessary risks and/or expenses". Furthermore, we should consider that, according to Article 16 of Law n. 6.360/1976[3], only drugs that have the above-mentioned quality, safety and efficacy parameters confirmed by the regulatory agency may be on the market.

Considering that 247 (65.0%) of the 378 automatically revalidated drugs are in the similar category, we see that it is possible to keep a drug on the market without Anvisa's assessment of compliance with quality, safety and efficacy requirements, since this compliance has not yet been fully analyzed, despite the fact that the companies have submitted the studies requested by RDC n. 134/2003[10].

As for the rejections, these account for a small number of the analyzed requests (51 requests, 9.5% of the total of requests analyzed by the GGMED in the period). These data demonstrate that most companies have fulfilled the requirements of RDC n. 200/2017[6] for the renewal of marketing authorization. When analyzed, most requests for renewal of marketing authorization were granted.

Furthermore, it appears that these reasons for rejections, although not many, are responsible for a large part of the technicians' work, since each rejected request generates an appeal, to be analyzed by the official responsible for the decision, as determined by Law n. 9.784, of January 29, 1999, the regulatory instrument for administrative proceedings within the federal public administration.

The appeals granted by the Dicol are those that were not retracted by the technical area responsible for the rejection, but that were subsequently accepted by Anvisa's Board of Directors in a collegiate meeting. The appeal granted by the Dicol returns for reanalysis by the technical area, under the

terms of RDC n. 266/2019[8], and may be dismissed or granted according to the new analysis. In the analyzed data, six of the rejected requests, that is, 12.0% of the rejected, in the period of this study, had already been rejected before (Chart). Therefore, these data demonstrate that the appeals granted by the Dicol, even if rejected again after reanalysis by the technicians, have not had significant impact on the work of the technical areas of the GGMED related to the analysis of marketing authorization renewals.

Thus, it is understood that the percentage of technical and technical-administrative rejections of requests for marketing authorization renewal, as well as the reanalysis of these requests after granting of appeals, has not caused losses to the public administration nor increased the length of Anvisa's analyses, since the percentage of rejections for these reasons is very low, 51 (3.5%) rejected in a total of 1,450 requests processed by the GGMED in the period of this study. On the other hand, the number of rejections must be monitored, since their increase can compromise the Agency's efficiency with regard to the analysis of marketing authorization renewals. This is because rejections are a very expensive activity for the agency. They require the mobilization of human, technological and physical resources, preventing other demands from being met.

Additionally, the results of this survey are different from those found in the study by Carmo et al.[19], who researched the technical-administrative reasons for the rejection of marketing authorization requests in 2015. That study found a significant amount of rejections for this reason. This landscape is different from what was demonstrated in this study, in which the rejections of marketing authorization renewal were analyzed.

Nevertheless, both studies point to a possible shortcoming of the Agency with regard to instructions on how to comply with its standards, like when companies fail to file the RPF. RDC n. 200/2017[6] is clear as to the need for this protocol. However, even though some companies had this documentation, they did not file it, which suggests flawed communication from Anvisa in the sense of providing guidance on the procedural instruction of the requests for drug marketing authorization renewal. In turn, as in the case of the absence of invoices, there is an explicit failure to comply with health regulations. This fact occurred to a greater extent in the rejections of drug marketing authorization for administrative reasons[19].

CONCLUSIONS

The analyzed data have shown a substantial occurrence of automatic revalidations of the marketing authorization of generic and similar drugs by Anvisa in the period evaluated in this study. This may hinder the fulfillment of the institutional mission of this regulatory body, since the renewal of the marketing authorization is the opportunity that Anvisa has to verify whether the product fulfills the technical and health-related conditions to remain on the market.

In turn, the results of this study demonstrated that few requests for marketing authorization renewal were rejected, only 51 (3.5%) rejected from a total of 1,450 requests processed by the GGMED during the period of this study. However, these data are relevant, since the rejections are important to measure the technical and administrative results of Anvisa's actions.

In addition, it appears that the landscape presented by the TCU audit, done in 2016, is still part of the Agency's work routine, because automatic revalidations of marketing authorizations continue to be common practice in the Agency's work process.

Finally, we conclude that there was a significant number of automatic revalidations of marketing authorization in the period of this study and that this situation raises concern, considering that the liability arising from the drugs that fall under the RDC n. 134/2003[10] can harm Anvisa's efficiency in regulating the marketing authorization renewal of generic and similar drugs.

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Authors' Contribution

Oliveira HMR – Conception, planning (study design), acquisition, analysis, interpretation of data, writing and review of the paper. The author approved the final draft of the paper.

Conflict of Interest

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