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Main non-technical reasons to refuse pharmaceutical drug products registration in 2015

Principais razões não técnicas para o indeferimento de registro de medicamentos em 2015

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ABSTRACT

The registration of pharmaceutical drug products involves reviewing company's administrative aspects as well as technical-scientific aspects related to efficacy, safety and quality. This study evaluated the main administrative reasons for registration refusals of new, generic and similar (branded generic) pharmaceutical drug products in Brazil. Actual submission procedure and process instruction is presented in detail. The aim is to contribute for the improvement of novel applications, reducing non-technical refusals. A retrospective search of registration refusals in 2015 published by the Brazilian Government Official Gazette using Anvisa database, called Datavisa, was performed. The main reasons for non-technical registration refusals of generic and similar pharmaceutical drug products were deadline non-compliance (61.7%), preliminary review (19.8%) and insufficient documentation to permit a substantial full review (18.5%). Disclosure of administrative reasons behind failed applications is a step forward on regulatory transparency, and on internal and external orientation about regulatory mechanisms.

KEYWORDS: Anvisa; Products Registration; Generic Drug; Similar Drug; Sanitary Surveillance

RESUMO

O registro de medicamentos contempla a avaliação do cumprimento do caráter administrativo da empresa requerente do registro e o caráter técnico-científico relacionado à eficácia, à segurança e à qualidade do medicamento. Esse trabalho buscou identificar os principais motivos administrativos de indeferimento de registro de medicamentos novos, genéricos e similares no Brasil, além de detalhar o procedimento atual de submissão e instrução de processos de registro. Espera-se que, a partir desta análise, futuros peticionamentos possam ser aprimorados e indeferimentos por tais razões, reduzidos. Para isso, foi realizado levantamento das normas vigentes para o detalhamento do processo de submissão de registro e uma análise retrospectiva dos indeferimentos publicados no Diário Oficial da União através do banco de dados da Agência Nacional de Vigilância Sanitária, Datavisa, do ano de 2015. As principais razões de indeferimento por motivos administrativos foram levantadas nos pareceres de indeferimento e constituem o não cumprimento de prazos (61,7%), a avaliação preliminar de processo (19,8%) e a documentação insuficiente para análise técnica (18,5%). A divulgação de tais razões contribui para a transparência do processo regulatório, orientação interna e externa quanto à aplicabilidade dos atos normativos.

PALAVRAS-CHAVE: Anvisa; Registro de Medicamento; Medicamento Genérico; Medicamento Similar; Vigilância Sanitária

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INTRODUCTION

The Brazilian Health Surveillance Agency (Anvisa) was created with the objective of protecting the health of the population by performing the sanitary control of the production and marketing of products subject to health surveillance, including pharmaceutical drugs[1].

For a pharmaceutical drug to be marketed in Brazil, it must be registered first[2]. This can only be done by Anvisa, which is also responsible for establishing the requirements for pharmaceutical drug registration in Brazil through regulations[1].

Drug registration is an important sanitary control tool. It enables the assessment of the administrative status of the company requesting registration and of technical-scientific aspects related to the efficacy, safety and quality of the drug to be supplied to the population[3]. Any act related to the registration must be published in the Official Gazette (DOU)[2] and include key information about the product, such as the name of the company requesting the registration, the active ingredient, the name of the medicine, the pharmaceutical form, the concentration (dosage), primary and secondary packaging, number of unit doses and Anvisa's decision on the application, i.e. whether the drug was approved or rejected. In cases of refusal, the complete motivation is to be shared with the company that requested the registration.

Compliance with and fulfillment of all legal and non-statutory requirements is essential to the analysis and subsequent approval of the registration application, especially those of an administrative nature, whose noncompliance leads to the refusal of the registration without the technical analysis of the petition, that is, without proper assessment of the quality, safety and efficacy of the drug. Thus, the population is deprived of access to pharmaceutical drugs because of noncompliance with non-technical aspects related to public administration, increasing the waste of resources by both companies and regulatory bodies.

In Brazil, there are different categories of drug registration. To contextualize this article, we will address only synthetic drugs classified as new, generic, similar and clone drugs.

New pharmaceutical drugs are those containing an active ingredient that is not yet registered in the country, including new salts, isomers, esters, ethers, complexes or other derivatives not yet registered. Their efficacy and safety are to be proven through clinical trials. These are usually new products whose active ingredient has patent protection. They are also identified by a brand name[4].

According to Law n. 6.360, of September 23, 1976, similar drugs have the same active ingredient, concentration, pharmaceutical form, route of administration, dosage and therapeutic indication. They are pharmaceutical equivalents of the reference drug. They are identified by a brand name. Generic drugs are interchangeable with the reference drug, with proven safety and efficacy, designated by the Common Brazilian Denomination (DCB) or, in its absence, by the International Non-proprietary Name (INN). It is generally produced after expiration or waiver of the patent protection of the reference product[2].

In 2014, RDC n. 31, of May 29, 2014, created the category of clone drugs, which can only differ from the reference drug (matrix process) as to the name of the drug, the packaging layout and the legal information on the package insert and on the label. The registration process is simplified and the decision will be the same as the decision of the matrix process[5].

Therefore, this study aims to identify the main reasons for refusal to register new, generic and similar drugs because of administrative reasons and to detail Anvisa's current rules on the submission of petitions and procedural instructions for the registration of synthetic drugs in Anvisa, to improve future petitions and contribute to reducing the number of rejections for these reasons.

METHOD

We did a retrospective analysis of the requests for registration of new, generic and similar drugs refused in the year 2015 and published in the DOU.

Based on the survey of rejected requests from 2015, we analyzed the refusal reports looking for detailed reasons for the refusal of each of the processes we retrieved from the Datavisa system. This system consists of Anvisa's database with information about the product, such as registration applicant, formulation, in addition to approval or rejection reports.

We selected data on refusals due to administrative reasons.

To find details on the submission of registration processes of synthetic drugs to Anvisa, we surveyed the current norms related to this subject.

RESULTS

Procedures for the submission of registration of synthetic drugs and procedural instructions are regulated mainly by RDC n. 204, of July 6, 2005, and RDC n. 25, of June 16, 2011. They must meet the requirements and deadlines described in the Figure[6,7].

Between January 1, 2015, and December 31, 2015, 272 decisions were published in the DOU regarding generic, similar and new drugs in Brazil. Of these decisions, 136 (50%) were refusals of generic and similar drugs. No new drugs were rejected. Of the 136 rejections, six were disregarded because they were requests for clone drugs, which would lead to duplicate results. Therefore, 130 rejections were considered in this study: 93 (35%) referring to generic drugs and 37 (14%) to similar drugs[8].

For the 130 published processes, we listed 501 motivations for refusal, of which 81 (16%) resulted from the noncompliance with administrative aspects regulated by Anvisa.

Administrative reasons are those related to compliance with deadlines, documentation and preliminary assessment of the registration process, distributed according to the Table.

DISCUSSION

The drug registration process, as well as other documents that are presented to Anvisa, is filed in the Document Management Department (GEDOC)[7].

For synthetic pharmaceutical drugs classified as new, generic and similar, the analysis covers quality assessment (pharmaceutical technology), safety and efficacy. RDC n. 60, of October 10, 2014, establishes the criteria for granting registration for these categories[4].

The registration processes of generic and similar drugs in Anvisa are to be physically submitted exclusively to agency's headquarters in Brasília, whereas new drugs are registered online through the Electronic Drug Registration System (SISREGMED)[7,9]. We did not find any rejection of these categories due to mistakes resulting from the petitioned matter. It should be noted that RDC n. 86, of June 27, 2016, ruled that, as of June 2017, documentation of registration of similar and generic drugs in electronic format is mandatory[10].

Before the technical review begins, the registration process of generic and similar drugs is subject to a preliminary assessment, in which it is ascertained whether all the documents required for the technical evaluation per se have been examined[6,11,12]. If so, the process goes to technical analysis (Figure). Anvisa may request further information or clarification on the requested documentation through a requirement

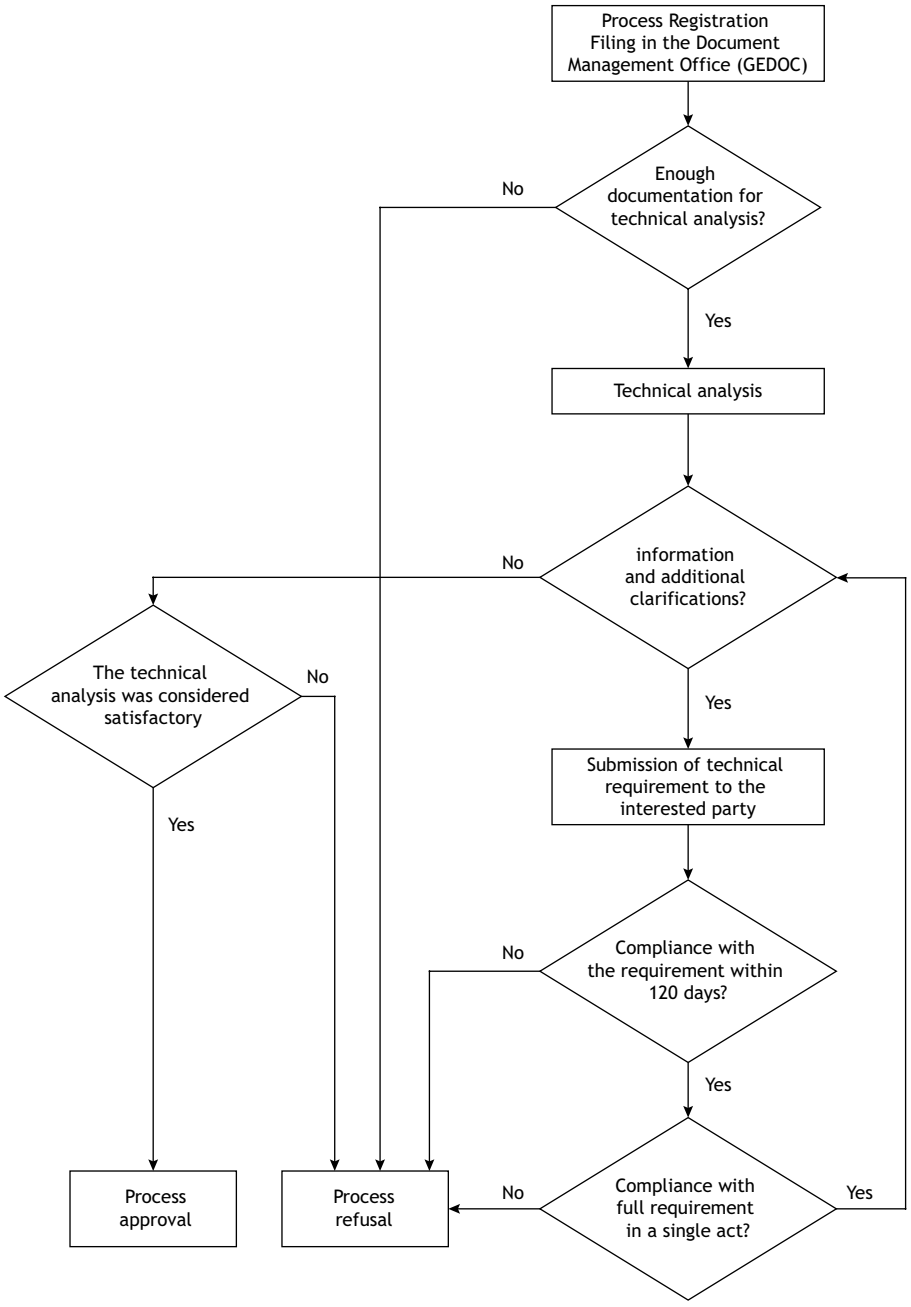

Figure. Flowchart of protocol for analysis of drug registration petitions in Anvisa.

Table. Administrative reasons for refusal of generic and similar drug registrations in Brazil in 2015.

Administrative reason for refusal	n	%
Deadlines	50	61.7
No adequacy as clone medication was requested	33	40.7
Failure to comply with legal requirements	13	16
The extension of the term to fulfill the requirement within the legal deadline was not requested	2	2.5
The reopening the process was not requested within the legal deadline	2	2.5
Preliminary assessment	16	19.8
No documentation was submitted regarding the quality control carried out by the importer	3	3.7
No production process validation summary report was submitted	3	3.7
No documentation was submitted on the development of the formulation	2	2.5
No documentation was submitted regarding the quality control carried out by the drug manufacturer	2	2.5
The photo-stability study of the drug was not submitted	2	2.5
No IFA quality control reports have been issued by the IFA manufacturer*	1	1.2
No certificate of registration of the drug in the country of origin	1	1.2
No information on the finished product was submitted according to the template set out in Annex I of RDC n. 60/2014	1	1.2
The validation of analytical methods for the IFA performed by the manufacturer of the drug was not submitted	1	1.2
Documentation	15	18.5
Absence of current GMPC**	9	11.1
Absence of GMPC for pilot plant	2	2.5
Sanitary permit expired at the time the registration was requested	1	1.2
Duplicate registration	1	1.2
Absence of electronic media	1	1.2
In disagreement with RDC n. 60/2014	1	1.2

sent to the applicant. The petitioner's response is to be submitted to the Agency through the fulfillment of this requirement[6].

In 2014 and 2015, regulations that directly impacted the drug registration submission process and the number of refusals were published and came into force.

The main reason for refusal of registration for administrative reasons was noncompliance with deadlines, mainly due to the absence of a request for adequacy as clone medication. According to RDC n. 31/2014, companies should have 90 days after the date of publication of the resolution to request the adequacy of the drug to the clone drug category for the registration of generic and similar drugs already filed under the previous regulation[5,13] and still pending technical analysis. If the company did not request the adjustment, the process was subject to refusal[5]. For 33 petitions (40.7%), the adequacy procedure was not adopted, which led to a high number of cases of this type in 2015. However, this was typical of the year 2015 and should not lead to similarly high numbers in the following years.

In 2015, deadlines for complying with the requirement and unlocking processes were modified by RDC n. 23, of June 5, 2015[14]. Prior to the publication of these regulations, the deadline for complying with the requirement was 30 days from the date of confirmation of receipt of the requirement, extendable for 60 days at the request of the notified party for duly justified reasons[6]. As of June 2015, the deadline for compliance with the requirement has been extended to 120 non-extendable days, counted from the date of confirmation of requirement receipt. Therefore, the reasons for refusal we identified were failure to comply with the requirement within the legal deadline - 30 or 120 days, depending on the maturity of the deadline in the first or second half of 2015 - and the absence of a request to extend the deadline for 30 days in the first half of the same year.

Upon receipt of a requirement, the respondent could request temporary closure of the process in order to comply with the requirement first[15]. However, this procedure was suspended in 2014 through RDC n. 7, of February 28, 2014[16]. In 2015, as of the publication of RDC n. 23/2015[14], temporarily archived petitions should be re-opened at the request of the interested party within a period of up to one year from the date of archiving. Failure to request process reopening within the deadline led to the rejection of two cases (2.5%).

Currently, the queue of registration petitions for generic and similar drugs awaiting analysis is of about 800 applications, some filed in 2010[17]. Failure to meet deadlines in general may indicate lack of interest of petitioners in filing processes that have been in the queue for many years. Instead of using the instrument to waive cases in which there is no longer interest[18], companies prefer to wait for the publication of the rejection due to the deadline. Refusal and cancellation do not incur costs for the petitioners. They should prepare a petition to withdraw the process, but that consists of a simple document. However, withdrawal requests are less costly for public administration than the rejection of the case. Considering the queue of petitions awaiting analysis, the time saved with petitions in which there is no interest would contribute to expedite the procedures and ensure more availability of medicines in the market.

Failure to comply with the preliminary assessment was the second reason for refusal for administrative reasons. In this regard,

17.3% of the rejected cases had insufficient documentation in accordance with the current standard of drug registration, RDC n. 60/2014[4], and 2.4% did not allow the analysis based on RDC n. 16, of March 2, 2007[19], which regulated the registration of generic drugs and was revoked by RDC n. 60/2014[4]. However, except for the requests for the summary report on validation of productive processes and documentation on formulation development (totaling 6.2%), which were included in RDC n. 60/2014, the other requirements were already requested by previous regulations that dealt with the registration of generic and similar drugs and date from 2007[19,20]. Considering the time elapsed between the filing of the registration process and the actual assessment of the processes waiting in the analysis queue, we can infer that the processes were complemented while awaiting analysis. To do that, they often use the undue tool of amendment[6], which allows the applicants to amend the process after filing it. However, starting in 2014, the preliminary assessment began to be adopted, reducing the number of incomplete cases that were unduly awaiting analysis and consequently delaying the registration of other drugs.

Among the reasons related to documentation, the lack of a Good Manufacturing Practice Certificate (GMPC) in force for the plant and the pilot plant are the main reasons. In accordance with RDC n. 16/2007 and 17, of March 2, 2007, the company must have a GMPC in force at the time of registration filing[19,20]. For the pilot plant, no specific GMPC is required, but these documents must be available for the plant inspected by the Health Surveillance for GMPC concession purposes. However, according to RDC n. 60/2014, the lack of a valid GMPC does not preclude the submission of the registration application, but its approval[4]. Therefore, this item will not provide grounds for refusal prior to the technical analysis for petitions filed under the current regulation[4].

The large number of cases refused for non-technical reasons is a highly costly activity for Anvisa, since verification of the process, preparation of the refusal report and its publication in the DOU require the Agency's technological, personal and physical resources. Compliance with regulatory requirements for submission of processes with complete and timely documentation would avoid wasting public funds and contribute to greater agility in the drug registration process in Brazil.

In 2008, Anvisa implemented the Regulatory Process Improvement Program, which aims to modernize and qualify the Agency's regulations, contributing to: effectiveness of regulatory acts; transparency; improvement of mechanisms for the participation of the society in the regulatory process; reducing bureaucracy and enabling easier access to regulation[21]. The publication of regulations in 2014 and 2015 had a direct impact on the registration submission procedure and is a consequence of the implementation of the Program. They demonstrate the Agency's willingness to simplify and expedite the process. The petitioning of new drugs through exclusively electronic means modernizes the procedure and promotes agility and economy in the registration process.

On the other hand, the high number of refusals for non-technical reasons may indicate failure in the application of regulatory requirements, publication and clarification regarding new norms and deadlines. The changes in the requirements for filing and reopening processes in 2014 and 2015 and in the deadlines related to the fulfillment of requirements exemplify the intense variation of resolutions related to the subject without due harmonization regarding the new deadlines, which contributed to the refusals. They also represent challenges for the implementation of the Regulatory Process Improvement Program in the aspects related to the publication and transparency of regulations, and internal and external guidance regarding the applicability of normative acts. The monitoring by Anvisa's management to improve the evaluation process of the proposals for revision and new resolutions is fundamental for the regulatory modernization of the agency in harmony with international regulations and for their effective enforcement.

CONCLUSIONS

The main reasons for refusal for administrative reasons in 2015 include noncompliance with deadlines, preliminary process evaluation and insufficient documentation for technical analysis. The identification of these reasons contributes to the implementation of the Regulatory Process Improvement Program as an important step to promote the transparency of Anvisa's regulatory process and to guide the updating of regulatory acts.

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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.